

INHIBITORS OF NLRP3 INFLAMMASOME

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/164,780, filed
5 on March 23, 2021, and U.S. Provisional Application No. 63/219,538, filed on July 8, 2021,
the entire contents of which are hereby incorporated in its entirety.

BACKGROUND

Aging frailty poses a very concerning problem for the overall health and well-being of
10 individuals and is characterized as a syndrome of multisystem physiological dysregulation.
Aging frailty is a geriatric syndrome characterized by weakness, low physical activity, slowed
motor performance, exhaustion, and unintentional weight loss (Yao, X. et al., *Clinics in
Geriatric Medicine* 27(1): 79-87 (2011)). Furthermore, there are many studies showing a
direct correlation between aging frailty and inflammation (Hubbard, R. E., et al.,
15 *Biogerontology* 11(5):635-641 (2010)). Immunosenescence is characterized by a low grade,
chronic systemic inflammatory state known as inflammaging (Franceschi, C. et al., *Annals of
the New York Academy of Sciences* 908:244-254 (2000)). This heightened inflammatory
state or chronic inflammation found in aging and aging frailty leads to immune dysregulation
and a complex remodeling of both innate and adaptive immunity.

20 Inhibiting the NLRP3 inflammasome, an oligomeric protein complex that includes
ASC and caspase-1, mediates inflammation in an extensive number of preclinical models
(Schwaid, A. G., *J. Med. Chem.* **2021**, 64(1), 101-122). At the same time, the NLRP3
inflammasome is part of a larger pro-inflammatory pathway, whose modulation is also being
explored. NLRP3 is an inflammasome sensor protein that has been well studied in a number
25 of disease contexts. Many different indications are associated with the NLRP3
inflammasome including diseases related to aging, cryopyrin-associated periodic syndrome
(CAPS), nonalcoholic steatohepatitis (NASH), gout, coronary artery disease, Crohn's
disease, osteoarthritis, rheumatoid arthritis, Alzheimer's disease, Parkinson's disease,
intestinal disorders, acute respiratory distress syndrome (ARDS), amyotrophic lateral
30 sclerosis (ALS), cancer, and dermatological diseases.

Inflammation, as well as activation of the NLRP3 inflammasome, have also been
shown to result in hearing loss (Nakanishi, H., et al., *Frontiers in Neurology*, **2020**, 11, 1-7;
Nakanishi, H., et al., *PNAS*, **2017**, E7766-E7775). The inflammation-related hearing loss can
be age-dependent (Fischer, N., et al., *Gerontology*, **2019**, 1-7), noise-induced (Le Prell, C.
35 G., et al. *Current Opinion in Physiology*, **2020**, 18, 32-36), and the result of a viral infection
such as Zika virus and coronavirus (Yee, K. T., et al., *Hearing Research*, **2020**, 395, 1-15).

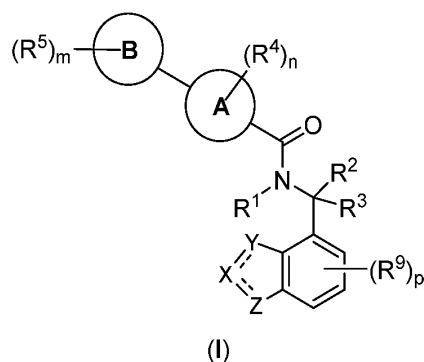
The NLRP3 inflammasome is therefore a promising drug target. The breadth of the indications it is implicated in speak to the need for therapeutics that target the NLRP3 inflammasome.

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SUMMARY

Provided here are compounds that inhibit the NLRP3 inflammasome. As such, these compounds are useful in the treatment of a variety of indications, including inflammaging and inflammation.

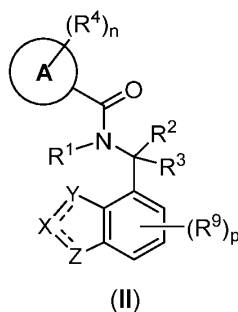
In an aspect, provided herein is a compound of Formula I:



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or a pharmaceutically acceptable salt thereof.

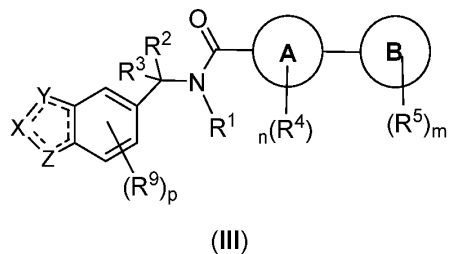
In an embodiment, the compound of Formula I is a compound of Formula II:



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or a pharmaceutically acceptable salt thereof.

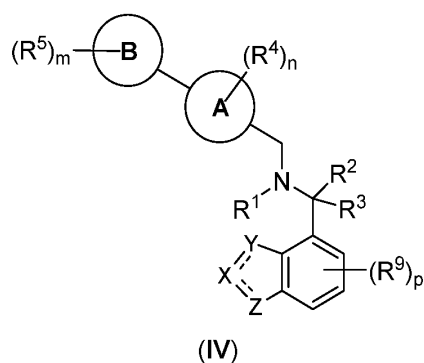
In another aspect, provided herein is a compound of Formula III:



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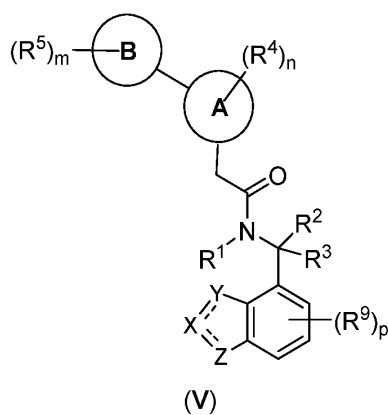
or a pharmaceutically acceptable salt thereof.

In yet another aspect, provided herein is a compound of Formula IV:



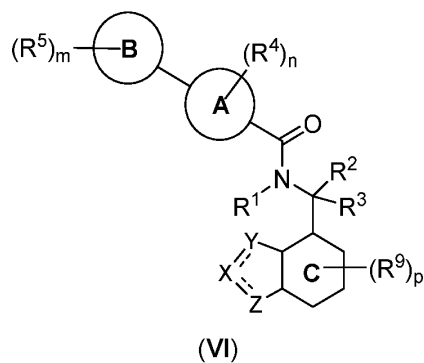
or a pharmaceutically acceptable salt thereof.

In still another aspect, provided herein is a compound of Formula V:



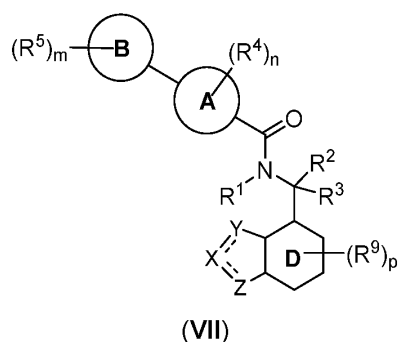
or a pharmaceutically acceptable salt thereof.

In an aspect, provided herein is a compound of Formula VI:



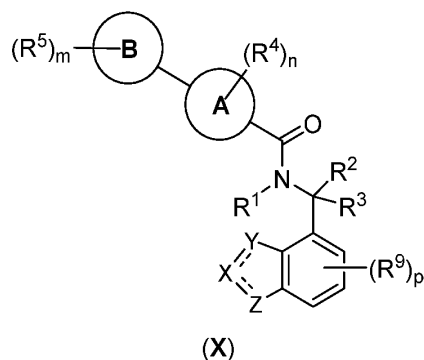
or a pharmaceutically acceptable salt thereof.

In an aspect, provided herein is a compound of Formula VI:



or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula X:



or a pharmaceutically acceptable salt thereof.

In yet another aspect, provided herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another aspect, provided herein is a method of inhibiting NLRP3 inflammasome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound described herein.

DETAILED DESCRIPTION

Provided here are compounds that inhibit the NLRP3 inflammasome. As such, these compounds, as well as pharmaceutical compositions that comprise these compounds, are useful in the treatment of a variety of indications, including inflammation, and other age-related diseases.

Definitions

Listed below are definitions of various terms used to describe the compounds and compositions disclosed herein. These definitions apply to the terms as they are used

throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art.

- 5 Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

As used herein, the articles “a” and “an” refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means
10 one element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the
15 term “about” is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, including $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

The term “administration” or the like as used herein refers to the providing a therapeutic agent to a subject. Multiple techniques of administering a therapeutic agent exist
20 in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term “treat,” “treated,” “treating,” or “treatment” includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises alleviating or preventing the
25 symptoms of inflammaging and age-related disorders.

As used herein, the term “contacting” refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, “contacting” a cell with a compound includes the administration of a compound of the present invention to an individual, subject, or patient, such as a human, as well as, for example, introducing a
30 compound into a sample containing a purified preparation containing the cell.

As used herein, the term “cell” is meant to refer to a cell that is *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a
35 mammal.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there

had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term "patient," "individual," or "subject" refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and marine mammals. Preferably, the patient, subject, or individual is human.

As used herein, the terms "effective amount," "pharmaceutically effective amount," and "therapeutically effective amount" refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term "pharmaceutically acceptable" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic 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 base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. The phrase "pharmaceutically acceptable salt" is not limited to a mono, or 1:1, salt. For example, "pharmaceutically acceptable salt" also includes bis-salts, such as a bis-hydrochloride salt. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term "composition" or "pharmaceutical composition" refers to a mixture of at least one compound useful within the disclosure with a pharmaceutically

acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

5 As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the disclosure within or to the patient such that it may perform its intended function. Typically,
10 such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the disclosure, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and
15 sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and
20 polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

25 As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the present disclosure, and are physiologically acceptable to the patient. Supplementary active compounds may also be incorporated into the compositions. The “pharmaceutically acceptable carrier” may
30 further include a pharmaceutically acceptable salt of the compound disclosed herein. Other additional ingredients that may be included in the pharmaceutical compositions are known in the art and described, for example, in Remington’s Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

 As used herein, “inflammaging” is defined as chronic sterile inflammation that is
35 associated with numerous age-related diseases.

 As used herein, “age-related disorder” refers to disorders that are associated with the aging process. Stated alternatively, age-related disorders are diseases associated with the

elderly. Non-limiting examples of age-related diseases include atherosclerosis and cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension, and Alzheimer's disease. The incidence of all of these diseases increases exponentially with age.

5 As used herein, the term "alkyl," by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (i.e., C₁-C₆ alkyl means an alkyl having one to six carbon atoms) and includes straight and branched chains. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert butyl, pentyl, neopentyl, and hexyl. Other examples of C₁-C₆
10 alkyl include ethyl, methyl, isopropyl, isobutyl, n-pentyl, and n-hexyl.

 As used herein, the term "haloalkyl" refers to an alkyl group, as defined above, substituted with one or more halo substituents, wherein alkyl and halo are as defined herein. Haloalkyl includes, by way of example, chloromethyl, trifluoromethyl, bromoethyl, chlorofluoroethyl, and the like.

15 As used herein, the term "halo" or "halogen" alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

 As used herein, the term "cycloalkyl" means a non-aromatic carbocyclic system that is fully saturated having 1, 2 or 3 rings wherein such rings may be fused. The term "fused"
20 means that a second ring is present (i.e., attached or formed) by having two adjacent atoms in common (i.e., shared) with the first ring. Cycloalkyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms. The term "cycloalkyl" includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[3.1.0]hexyl, spiro[3.3]heptanyl, and bicyclo[1.1.1]pentyl. In
25 an embodiment, cycloalkyl refers to C₃₋₁₀ cycloalkyl. In another embodiment, cycloalkyl refers to C₃₋₆ cycloalkyl.

 As used herein, the term "heterocyclyl" or "heterocycloalkyl" means a non-aromatic carbocyclic system containing 1, 2, 3 or 4 heteroatoms selected independently from N, O, and S and having 1, 2 or 3 rings wherein such rings may be fused, wherein fused is defined
30 above. Heterocyclyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms, and containing 0, 1, or 2 N, O, or S atoms. The term "heterocyclyl" includes cyclic esters (i.e., lactones) and cyclic amides (i.e., lactams) and also specifically includes, but is not limited to, epoxidyl, oxetanyl, tetrahydro-furanyl, tetrahydropyranyl (i.e., oxanyl), pyranyl, dioxanyl, aziridinyl, azetidiny, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, oxazolidinyl, thiazolidinyl, piperidinyl,
35 morpholinyl, piperazinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, 2-azabicyclo[2.1.1]hexanyl, 5-azabicyclo[2.1.1]-hexanyl, 6-azabicyclo[3.1.1] heptanyl, 2-

azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 2-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, 2-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl, 3-oxa-9-azabicyclo[3.3.1]nonanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxaspiro[3.3]heptanyl, 2-oxaspiro[3.5]nonanyl, 3-oxaspiro[5.3]nonanyl, and 8-oxabicyclo[3.2.1]octanyl. In an embodiment, heterocycloalkyl refers to 3-10 membered heterocycloalkyl. In another embodiment, heterocycloalkyl refers to 4-10 membered heterocycloalkyl. In another embodiment, heterocycloalkyl refers to 3-6 membered heterocycloalkyl.

As used herein, the term “aromatic” refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, i.e., having $(4n + 2)$ delocalized π (pi) electrons, where n is an integer.

As used herein, the term “aryl” means an aromatic carbocyclic system containing 1, 2 or 3 rings, wherein such rings may be fused, wherein fused is defined above. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) may be fully saturated, partially unsaturated or fully unsaturated. The term “aryl” includes, but is not limited to, phenyl, naphthyl, indanyl, and 1,2,3,4-tetrahydronaphthalenyl. In some embodiments, aryl groups have 6 carbon atoms. In some embodiments, aryl groups have from six to ten carbon atoms. In some embodiments, aryl groups have from six to sixteen carbon atoms. In an embodiment, the aryl group has six to ten carbon atoms.

As used herein, the term “heteroaryl” means an aromatic carbocyclic system containing 1, 2, 3, or 4 heteroatoms selected independently from N, O, and S and having 1, 2, or 3 rings wherein such rings may be fused, wherein fused is defined above. The term “heteroaryl” includes, but is not limited to, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyridinyl, 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinolinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, 6,7-dihydro-5H-cyclopenta-[c]pyridinyl, 1,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 2,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydro-1H-indazolyl and 4,5,6,7-tetrahydro-2H-indazolyl. In embodiment, heteroaryl is 5-10 membered heteroaryl. In another embodiment, heteroaryl is 5-6 membered heteroaryl.

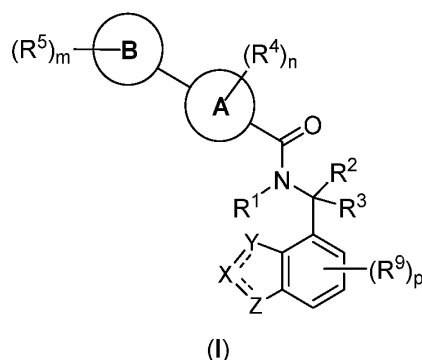
It is to be understood that if an aryl, heteroaryl, cycloalkyl, or heterocyclyl moiety may be bonded or otherwise attached to a designated moiety through differing ring atoms (i.e., shown or described without denotation of a specific point of attachment), then all possible

points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term “pyridinyl” means 2-, 3- or 4-pyridinyl, the term “thienyl” means 2- or 3-thienyl, and so forth.

5 Compounds

Provided herein are compounds that are inhibitors of the NLRP3 inflammasome and are thus useful in the treatment of inflammatory disorders, including cancer and other proliferation diseases.

In an aspect, provided herein is a compound of Formula I:



or a pharmaceutically acceptable salt thereof;

wherein

$\equiv$ is an optional double bond;

X is CH or N;

Y and Z are each independently selected from the group consisting of NH, NR^9 , O, S, N, CH, and CR^9 ;

Ring A is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{4-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B is absent and m is 0;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, and C_{3-6} cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R^6 ;

R^2 and R^3 are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, R^2 and R^3 , together with the atom to which they are attached, form a ring selected from the group consisting of C_{3-7} cycloalkyl and 3-7 membered heterocycloalkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, and COR^6 ;

alternatively, two R^4 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^5 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6 , and SO_2R^6 ;

alternatively, two R^5 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-6} alkyl- C_{6-10} aryl, C_{0-6} alkyl-5-10 membered heteroaryl, OC_{1-6} alkyl, C_{3-6} cycloalkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

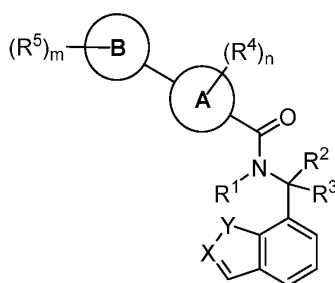
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

In an embodiment of Formula I, Ring A is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, and C_{4-10} cycloalkyl.

In an embodiment, the compound of Formula I is a compound of Formula Ia:



(Ia)

or a pharmaceutically acceptable salt thereof;

wherein

X is CH or N;

Y is NH, O, or S;

5 Ring A is phenyl or 5-6 membered heteroaryl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

R¹ is H or C₁₋₆ alkyl;

R² and R³ are each independently H or C₁₋₆ alkyl;

10 each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

each R⁵ is independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-15 7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₆₋₁₀ aryl, C₅₋₁₀ heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

m is 1, 2, or 3; and

n is 0, 1, 2, or 3.

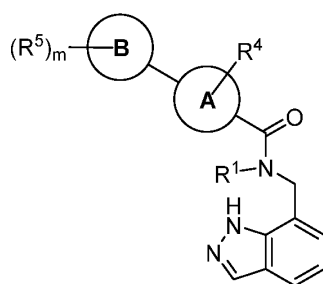
20 In another embodiment, Ring A is selected from the group consisting of phenyl, pyridine, pyrimidine, and pyrazine. In yet another embodiment, Ring A is selected from the group consisting of phenyl, pyridine, pyridazine, pyrimidine, imidazole, pyrazole, and C₃₋₆ cycloalkyl.

In an embodiment, two R⁴, together with the atoms to which they are attached, 25 together with Ring A, form a ring selected from the group consisting of dihydrobenzofuran, benzofuran, dihydrobenzooxazine, dihydrobenzodioxine, indazole, and indole, all of which are optionally substituted with one, two, or three R⁷.

In still another embodiment, R¹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl, optionally substituted with C₁₋₆ alkyl.

30 In an embodiment, Y is NH, X is N, and Z is CH. In another embodiment, Y is NH, X is CH, and Z is CH. In yet another embodiment, Y is CH, X is N, and Z is NH. In still another embodiment, Y is CH, X is CH, and Z is N.

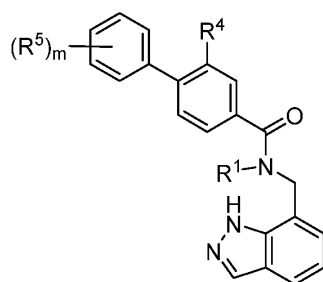
In an embodiment, the compound of Formula I is a compound of Formula Ib:



(Ib)

or a pharmaceutically acceptable salt thereof.

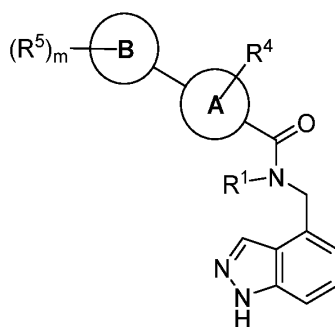
In another embodiment, the compound of Formula I is a compound of Formula Ic:



(Ic)

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the compound of Formula I is a compound of Formula Id:



(Id)

or a pharmaceutically acceptable salt thereof.

In still another embodiment, R^4 is OC_{1-6} alkyl.

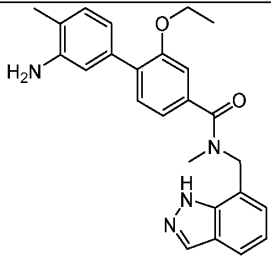
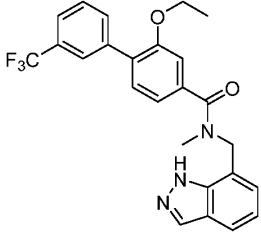
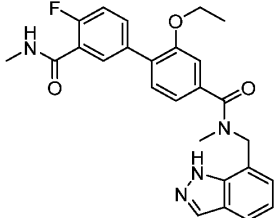
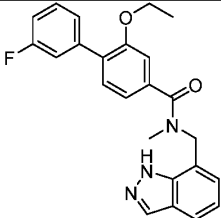
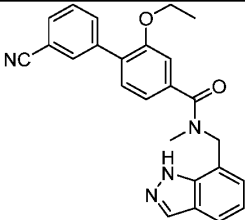
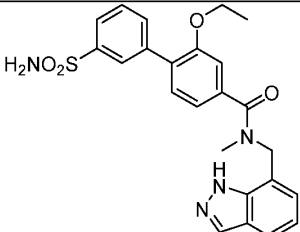
In an embodiment, R^5 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, NH_2 , CN, $CONH_2$, $CONH(C_{1-6}$ alkyl), and SO_2NH_2 .

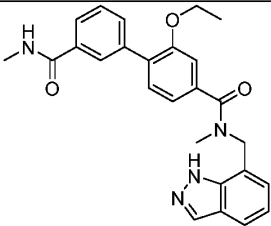
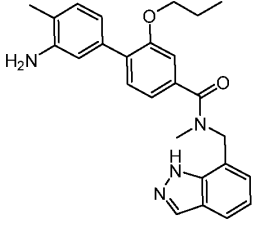
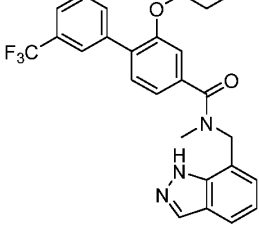
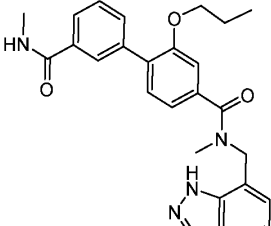
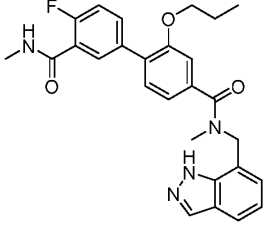
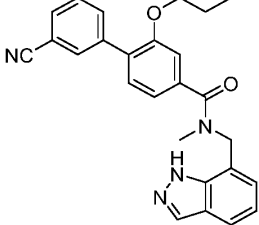
In another embodiment, Ring B is not absent.

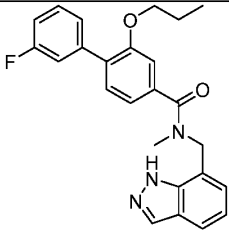
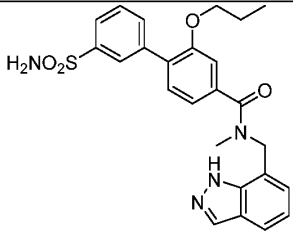
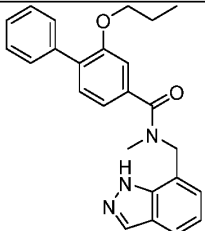
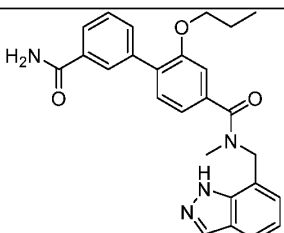
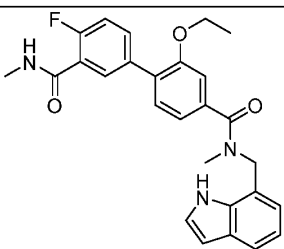
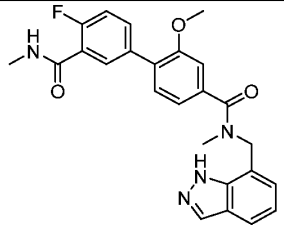
In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

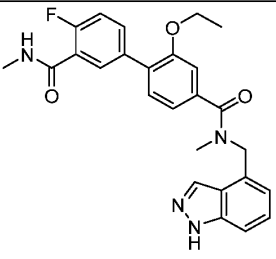
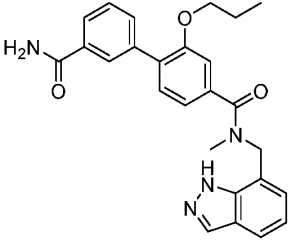
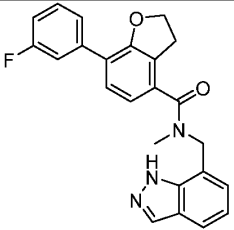
In another embodiment, the compound of Formula I is selected from the group consisting of a compound from Table 1.

Table 1.

Structure	No.
	001
	002
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	006

	007
	008
	009
	010
	011
	012

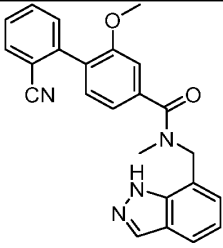
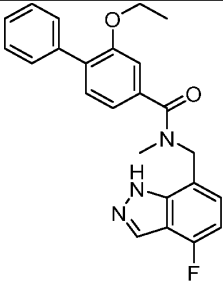
	013
	014
	017
	018
	019
	020

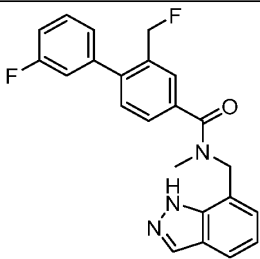
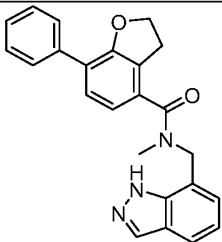
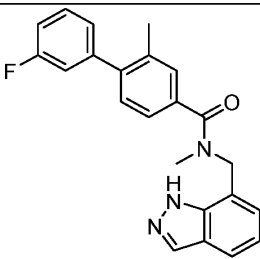
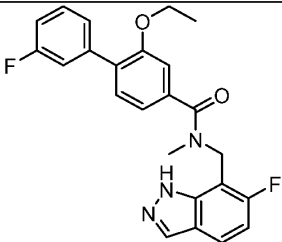
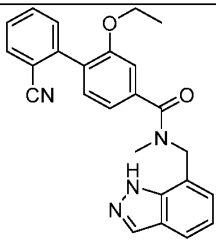
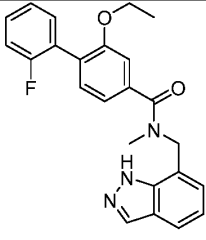
	021
	022
	023

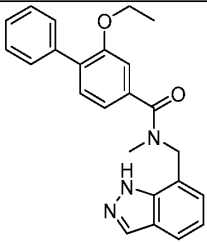
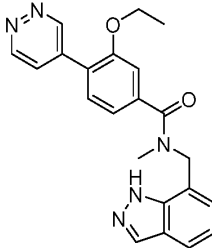
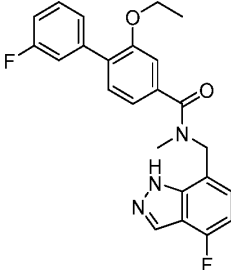
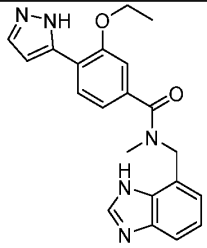
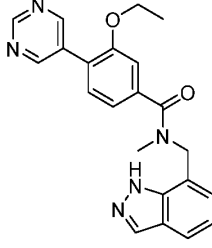
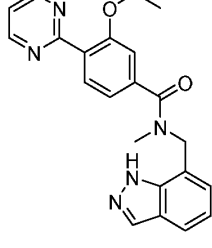
or a pharmaceutically acceptable salt thereof.

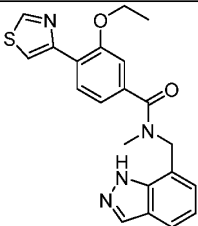
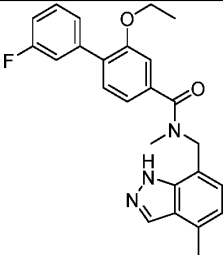
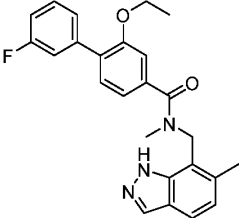
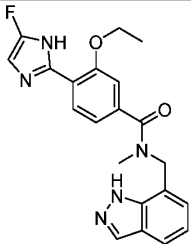
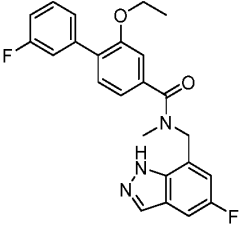
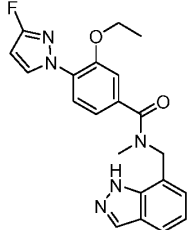
In another embodiment, the compound of Formula I is selected from the group consisting of a compound in Table 2.

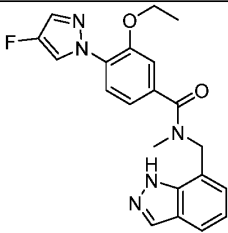
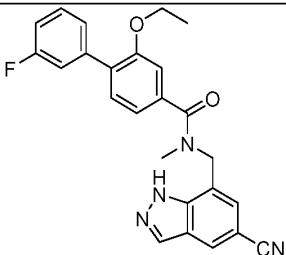
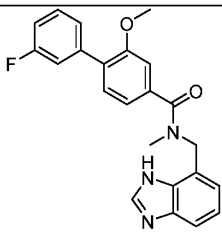
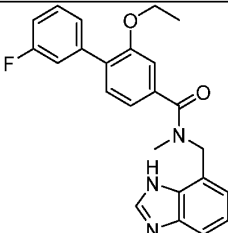
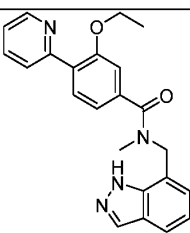
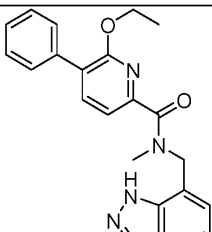
Table 2.

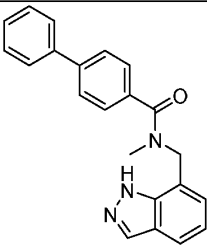
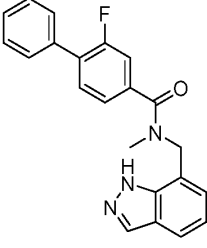
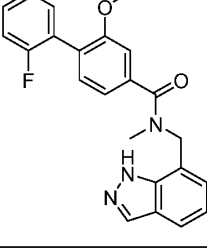
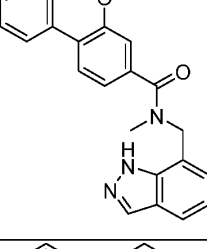
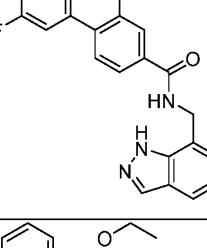
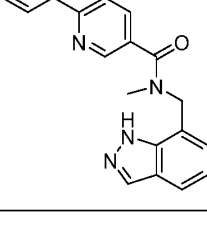
Structure	No.
	028
	029

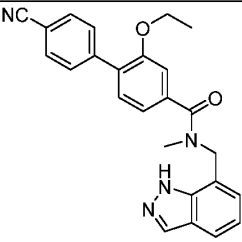
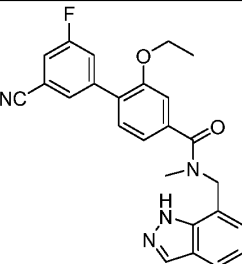
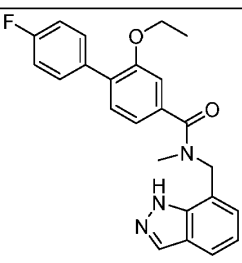
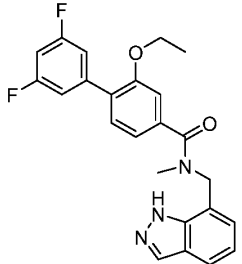
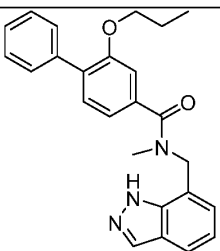
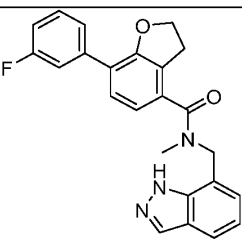
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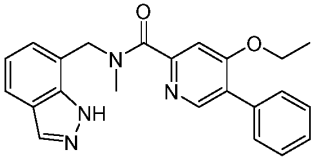
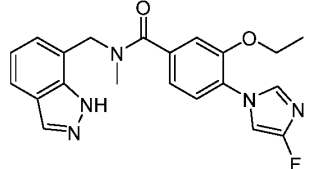
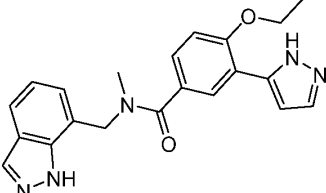
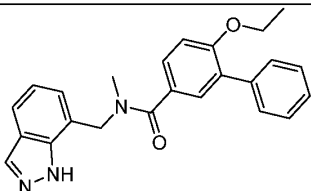
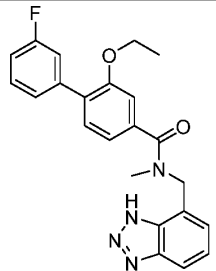
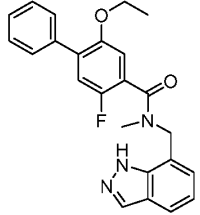
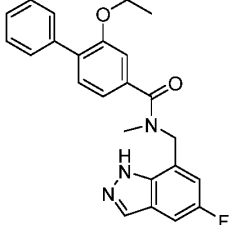
	036
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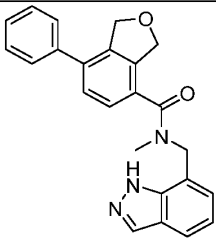
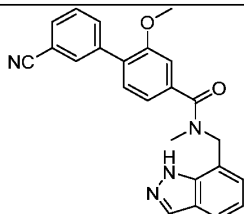
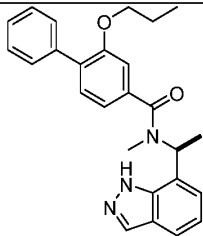
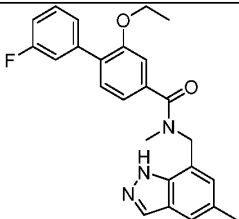
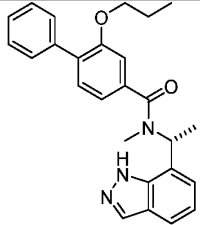
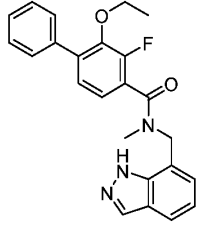
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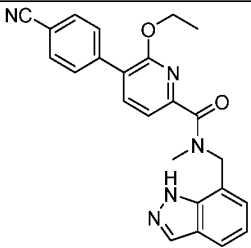
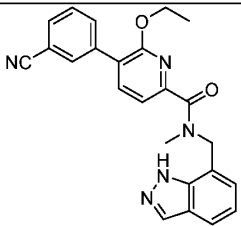
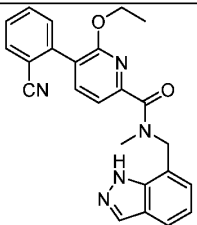
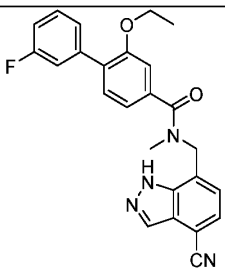
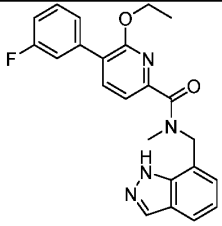
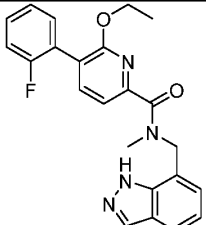
	048
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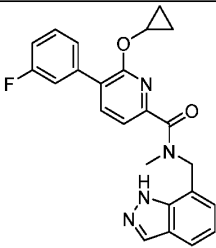
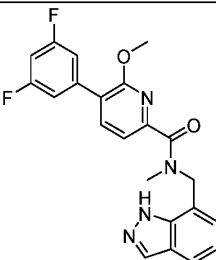
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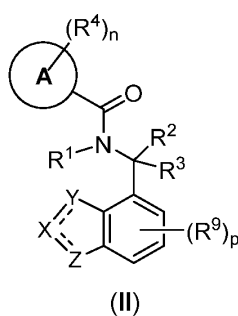
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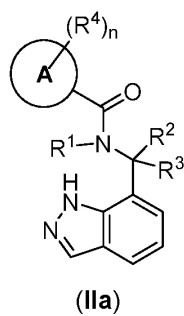
or a pharmaceutically acceptable salt thereof.

In still another embodiment, the compound of Formula I is a compound of Formula II:



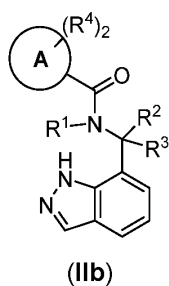
5 or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formula II is a compound of Formula IIa:



or a pharmaceutically acceptable salt thereof.

10 In an embodiment, the compound of Formula II is a compound of Formula IIb:



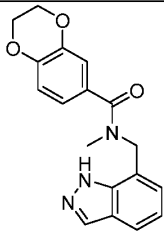
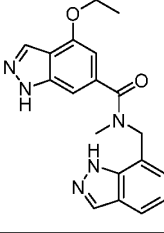
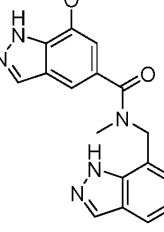
or a pharmaceutically acceptable salt thereof;

- wherein two R^4 , together with Ring A, form a ring selected from the group consisting of dihydrobenzooxazine, dihydrobenzodioxine, indazole, and indole, all of which are optionally substituted with one, two, or three R^7 .

In another embodiment, the compound of Formula II is selected from the group consisting of a compound in Table 3.

Table 3.

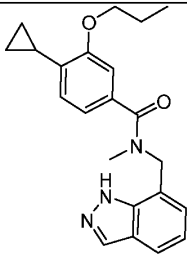
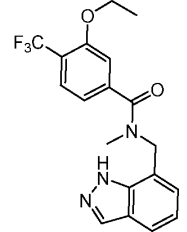
Structure	Compound No
	015
	016
	024

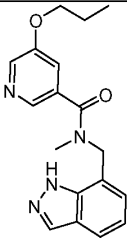
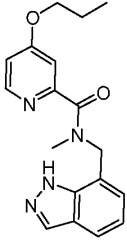
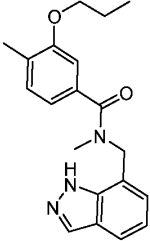
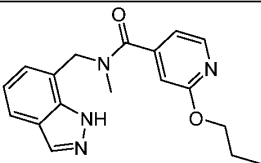
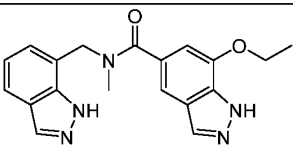
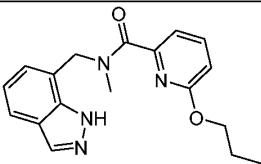
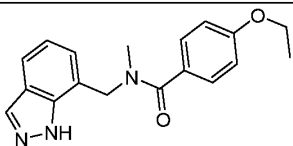
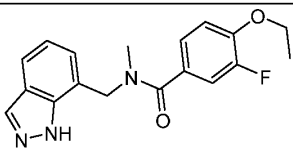
	025
	026
	027

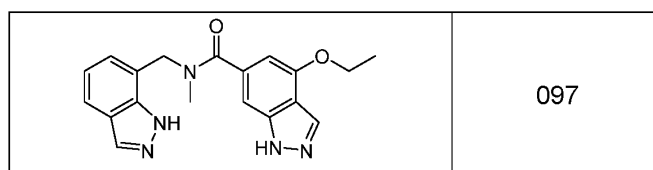
or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of Formula II is selected from the group consisting of a compound from Table 4.

Table 4.

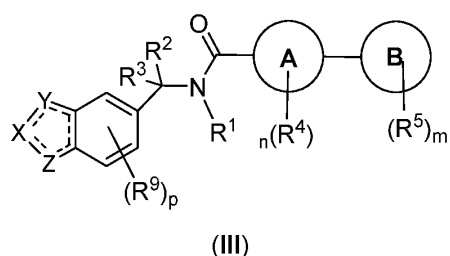
Structure	No.
	087
	088

	089
	090
	091
	092
	093
	094
	095
	096



or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula III:



5 or a pharmaceutically acceptable salt thereof;

wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S,
10 N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl,
C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆
16 cycloalkyl, and 3-6 membered heterocycloalkyl;

15 alternatively, Ring B is absent and m is 0;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein
alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl,
C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

20 alternatively, R² and R³, together with the atom to which they are attached, form a
ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered
heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH,
OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7
25 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring
selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and
4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three
R⁷;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6 , and SO_2R^6 ;

alternatively, two R^5 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-6} alkyl- C_{6-10} aryl, C_{0-6} alkyl-5-10 membered heteroaryl, OC_{1-6} alkyl, C_{3-6} cycloalkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

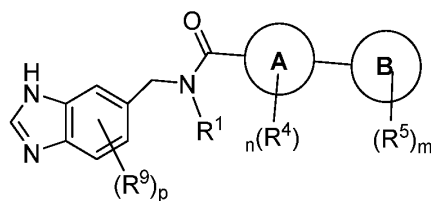
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

In an embodiment of Formula III, Ring A is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, and C_{4-10} cycloalkyl. In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

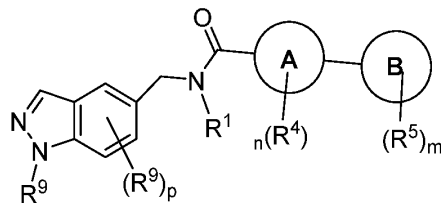
In an embodiment, the compound of Formula III is a compound of Formula IIIa:



(IIIa)

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of Formula III is a compound of Formula IIIb:



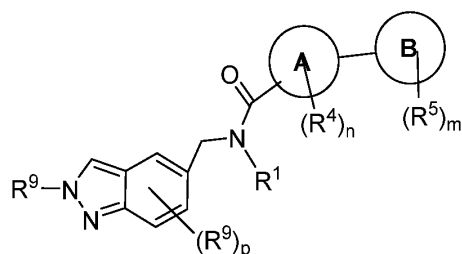
(IIIb)

wherein p is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the compound of Formula III is a compound of Formula

5 IIIc:



(IIIc)

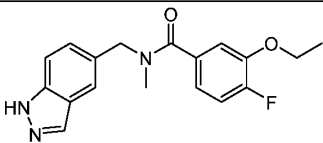
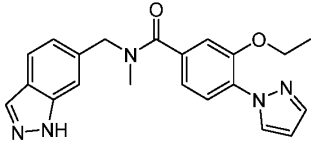
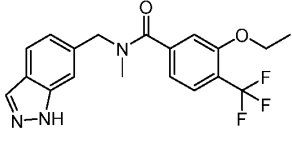
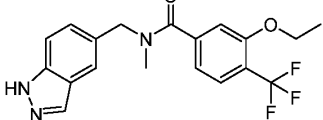
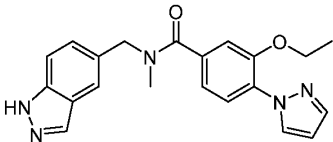
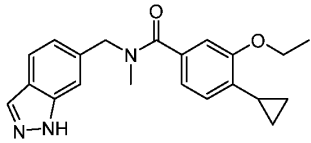
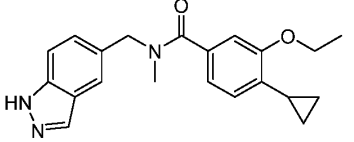
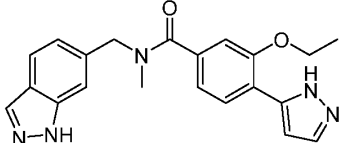
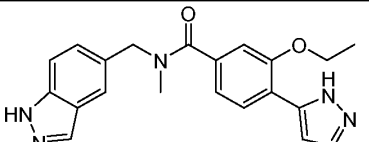
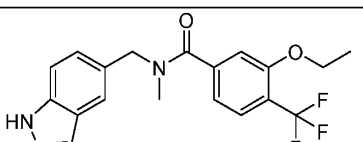
wherein p is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

10 In still another embodiment, the compound of Formula III is selected from the group consisting of a compound of Table 5.

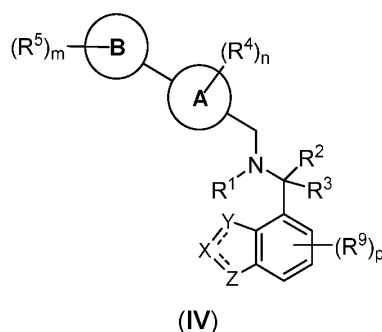
Table 5.

Structure	No.
	098
	099
	100
	101
	102

	103
	104
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	106
	107
	108
	109
	110
	111
	112

or a pharmaceutically acceptable salt thereof.

In yet another aspect, provided herein is a compound of Formula IV:



5 or a pharmaceutically acceptable salt thereof;

wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S,
10 N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl,
C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆
cycloalkyl, and 3-6 membered heterocycloalkyl;

15 alternatively, Ring B is absent and m is 0;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein
alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl,
C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

20 alternatively, R² and R³, together with the atom to which they are attached, form a
ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered
heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH,
OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7
25 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring
selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and
4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three
R⁷;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6 , and SO_2R^6 ;

alternatively, two R^5 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-6} alkyl- C_{6-10} aryl, C_{0-6} alkyl-5-10 membered heteroaryl, OC_{1-6} alkyl, C_{3-6} cycloalkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

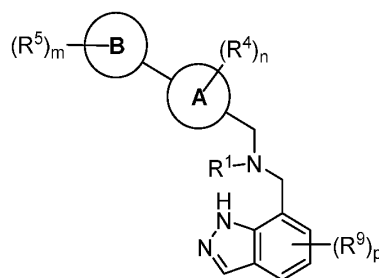
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

In an embodiment of Formula IV, Ring A is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, and C_{4-10} cycloalkyl. In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

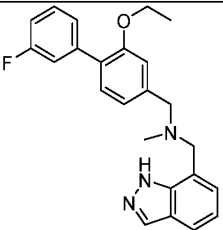
In an embodiment, the compound of Formula IV is a compound of Formula IVa:



(IVa)

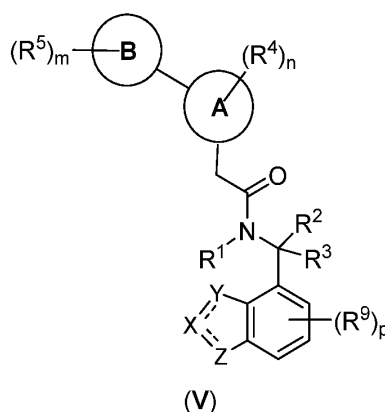
or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the compound of Formula IV is

Structure	No.
	113

or a pharmaceutically acceptable salt thereof.

In still another aspect, provided herein is a compound of Formula V:



5 or a pharmaceutically acceptable salt thereof;

wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S,

10 N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

15 alternatively, Ring B is absent and m is 0;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

20 alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁹ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, CN, OH, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

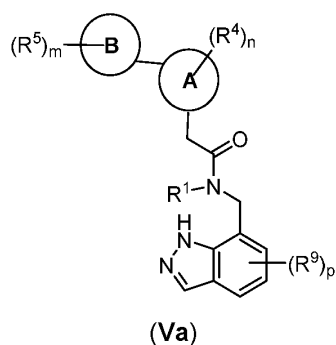
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

In an embodiment of Formula V, Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, and C₄₋₁₀ cycloalkyl. In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

In an embodiment, the compound of Formula V is a compound of Formula Va:



or a pharmaceutically acceptable salt thereof.

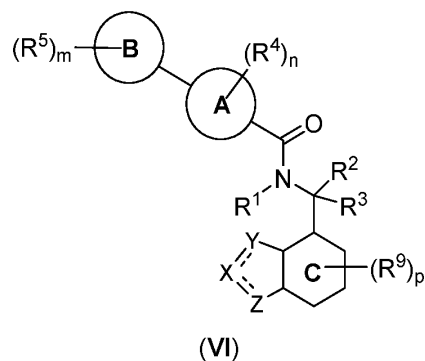
In another embodiment, the compound of Formula V is selected from the group

5 consisting of

Structure	No.
	114
	115

or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a compound of Formula VI:



10 or a pharmaceutically acceptable salt thereof;

wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S,

15 N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

5 alternatively, Ring B is absent and m is 0;

Ring C is pyridine;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

10 R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

15 each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

25 alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

35 each R⁹ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, CN, OH, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

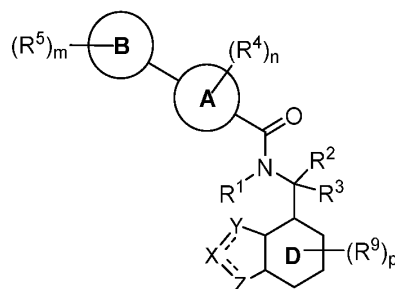
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

In an embodiment of Formula VI, Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, and C₄₋₁₀ cycloalkyl. In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

In another aspect, provided herein is a compound of Formula VII:



(VII)

- or a pharmaceutically acceptable salt thereof, wherein
- == is an optional double bond;
- X is CH, N, NH, or N(C₁₋₆ alkyl);
- Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;
- Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;
- Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;
- alternatively, Ring B is absent and m is 0;
- Ring D is phenyl or pyridine;
- R¹ is selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, OC₁₋₆ alkyl, OC₃₋₆ cycloalkyl, O(C₀₋₆ alkyl-C₆₋₁₀ aryl), C₀₋₆ alkyl-C₆₋₁₀ aryl, and OH, wherein alkyl, aryl, and cycloalkyl are each optionally substituted with R⁶;
- R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;
- alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;
- each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl-NHCOR⁶, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

- 5 each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

- alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

- each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

- 15 each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

- each R⁹ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OH, OC₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, O(C₃₋₆ cycloalkyl), halo, CN, OH, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

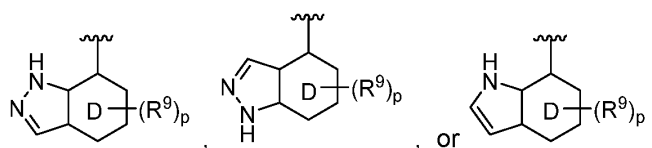
m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

- 25 In an embodiment of Formula VII,

X, Y, and Z are defined as having one of the following core structures:



Ring A is phenyl or 5-6 membered heteroaryl;

Ring B is phenyl or 5-6 membered heteroaryl;

- 30 Ring D is phenyl or pyridine;

R¹ is H or C₁₋₃ alkyl;

R² and R³ are each independently selected from the group consisting of H and C₁₋₃ alkyl;

each R⁴ is independently selected from the group consisting of halo, OH, OR⁶, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C₁₋₃ alkyl-NHCOR⁶, NHCOR⁶, CN, C₁₋₃ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

- each R⁵ is independently selected from the group consisting of C₁₋₃ alkyl, C₁₋₃ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-6 membered heteroaryl, OC₁₋₃ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH₂, NH(C₁₋₃ alkyl), and N(C₁₋₃ alkyl)₂;

- each R⁹ is independently selected from the group consisting of C₁₋₃ haloalkyl, C₁₋₃ alkyl-OH, OC₁₋₃ alkyl, halo, and CN;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

- In another embodiment of Formula VII,

X is N;

Y is NH;

Z is CH;

Ring A is phenyl or 5-6 membered heteroaryl;

- Ring B is phenyl or 5-6 membered heteroaryl;

Ring D is phenyl or pyridine;

R¹ is H or C₁₋₃ alkyl;

R² and R³ are each independently selected from the group consisting of H and C₁₋₃ alkyl;

- each R⁴ is independently selected from the group consisting of halo, OH, OR⁶, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C₁₋₃ alkyl-NHCOR⁶, NHCOR⁶, CN, C₁₋₃ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

each R⁵ is independently selected from the group consisting of C₁₋₃ alkyl, C₁₋₃ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-6 membered heteroaryl, OC₁₋₃ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH₂, NH(C₁₋₃ alkyl), and N(C₁₋₃ alkyl)₂;

- each R⁹ is independently selected from the group consisting of C₁₋₃ haloalkyl, C₁₋₃ alkyl-OH, OC₁₋₃ alkyl, halo, and CN;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1. In another embodiment, each R^9 is independently selected from the group consisting of C_{1-3} alkyl-OH, C_{1-3} haloalkyl, and CN.

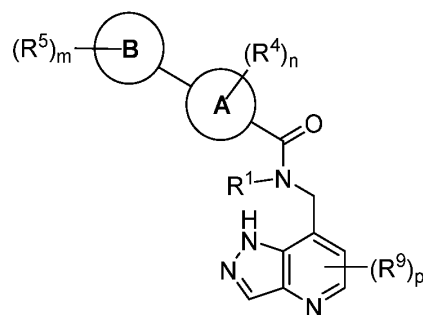
In another embodiment, each R^4 is independently selected from the group consisting of halo, OH, OR^6 , NH_2 , $NH(C_{1-3} \text{ alkyl})$, $N(C_{1-3} \text{ alkyl})_2$, CN, C_{1-3} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, and COR^6 ; and

each R^5 is independently selected from the group consisting of C_{1-3} alkyl, C_{1-3} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-3} \text{ alkyl})$, $N(C_{1-3} \text{ alkyl})_2$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl.

In an embodiment, each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, halo, NH_2 , $NH(C_{1-3} \text{ alkyl})$, and $N(C_{1-3} \text{ alkyl})_2$

In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

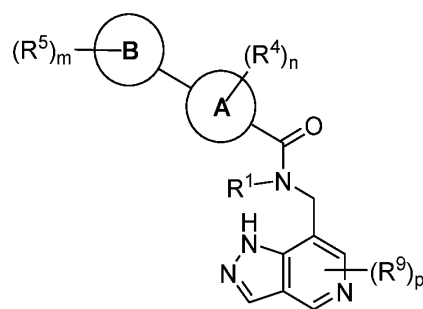
In an embodiment, the compound of Formula VI is a compound of Formula VIa:



(VIa)

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of Formula VI is a compound of Formula VIb:

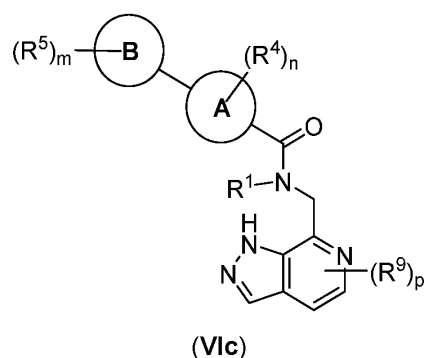


(VIb)

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the compound of Formula VI is a compound of Formula

VIc:



or a pharmaceutically acceptable salt thereof.

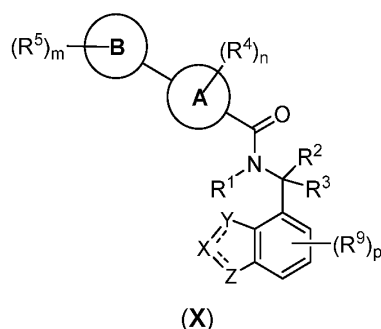
- In still another embodiment, the compound of Formula VI is selected from the group
- 5 consisting of a compound in Table 6.

Table 6.

Structure	No.
	116
	117
	118

or a pharmaceutically acceptable salt thereof.

In an aspect, provided herein is a compound of Formula X:



or a pharmaceutically acceptable salt thereof;

wherein

- 5 --- is an optional double bond;
- X is CH, N, NH, or N(C₁₋₆ alkyl);
- Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;
- Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl,
- 10 C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;
- Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;
- alternatively, Ring B is absent and m is 0;
- R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein
- 15 alkyl and cycloalkyl are each optionally substituted with R⁶;
- R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 4-10 membered heterocycloalkyl, wherein alkyl, cycloalkyl, and heterocycloalkyl are each optionally substituted with R⁶;
- alternatively, R² and R³, together with the atom to which they are attached, form a
- 20 ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;
- each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶ wherein alkyl, cycloalkyl, and
- 25 heterocycloalkyl are each optionally substituted with R⁶;
- alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, OH, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁹ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, CN, OH, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, C(O)NHR⁸, C(O)N(R⁸)₂, and NHC(O)R⁸;

m is 0, 1, 2, or 3;

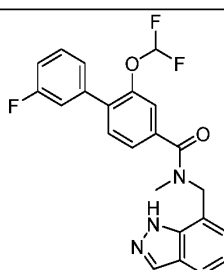
n is 1, 2, or 3; and

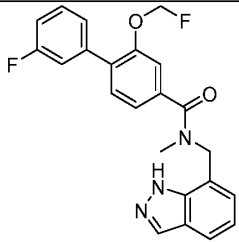
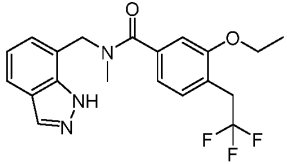
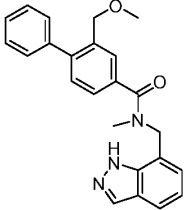
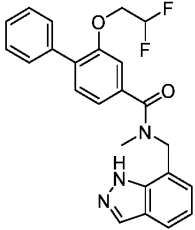
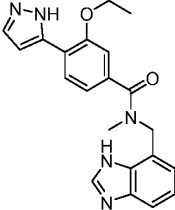
p is 0, 1, 2, or 3.

In an embodiment of Formula X, Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, and C₄₋₁₀ cycloalkyl. In an embodiment, m is 1 and n is 1. In another embodiment, m is 0 and n is 0. In another embodiment, m is 1 and n is 0. In another embodiment, m is 0 and n is 1.

In an embodiment, the compound of Formula X is selected from the group consisting of a compound in Table 7.

Table 7.

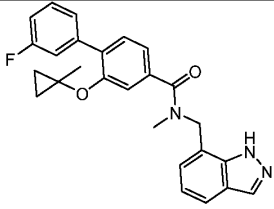
Structure	No.
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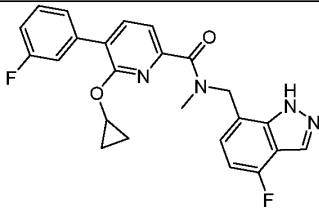
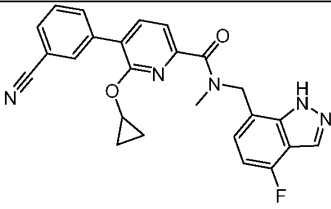
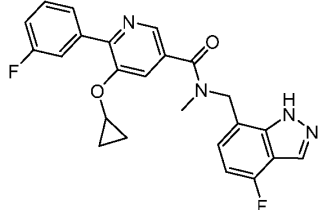
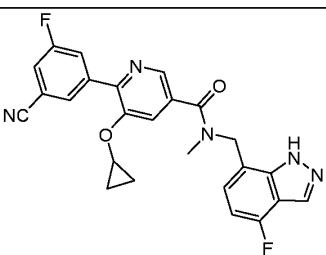
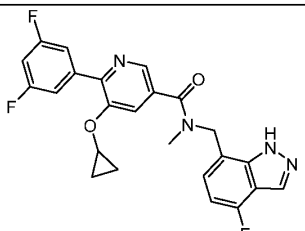
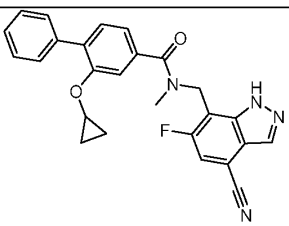
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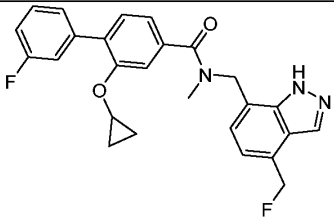
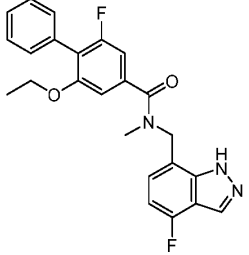
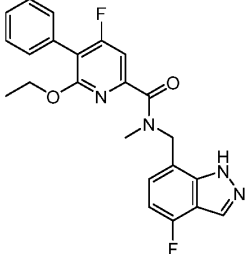
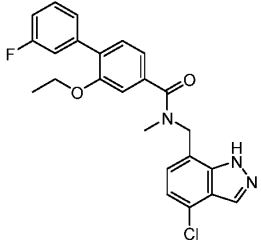
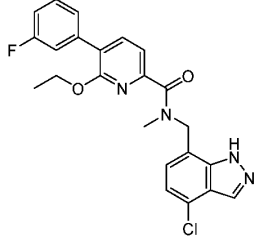
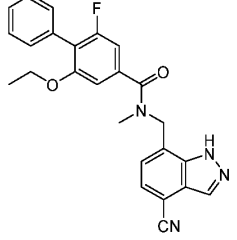
or a pharmaceutically acceptable salt thereof.

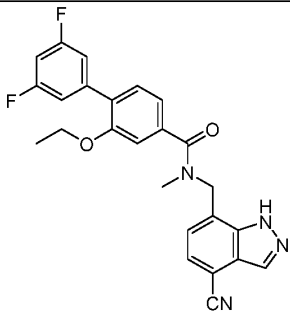
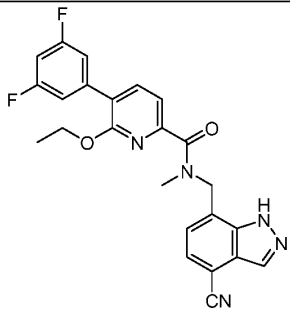
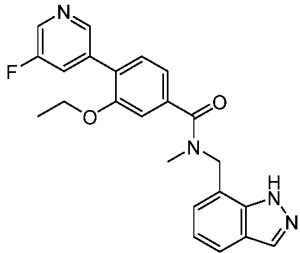
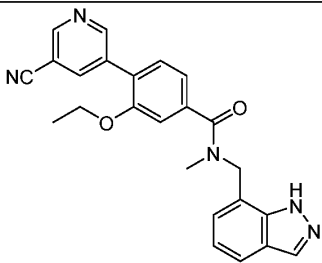
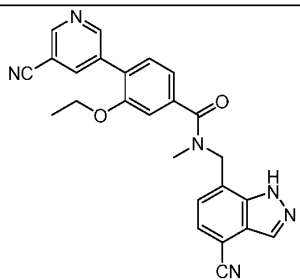
In another embodiment, the compound of the formulae provided herein is selected from the group consisting of a compound in Table 8.

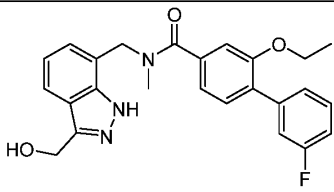
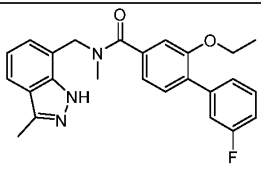
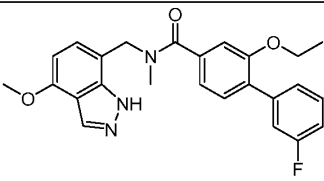
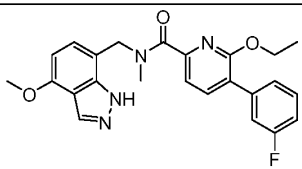
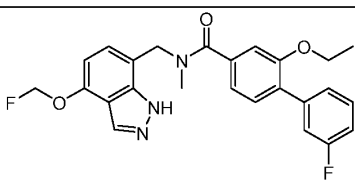
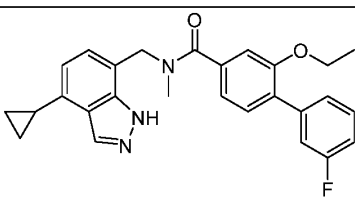
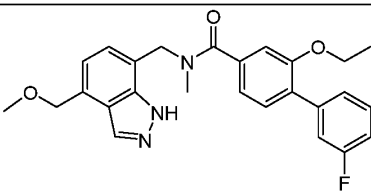
Table 8.

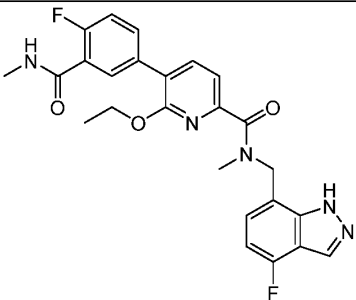
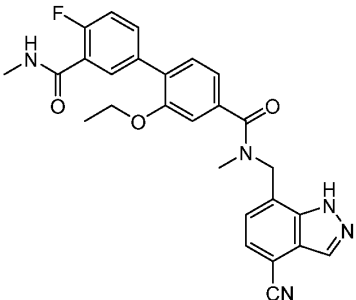
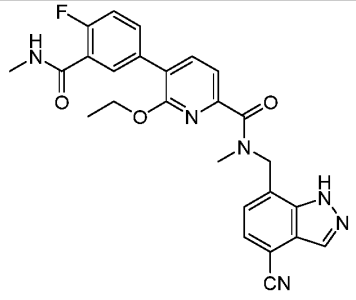
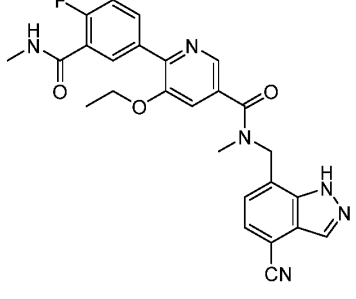
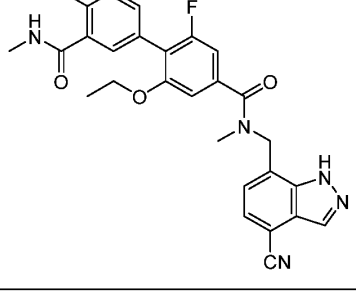
Structure	No.
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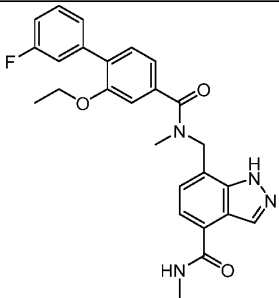
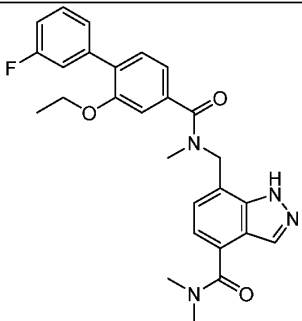
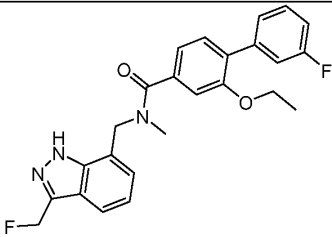
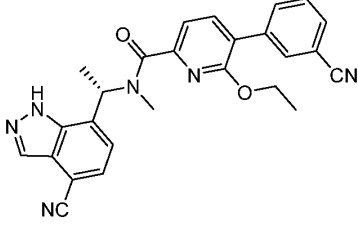
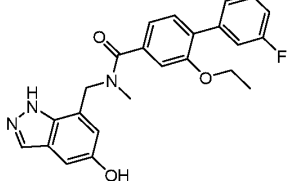
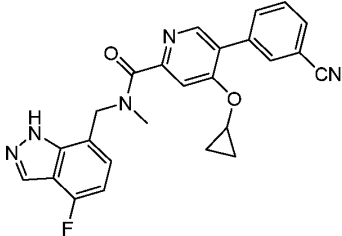
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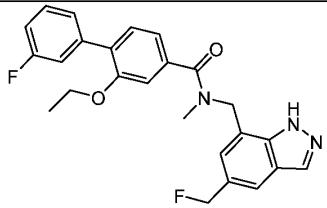
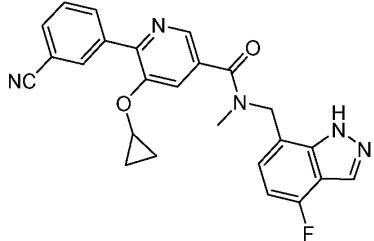
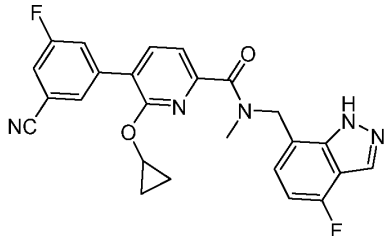
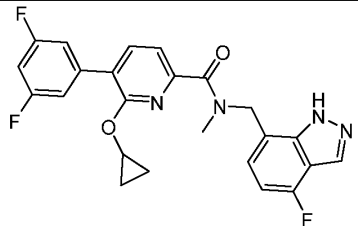
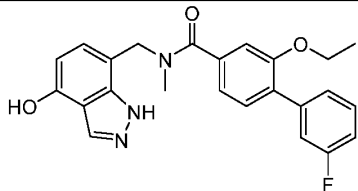
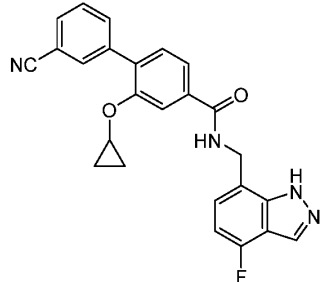
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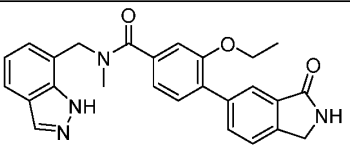
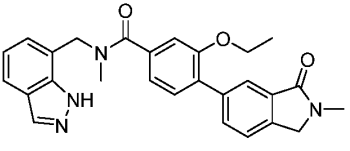
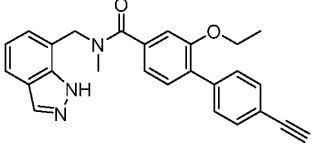
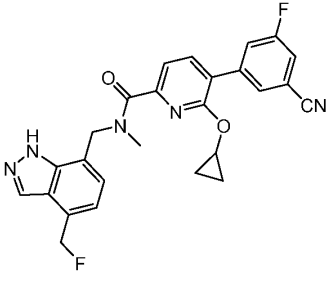
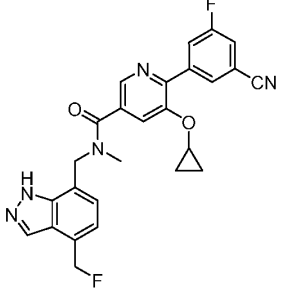
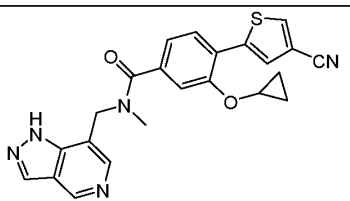
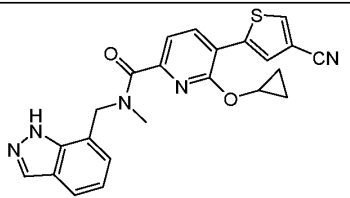
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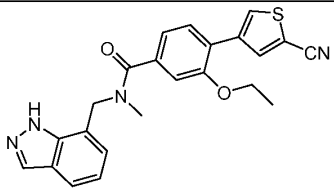
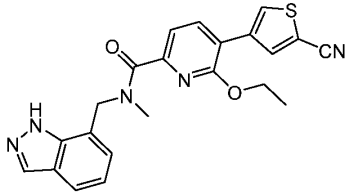
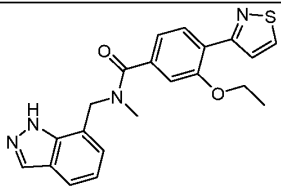
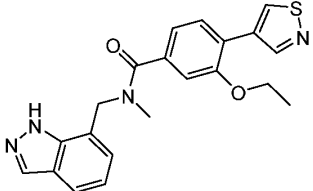
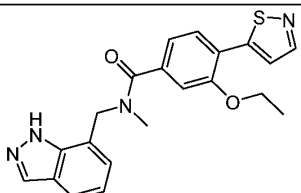
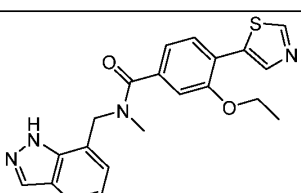
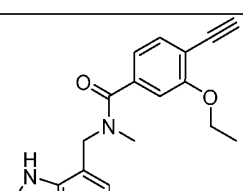
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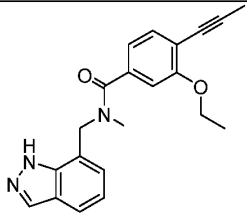
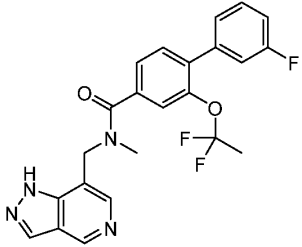
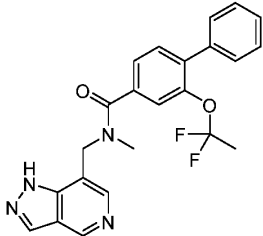
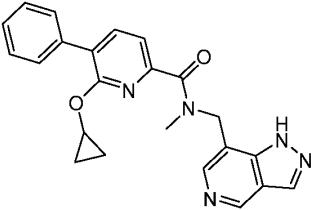
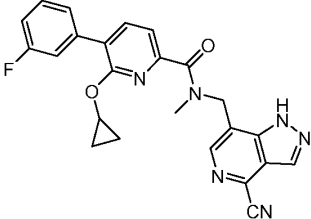
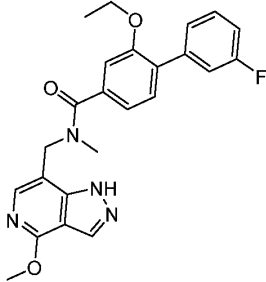
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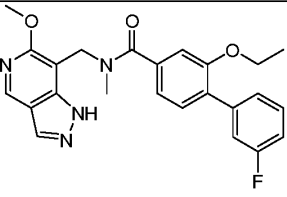
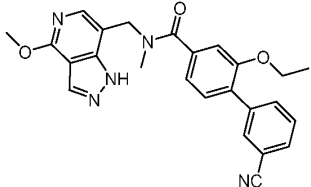
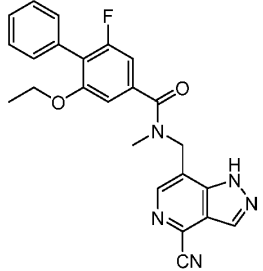
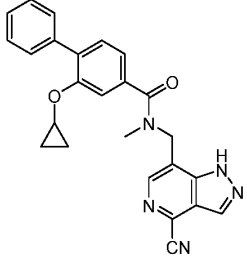
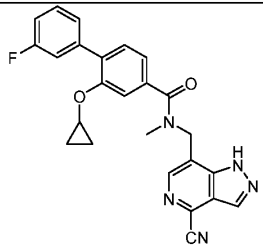
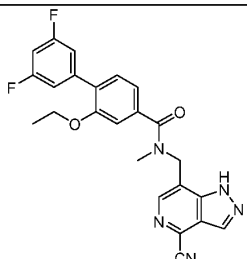
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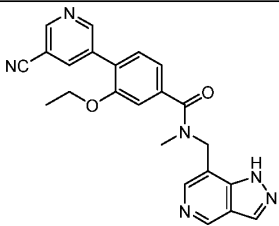
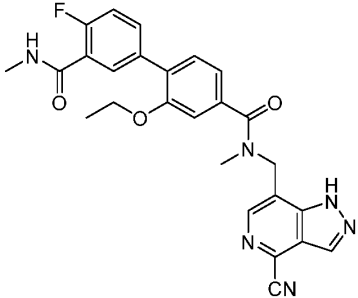
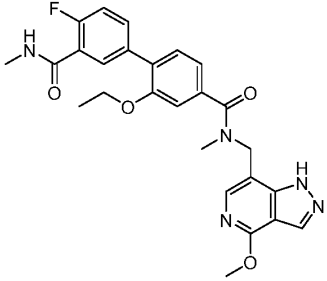
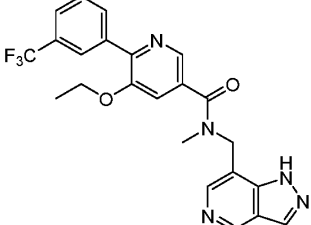
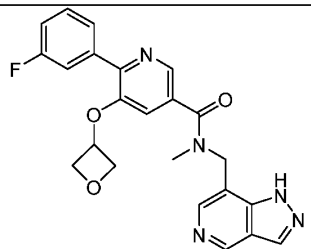
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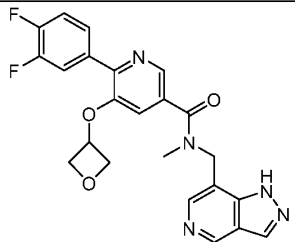
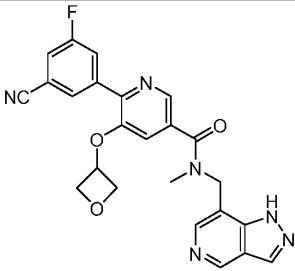
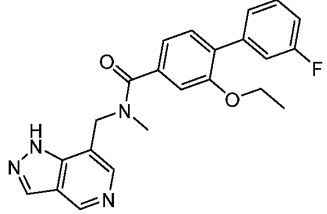
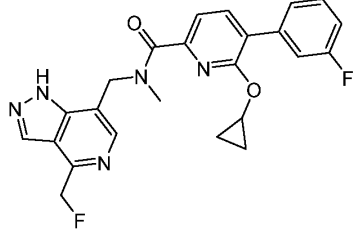
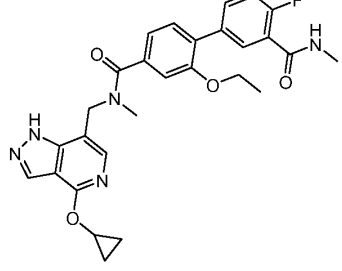
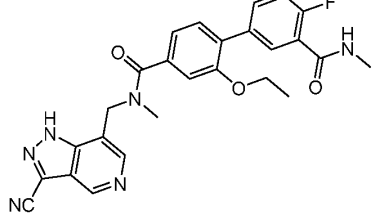
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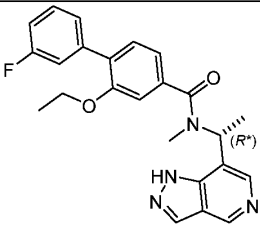
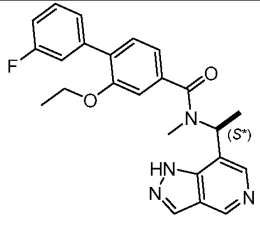
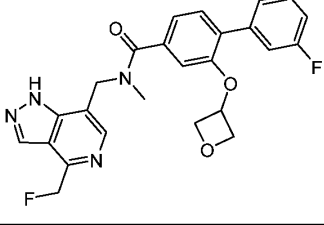
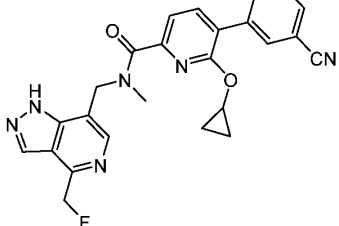
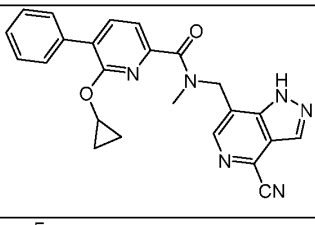
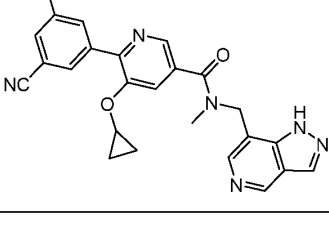
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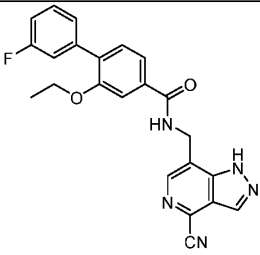
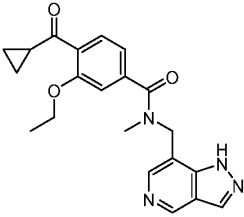
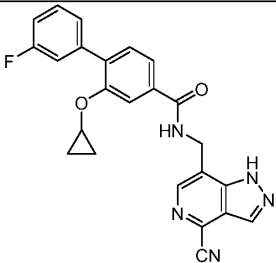
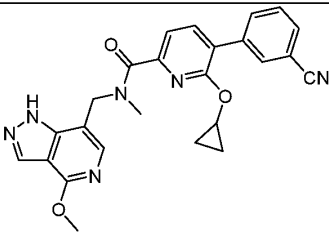
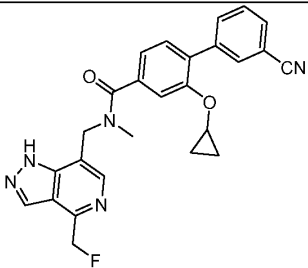
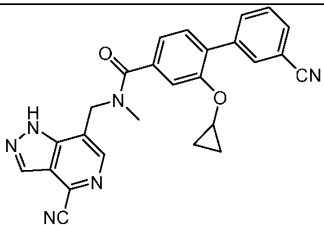
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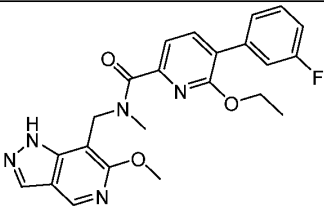
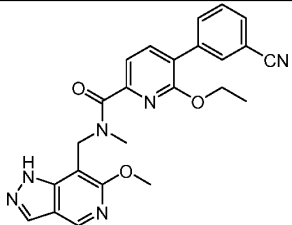
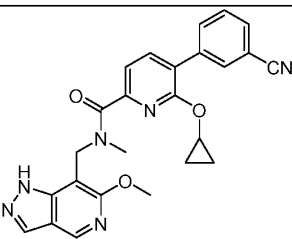
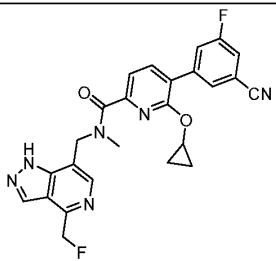
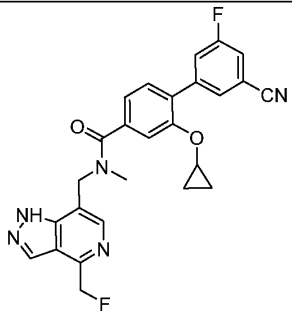
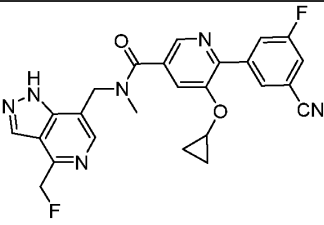
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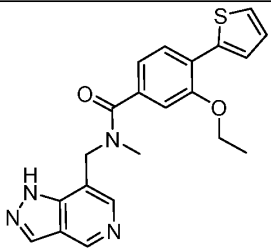
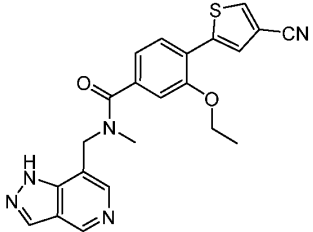
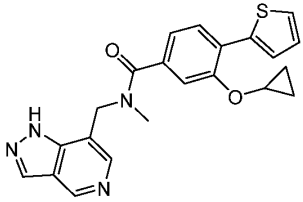
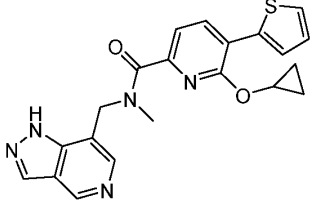
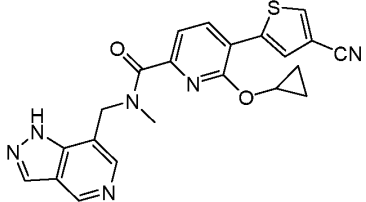
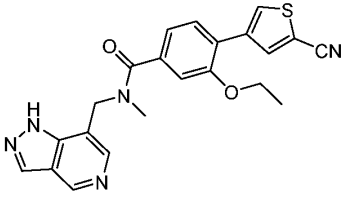
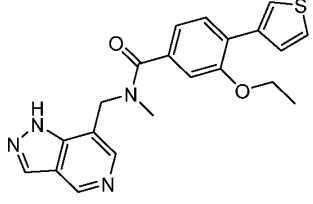
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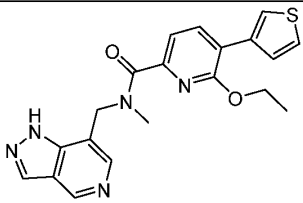
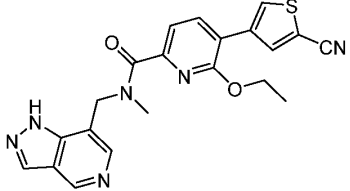
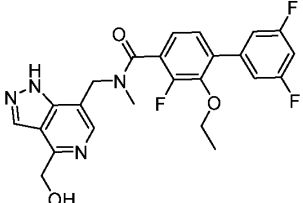
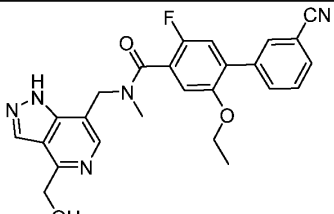
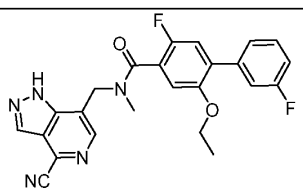
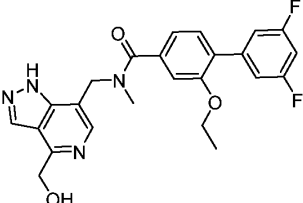
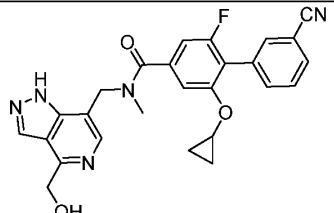
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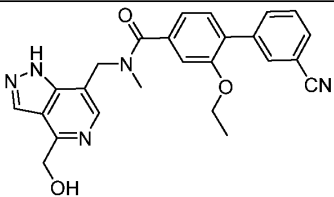
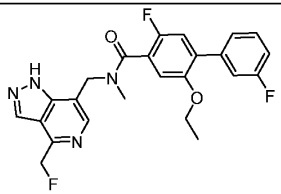
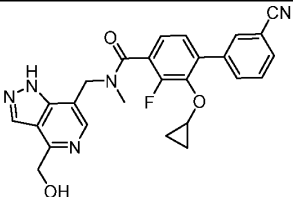
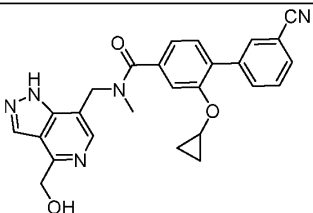
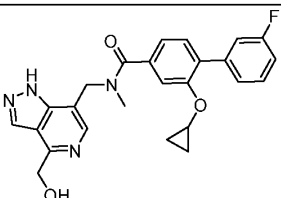
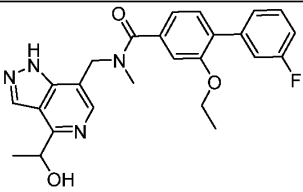
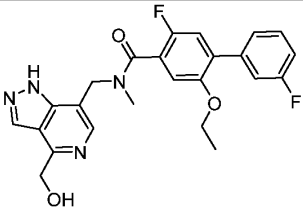
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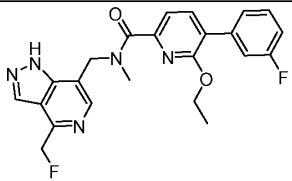
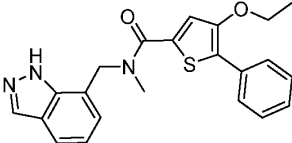
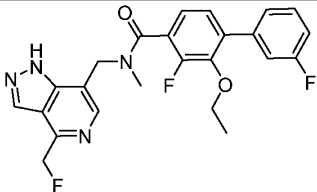
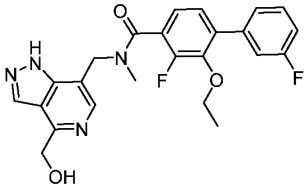
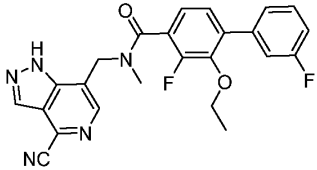
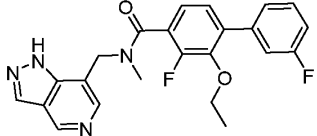
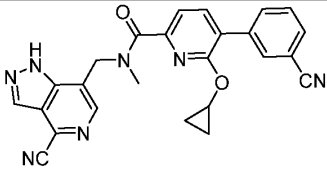
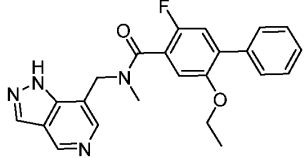
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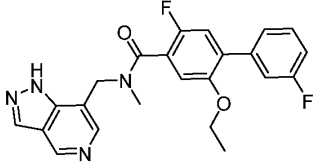
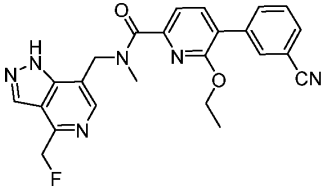
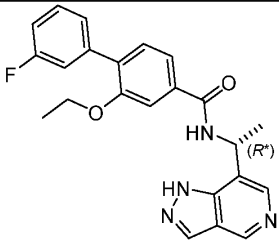
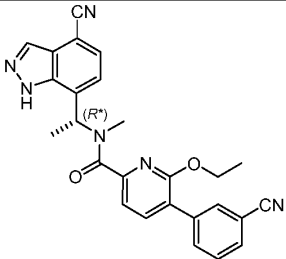
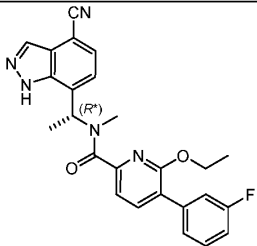
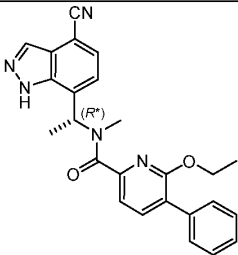
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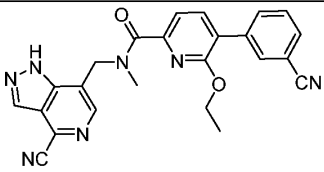
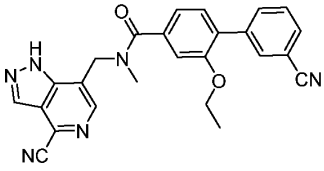
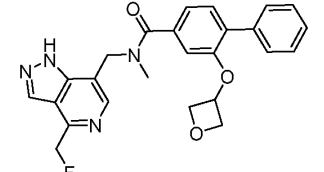
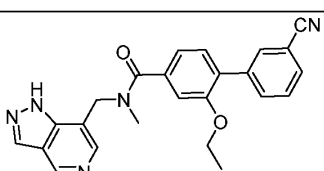
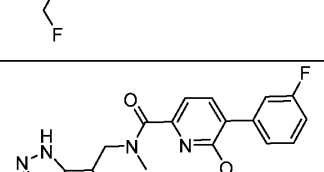
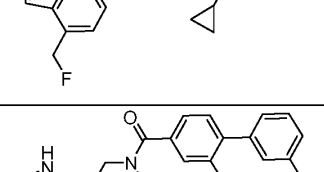
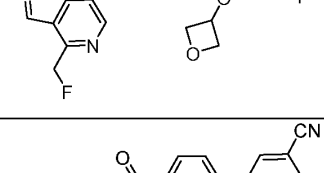
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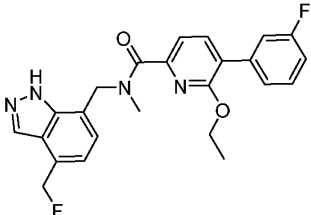
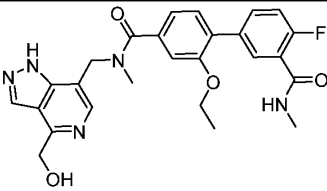
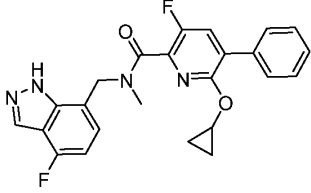
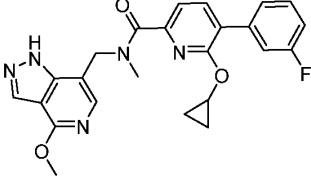
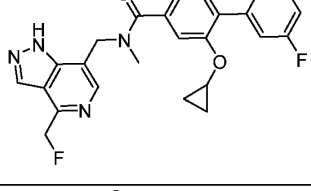
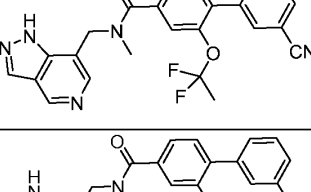
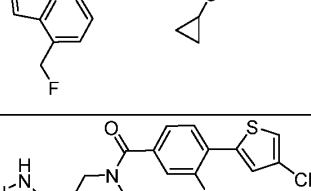
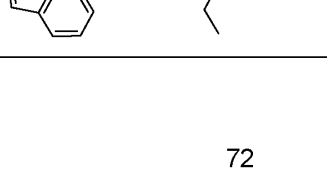
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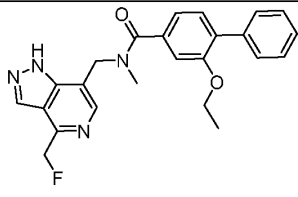
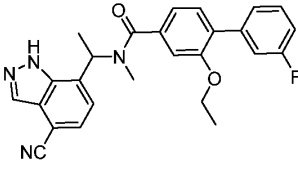
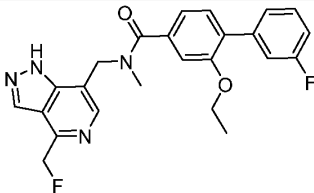
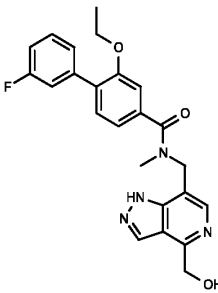
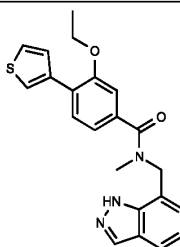
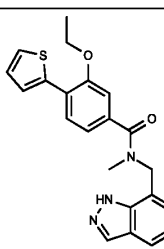
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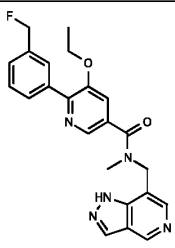
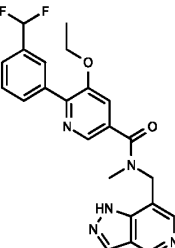
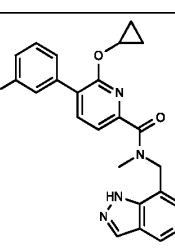
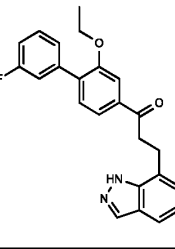
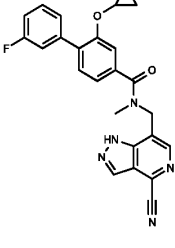
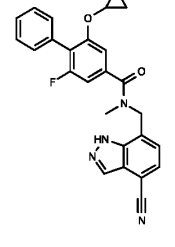
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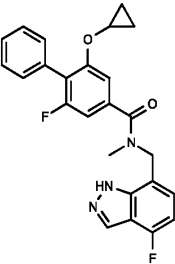
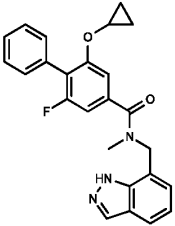
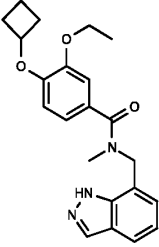
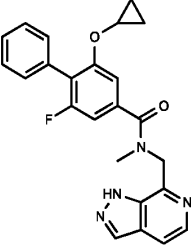
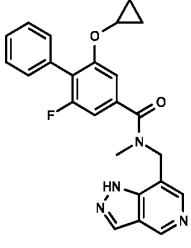
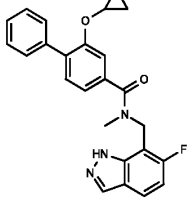
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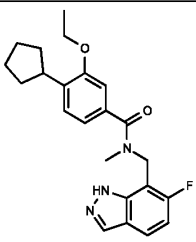
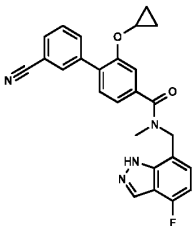
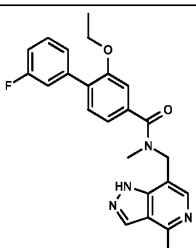
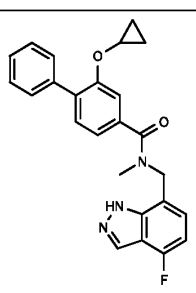
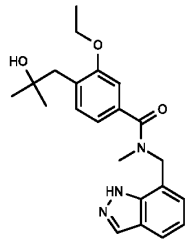
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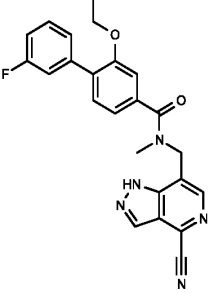
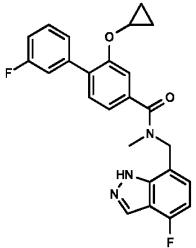
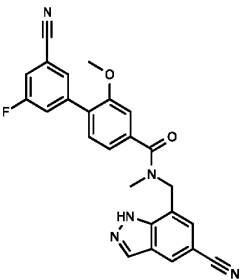
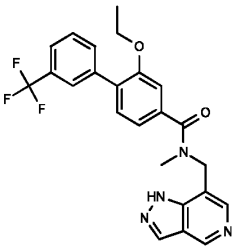
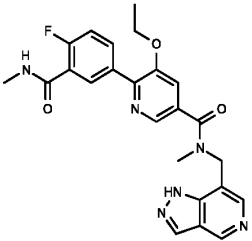
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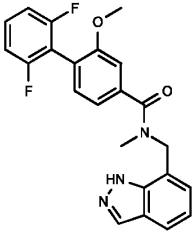
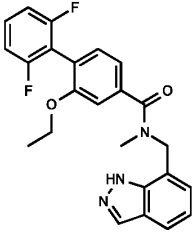
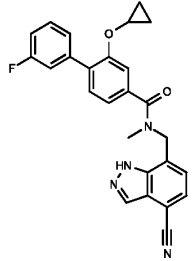
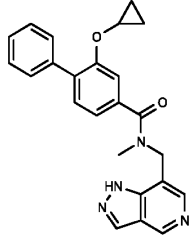
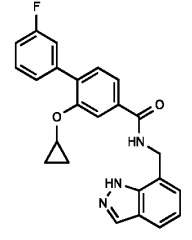
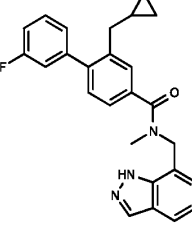
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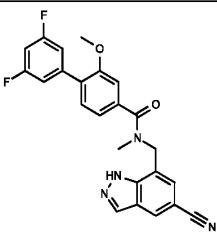
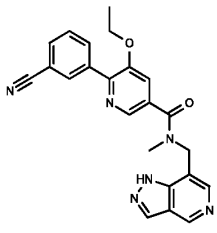
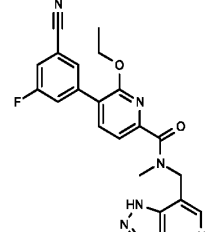
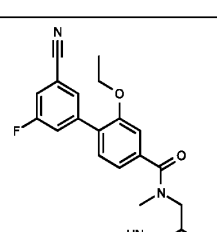
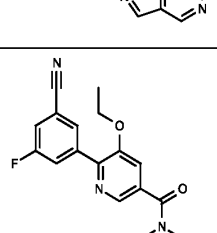
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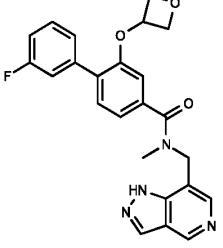
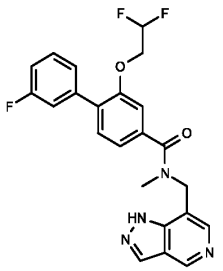
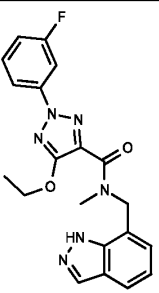
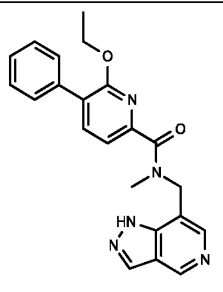
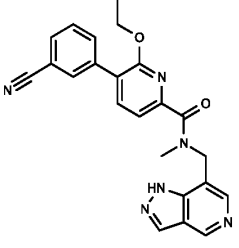
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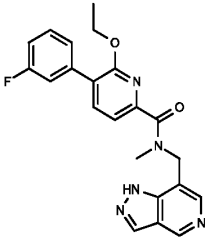
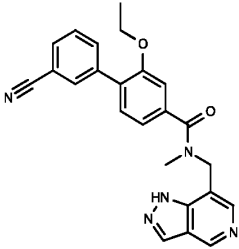
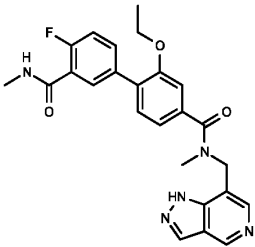
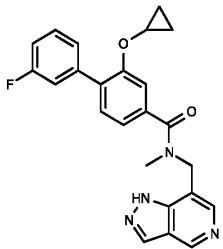
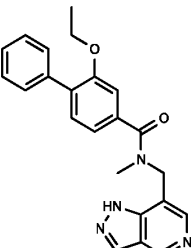
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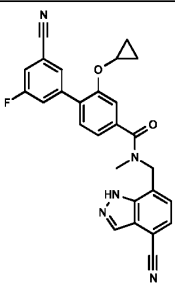
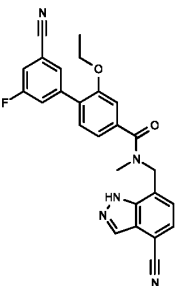
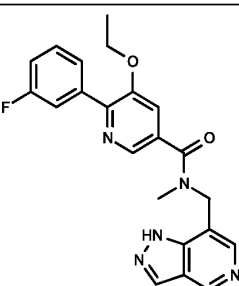
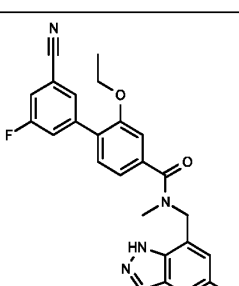
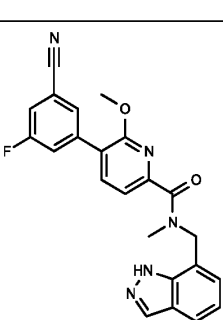
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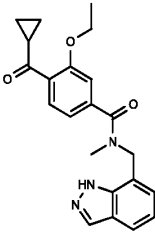
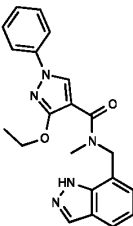
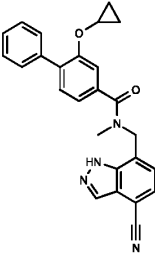
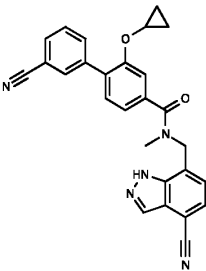
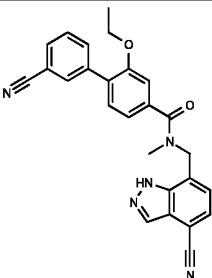
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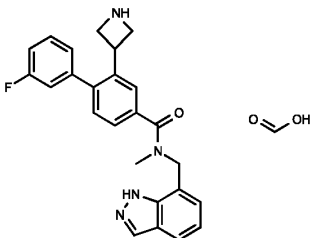
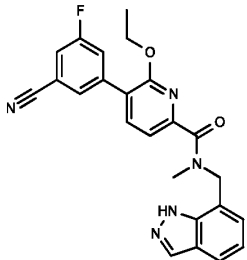
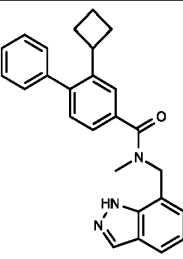
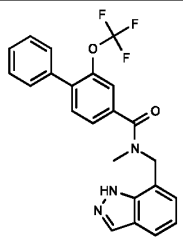
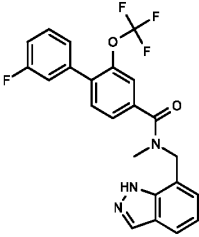
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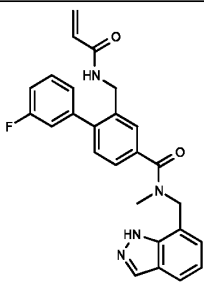
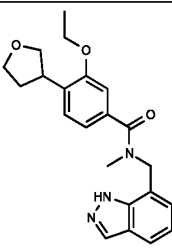
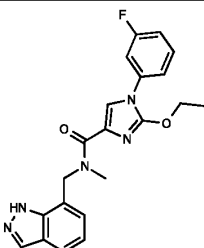
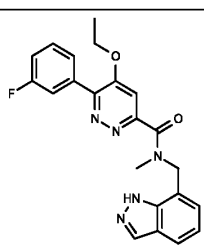
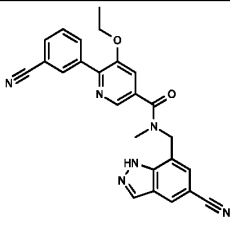
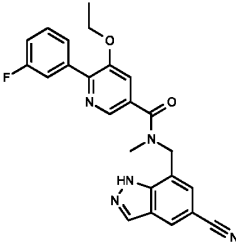
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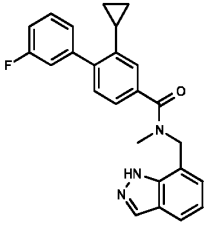
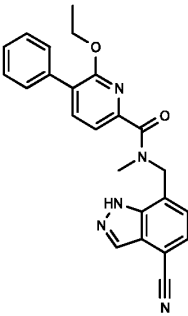
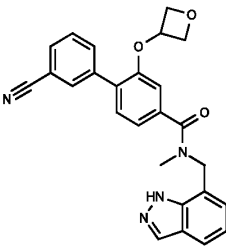
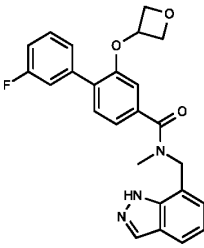
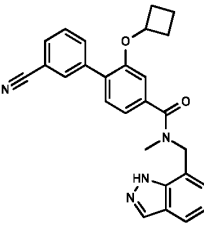
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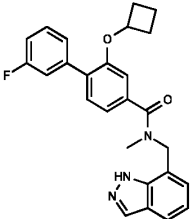
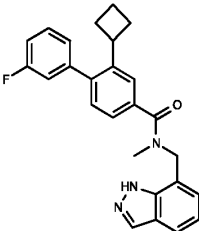
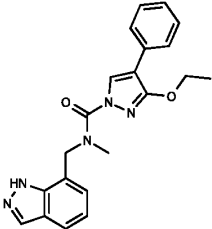
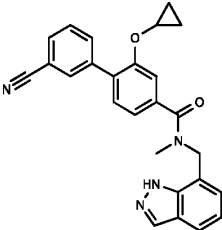
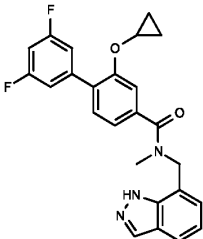
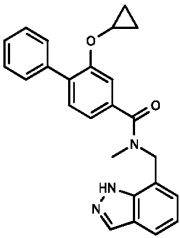
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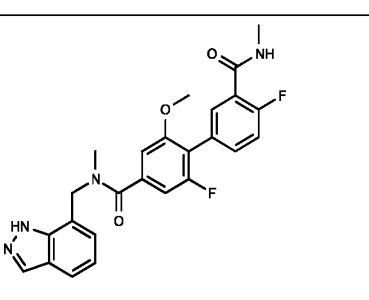
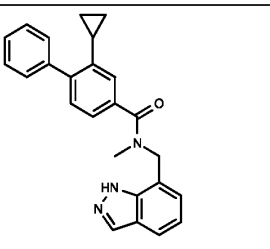
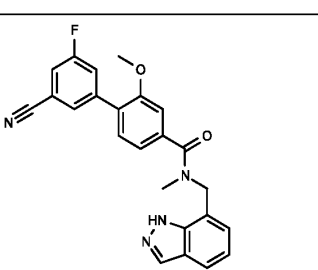
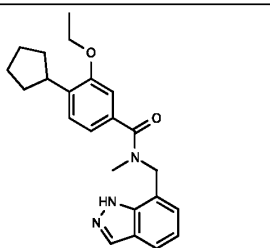
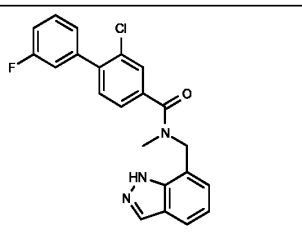
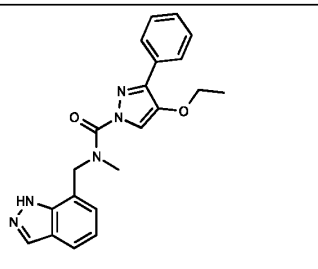
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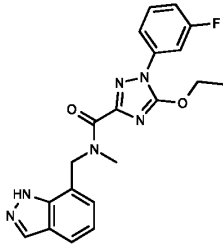
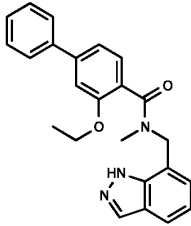
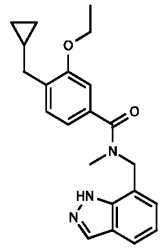
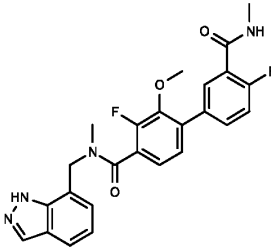
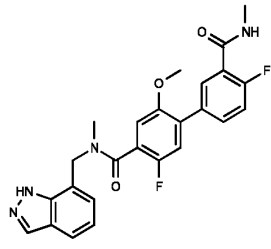
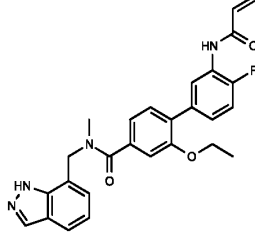
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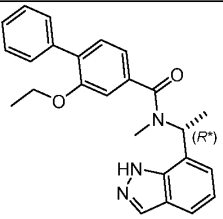
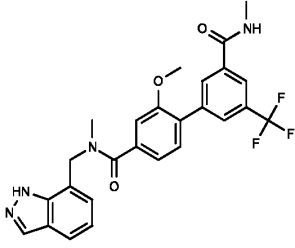
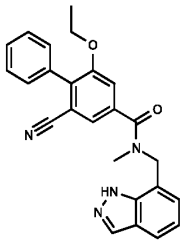
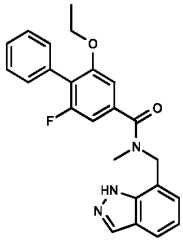
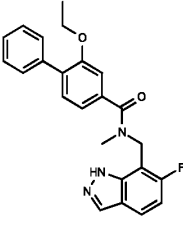
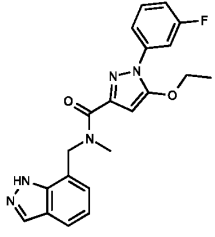
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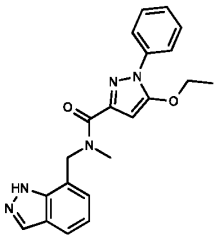
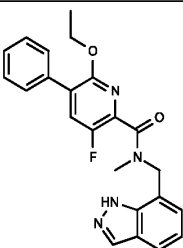
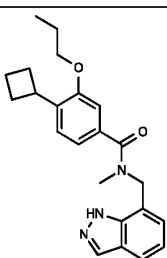
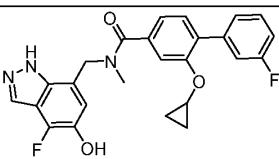
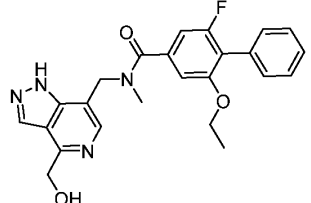
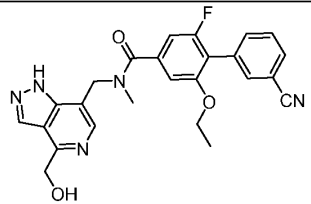
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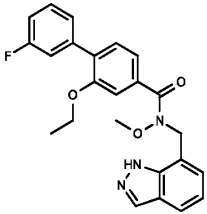
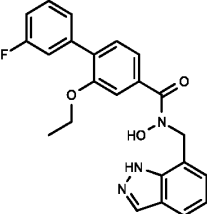
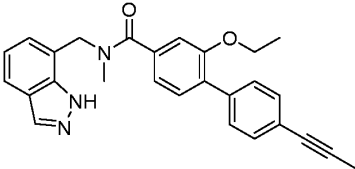
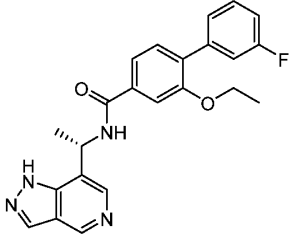
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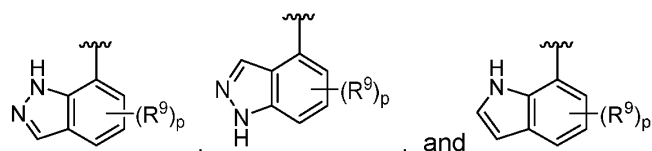
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or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound of the formulae herein has one of the following core structures:



5 In another aspect, provided herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The compounds disclosed herein may exist as tautomers and optical isomers (e.g., enantiomers, diastereomers, diastereomeric mixtures, racemic mixtures, and the like). The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system.

10 Chiral centers, of which the absolute configurations are known, are labelled by prefixes *R* and *S*, assigned by the standard sequence-rule procedure, and preceded when necessary by the appropriate locants (*Pure & Appl. Chem.* 45, 1976, 11–30). Certain examples contain

chemical structures that are depicted or labelled as an (*R**) or (*S**). When (*R**) or (*S**) is used in the name of a compound or in the chemical representation of the compound, it is intended to convey that the compound is a pure single isomer at that stereocenter; however, absolute configuration of that stereocenter has not been established. Thus, a compound designated as (*R**) refers to a compound that is a pure single isomer at that stereocenter with an absolute configuration of either (*R*) or (*S*), and a compound designated as (*S**) refers to a compound that is a pure single isomer at that stereocenter with an absolute configuration of either (*R*) or (*S*).

It is generally well known in the art that any compound that will be converted *in vivo* to provide a compound disclosed herein is a prodrug within the scope of the present disclosure.

Compounds provided herein can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art (Deuterium Labeling in Organic Chemistry by Alan F. Thomas (New York, N.Y., Appleton-Century-Crofts, 1971; The Renaissance of H/D Exchange by Jens Atzrodt, Volker Derdau, Thorsten Fey and Jochen Zimmermann, Angew. Chem. Int. Ed. 2007, 7744-7765; The Organic Chemistry of Isotopic Labelling by James R. Hanson, Royal Society of Chemistry, 2011). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

In the compounds provided herein, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural abundance isotopic composition. Also, unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

In embodiments, the compounds provided herein have an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each

designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Methods of Treatment

In an aspect, provided herein is a method of inhibiting NLRP3 inflammasome in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In another aspect, provided herein is a method of treating inflammation in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In another aspect, provided herein is a method of treating inflammaging in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In another aspect, provided herein is a method of treating cryopyrin-associated periodic syndrome (CAPS) in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the CAPS is selected from the group consisting of familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.

In another aspect, provided herein is a method of treating a dermatologic disease in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the dermatologic disease is selected from the group consisting of psoriasis, urticaria, skin photoaging, and eczema.

Also provided herein is a method of using the compounds provided herein for treatment or amelioration of aging or an aging-related condition negatively impacting longevity or quality of life, wherein the aging-related condition negatively impacting longevity or quality of life is selected from the group consisting of inflammation, anemia, hyperglycemia, dyslipidemia, hyperinsulinemia, insulin resistance, immunosuppression, liver disease, iron overload, hypertriglyceridemia, impaired skin integrity, wound healing, scarring, pain, allergies, sleep disorders and problems, gastrointestinal disorders and problems, Th1-type inflammation, Th2-type inflammation, an inflammatory disease involving T-cell dependent B cell proliferation, T-cell dependent B cell proliferation, allergy, asthma, atherosclerosis, autoimmunity, hypercholesterolemia, chronic inflammation, chronic

obstructive pulmonary disease (COPD), Crohn's disease, cutaneous responses to tissue damage, fibrosis, hematological oncology, metabolic diseases, cardiovascular disease, organ transplantation, psoriasis, liver fibrosis, dermatitis, pulmonary fibrosis, pulmonary responses to respiratory infections, restenosis, rheumatoid arthritis, sarcoidosis, stromal
5 biology in tumors, systemic lupus erythematosus (SLE), ulcerative colitis, vascular inflammation, and diseases that are driven or exacerbated by one or more factors selected from the group consisting of alpha smooth muscle actin (α SMA), CD40, CD69, collagen I, collagen III, decorin, e-selectin, eotaxin 3 (CCL26), fibroblast proliferation, human leukocyte antigen-DR isotype (HLA-DR), immunoglobulin G, interferon gamma-induced protein 10 (IP-
10 10/CXCL10), interferon-inducible T cell alpha chemoattractant (I-TAC/CXCL11), interleukin (IL)-1, IL-1.alpha., IL-2, IL-6, IL-8 (CXCL8), IL-10, IL-17A, IL-17F, keratin 8/81, macrophage colony-stimulating factor (M-CSF), matrix metalloproteinase (MMP)-1, MMP-9, monocyte chemoattractant protein 1 (MCP-1), monokine induced by gamma interferon (MIG/CXCL9), plasminogen activation inhibitor 1 (PAI-1), prostaglandin E2 (PGE2), serum amyloid A, T or
15 B cell proliferation, tissue plasminogen activator (tPA), tumor necrosis factor alpha (TNF.alpha.), vascular cell adhesion molecule (VCAM-1), and vascular endothelial growth factor 2 (VEGFR2), comprising: administering to a subject in need thereof a compound provided herein.

In an aspect, provided herein is a method of reversing a normal aging process in
20 subject comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of reversing a normal aging process in subject comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein or a pharmaceutically
25 acceptable salt thereof.

In yet another aspect, provided herein is a method of extending lifespan of a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof.

In still another aspect, provided herein is a method of extending lifespan of a subject
30 comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method to slow down and mitigate the aging process in a subject comprising administering to the subject a therapeutically effective
35 amount of a compound provided herein or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of inhibiting or modulating the pro-inflammatory pathway in a cell comprising contacting the cell with a compound provided

herein, or a pharmaceutically acceptable salt thereof. In yet another aspect, provided herein is a method of inhibiting or modulating NLRP3 in a cell comprising contacting the cell with a compound provided herein, or a pharmaceutically acceptable salt thereof.

5 Treatment of a cell (*in vitro* or *in vivo*) that expresses a NLRP3 inflammasome with a compound provided herein can result in inhibiting the pro-inflammatory pathway and inhibiting downstream events related to the signaling pathway such as inflammation or inflammaging.

10 In another aspect, provided herein is a method of treating a neurosensory disease in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the neurosensory disease is selected from the group consisting of hearing loss, hearing injury, and ocular disease. In an embodiment, the ocular disease is retinal and optic nerve injury.

15 In yet another aspect, provided herein is a method of treating an inflammatory disorder in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

20 In an embodiment, the inflammatory disorder is selected from the group consisting of allergy, asthma, atopic dermatitis, atherosclerosis, autoimmune diseases, coeliac disease, chronic inflammation, glomerulonephritis, hepatitis, inflammatory bowel disease, preperfusion injury, SARS-CoV-2 infection, transplant rejection, heart disease, diabetes, arthritis, Crohn's disease, ulcerative colitis, non-alcoholic steatohepatitis (NASH), gout, coronary artery disease, rheumatoid arthritis, intestinal disorders, and acute respiratory distress syndrome (ARDS).

25 In another embodiment, the inflammatory disorder is a neuroinflammatory disease. In yet another embodiment, the inflammatory disorder is inner ear inflammation.

30 In an embodiment, a chronic inflammation comprises a tissue inflammation. Tissue inflammation is a chronic inflammation that is confined to a particular tissue or organ. In an embodiment, a tissue inflammation comprises, e.g., a skin inflammation, ocular inflammation, a muscle inflammation, a tendon inflammation, a ligament inflammation, a bone inflammation, a cartilage inflammation, a lung inflammation, a heart inflammation, a liver inflammation, a pancreatic inflammation, a kidney inflammation, a bladder inflammation, a stomach inflammation, an intestinal inflammation, a neuron inflammation, and a brain inflammation.

35 In another embodiment, a chronic inflammation comprises a systemic inflammation. Although the processes involved are identical to tissue inflammation, systemic inflammation is not confined to a particular tissue but in fact overwhelms the body, involving the endothelium and other organ systems. When it is due to infection, the term sepsis is applied,

with the terms bacteremia being applied specifically for bacterial sepsis and viremia specifically to viral sepsis. Vasodilation and organ dysfunction are serious problems associated with widespread infection that may lead to septic shock and death.

In yet another embodiment, a chronic inflammation comprises an arthritis. Arthritis
5 includes a group of conditions involving damage to the joints of the body due to the inflammation of the synovium including, without limitation osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthropathies like ankylosing spondylitis, reactive arthritis (Reiter's syndrome), psoriatic arthritis, enteropathic arthritis associated with inflammatory bowel disease, Whipple disease and Behcet disease, septic arthritis, gout (also
10 known as gouty arthritis, crystal synovitis, metabolic arthritis), pseudogout (calcium pyrophosphate deposition disease), and Still's disease. Arthritis can affect a single joint (monoarthritis), two to four joints (oligoarthritis) or five or more joints (polyarthritis) and can be either an auto-immune disease or a non-autoimmune disease.

In still another aspect, provided herein is a method of treating an age-related disorder
15 in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the age-related disorder is selected from the group consisting of neurodegeneration, cardiovascular disease, insulin resistance, diabetes, osteoporosis, osteoarthritis, cognitive decline, dementia, frailty, cataracts, arthritis, obesity, hypertension,
20 angina, congestive heart failure, dyslipidemia, myocardial infarction, vascular disease, respiratory disease, kidney disease, cerebrovascular disease, peripheral vascular disease, Alzheimer's disease, cardiac diastolic dysfunction, benign prostatic hypertrophy, aortic aneurysm, and emphysema.

In another aspect, provided herein is a method of treating a metabolic condition in a
25 subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the metabolic condition is selected from the group consisting of diabetes, obesity, cystic fibrosis, and hyperthyroidism.

In yet another aspect, provided herein is a method of treating a neurodegenerative
30 disease in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Batten disease.

35 In an aspect, provided herein is a method of treating a disease or disorder of the inner ear in a subject in need thereof, comprising administering to the individual a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the disease or disorder of the inner ear is selected from the group consisting of hearing loss, hearing impairment, vertigo, Meniere's disease, and tinnitus. In another embodiment, the disease of the inner ear is hearing loss. In yet another embodiment, the disease of the inner ear is hearing impairment.

5 In another embodiment, the hearing loss is age-related, noise-induced, or the result of a viral infection. In yet another embodiment, the viral infection is Zika virus or coronavirus.

Potency of the inhibitor can also be determined by IC_{50} value. A compound with a lower IC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher IC_{50} value.

10 In an embodiment of the methods, the subject is a human.

In another aspect, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating or preventing a disease in which NLRP3 inflammasome plays a role.

15 In an aspect, provided herein is a method of treating a condition selected from the group consisting of autoimmune diseases, inflammatory diseases, proliferative and hyperproliferative diseases, immunologically-mediated diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cardiovascular diseases, hormone related diseases, allergies, asthma, and Alzheimer's disease. In other embodiments, said condition is selected from a proliferative disorder and a neurodegenerative disorder.

20 One aspect of this disclosure provides compounds that are useful for the treatment of diseases, disorders, and conditions characterized by excessive or abnormal cell proliferation. Such diseases include, but are not limited to, a proliferative or hyperproliferative disease, and a neurodegenerative disease. Examples of proliferative and hyperproliferative diseases include, without limitation, cancer.

25 Therefore, in an aspect, provided herein is a method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

In an embodiment, the cancer is selected from the group consisting of breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, colorectal, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon, rectum, large intestine, rectum, brain and central nervous system, chronic myeloid leukemia (CML), and leukemia.

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In another embodiment, the cancer is selected from the group consisting of myeloma, lymphoma, or a cancer selected from gastric, renal, head and neck, oropharyngeal, non-small cell lung cancer (NSCLC), endometrial, hepatocarcinoma, non-Hodgkin's lymphoma, and pulmonary.

5 In an embodiment, the cancer is selected from the group consisting of prostate cancer, colon cancer, lung cancer, squamous cell cancer of the head and neck, esophageal cancer, hepatocellular carcinoma, melanoma, sarcoma, gastric cancer, pancreatic cancer, ovarian cancer, breast cancer.

10 In an embodiment, the cancer is selected from the group consisting of tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. For example, cancers include, but are not limited to, mesothelioma, leukemias and lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotropic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic
15 lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, lymphomas, and multiple myeloma, non-Hodgkin lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), Hodgkin's lymphoma, Burkitt lymphoma, adult T-cell leukemia lymphoma, acute-myeloid leukemia (AML), chronic myeloid leukemia (CML), or hepatocellular carcinoma. Further examples include myelodysplastic syndrome, childhood
20 solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms' tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal, nasopharyngeal and esophageal), genitourinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular), lung cancer (e.g., small-cell and non-small cell), breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach
25 cancer, brain tumors, tumors related to Gorlin syndrome (e.g., medulloblastoma, meningioma, etc.), and liver cancer. Additional exemplary forms of cancer which may be treated by the subject compounds include, but are not limited to, cancer of skeletal or smooth muscle, stomach cancer, cancer of the small intestine, rectum carcinoma, cancer of the salivary gland, endometrial cancer, adrenal cancer, anal cancer, rectal cancer,
30 parathyroid cancer, and pituitary cancer.

Additional cancers that the compounds described herein may be useful in treating are, for example, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, or melanoma. Further, cancers include, but are not limited to, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue
35 carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, thyroid cancer (medullary and papillary thyroid carcinoma), renal carcinoma, kidney parenchyma carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion

carcinoma, testis carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyosarcoma, 5 craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma.

In another aspect, provided herein is the use of one or more compounds of the disclosure in the manufacture of a medicament for the treatment of cancer, including without limitation the various types of cancer disclosed herein.

10 In some embodiments, the compounds of this disclosure are useful for treating cancer, such as colorectal, thyroid, breast, and lung cancer; and myeloproliferative disorders, such as polycythemia vera, thrombocythemia, myeloid metaplasia with myelofibrosis, chronic myelogenous leukemia, chronic myelomonocytic leukemia, hypereosinophilic syndrome, juvenile myelomonocytic leukemia, and systemic mast cell 15 disease. In some embodiments, the compounds of this disclosure are useful for treating hematopoietic disorders, in particular, acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia, and acute lymphocytic leukemia (ALL).

20 Administration / Dosages / Formulations

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as 25 ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, com, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as 30 wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations (for example, sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a 35 sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and

isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

5 In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a
10 parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

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

 Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

20 The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent
25 such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

 Dosage forms for topical or transdermal administration of a compound of this
30 disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this disclosure.

35 The ointments, pastes, creams and gels may contain, in addition to an active compound of this disclosure, excipients such as animal and vegetable fats, oils, waxes,

paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this disclosure, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and
5 polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the
10 flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Compounds of the present disclosure can be administered intratympanically, wherein a long, narrow, bore needle is passed through the ear canal and through the eardrum to administer medications into the middle ear space where they are absorbed by the inner ear.

15 According to the methods of treatment of the present disclosure, disorders are treated or prevented in a subject, such as a human or other animal, by administering to the subject a therapeutically effective amount of a compound of the disclosure, in such amounts and for such time as is necessary to achieve the desired result. The term "therapeutically effective amount" of a compound of the disclosure, as used herein, means a sufficient
20 amount of the compound so as to decrease the symptoms of a disorder in a subject. As is well understood in the medical arts a therapeutically effective amount of a compound of this disclosure will be at a reasonable benefit/risk ratio applicable to any medical treatment.

In general, compounds of the disclosure will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly
25 or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g., humans, is in the
30 range from about 0.5 mg to about 100 mg, conveniently administered, e.g., in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

In certain embodiments, a therapeutic amount or dose of the compounds of the present disclosure may range from about 0.1 mg/Kg to about 500 mg/Kg, alternatively from
35 about 1 to about 50 mg/Kg. In general, treatment regimens according to the present disclosure comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this disclosure per day in single or multiple doses.

Therapeutic amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this disclosure may be administered, if necessary.

5 Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained; when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

10 It will be understood, however, that the total daily usage of the compounds and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed;
15 the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The disclosure also provides for a pharmaceutical combination, e.g., a kit, comprising
20 a) a first agent which is a compound of the disclosure as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers; alumina; aluminum stearate; lecithin;
25 serum proteins, such as human serum albumin; buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids; water; salts or electrolytes, such as protamine sulfate; disodium hydrogen phosphate; potassium hydrogen phosphate; sodium chloride; zinc salts; colloidal silica; magnesium trisilicate; polyvinyl pyrrolidone; polyacrylates; waxes;
30 polyethylenepolyoxypropylene-block polymers; wool fat; sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean
35 oil; glycols, such as propylene glycol or polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol;

and phosphate buffer solutions. Further, non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The protein

5 kinase inhibitors or pharmaceutical salts thereof may be formulated into pharmaceutical compositions for administration to animals or humans. These pharmaceutical compositions, which comprise an amount of the protein inhibitor effective to treat or prevent a protein kinase-mediated condition and a pharmaceutically acceptable carrier, are other embodiments of the present disclosure.

10

Kits

In an aspect, provided herein is a kit comprising a compound capable of inhibiting NLRP3 inflammasome activity selected from one or more compounds of disclosed herein, or pharmaceutically acceptable salts thereof, and instructions for use in treating a disorder

15 associated with NLRP3 inflammasomes.

In another aspect, the disclosure provides a kit comprising a compound capable of inhibiting NLRP3 inflammasome activity selected from a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

In yet another aspect, provided herein is a kit comprising a compound disclosed

20 herein, or a pharmaceutically acceptable salt thereof for the treatment of any of the indications disclosed herein.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were considered to be within the

25 scope of this disclosure and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, e.g., nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are

30 within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present disclosure. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present

35 application.

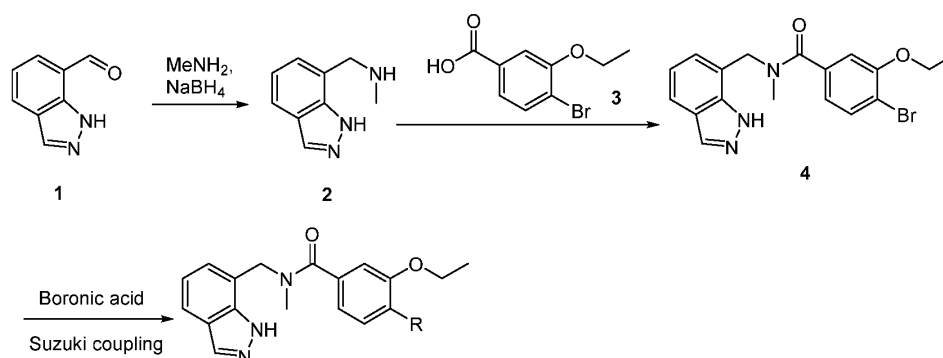
The following examples further illustrate aspects of the present disclosure. However, they are in no way a limitation of the teachings of the present disclosure as set forth.

EXAMPLES

The compounds and methods disclosed herein are further illustrated by the following examples, which should not be construed as further limiting. The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of organic synthesis, cell biology, cell culture, and molecular biology, which are within the skill of the art.

Abbreviations

ACN	acetonitrile
10 AcOH	acetic acid
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
15 dppf	1,1'-bis(diphenylphosphino)ferrocene
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
EtOH	ethanol
HPLC	high-performance liquid chromatography
20 LCMS	liquid chromatography-mass spectrometry
MeOH	methanol
NMR	nuclear magnetic resonance
PE	petroleum ether
THF	tetrahydrofuran
25 TLC	thin layer chromatography

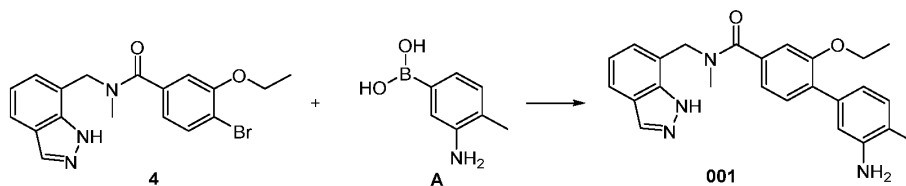
*Example 1: Synthetic Procedures***Scheme 1.**

30 To a solution of compound 1 (4 g, 27.37 mmol, 1 eq) in MeOH (20 mL) was added AcOH (164.36 mg, 2.74 mmol, 156.54 μ L, 0.1 eq) and MeNH₂ in MeOH (2 M, 41.05 mL, 3 eq), the mixture was stirred at 15 °C for 2 h, then NaBH₄ (1.14 g, 30.11 mmol, 1.1 eq) was added in portions at 0 °C, then the reaction was stirred at 30 °C for 16 h. LCMS showed the

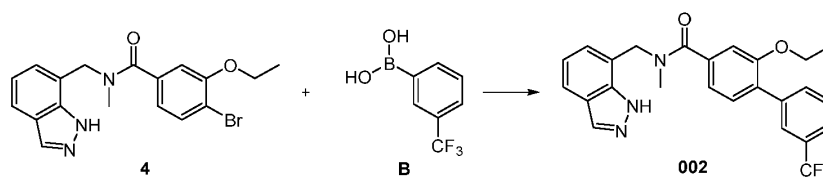
reaction was completed. After the reaction was completed, the mixture was poured into NH_4Cl (200 mL) and extracted with EtOAc (200 mL X3), the combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4 , and concentrated to give a crude product. The crude product used for next reaction without further purification.

5 Compound **2** (5 g, crude) was obtained as yellow oil. LCMS: $m/z = 162.2$ ($\text{M}+\text{H}^+$).

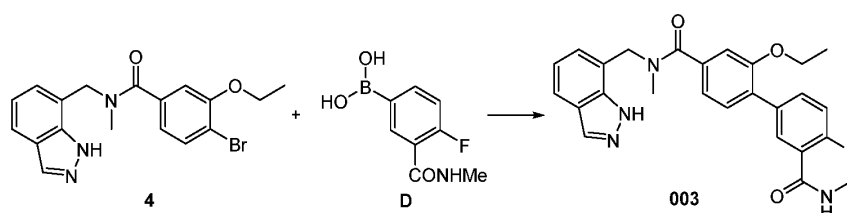
To a solution of compound **3** (1 g, 4.08 mmol, 1 eq) in DCM (20 mL) was added EDCI (1.02 g, 5.30 mmol, 1.3 eq), DMAP (49.85 mg, 408.05 μmol , 0.1 eq) and compound **2** (1.97 g, 12.24 mmol, 3 eq), the mixture was stirred at 30 °C for 12 h. LCMS showed the reaction was completed. The mixture poured into water (50 mL) and extracted with DCM (50mL X3), the combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated to give a crude product. The crude product was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10/1 to 1/1, desired product $R_f=0.6$). Compound **4** (1.2 g, 3.09 mmol, 75.74% yield, 100% purity) was obtained as white solid, confirmed by LCMS and ^1H NMR. LCMS: $m/z = 387.9$ ($\text{M}+\text{H}^+$) ^1H NMR (400 MHz, CHLOROFORM-d) $\delta = 8.21 - 7.98$ (m, 1H), 7.84 - 7.66 (m, 1H), 7.53 - 7.39 (m, 1H), 7.27 - 7.15 (m, 1H), 7.11 - 7.03 (m, 1H), 6.94 - 6.87 (m, 1H), 6.85 - 6.75 (m, 1H), 4.86 (s, 2H), 4.03 (d, $J = 7.0$ Hz, 2H), 2.87 (s, 3H), 1.40 (t, $J = 7.0$ Hz, 3H).



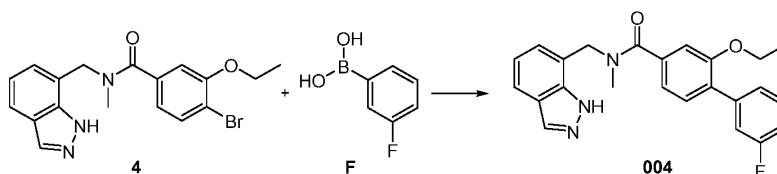
To a mixture of compound **4** (80 mg, 206.05 μmol , 1 eq), compound **A** (46.34 mg, 247.26 μmol , 1.2 eq, HCl), K_2CO_3 (85.43 mg, 618.15 μmol , 3 eq) in dioxane (2 mL) and H_2O (0.2 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ (33.65 mg, 41.21 μmol , 0.2 eq) under N_2 atmosphere, then the reaction mixture was stirred at 100 °C for 12 h. LCMS: $m/z = 415.0$ ($\text{M}+\text{H}^+$) showed **4** consumed completely and desired mass was detected. The reaction mixture was added thiourea resin, then the mixture was stirred for 4 hr. The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (0.225%FA)-ACN]; B%: 30%-60%, 10min), the purified solution was lyophilized to give a black brown solid. Compound **001** (21.2 mg, 50.64 μmol , 24.58% yield, 99.02 % purity) was obtained as a black brown solid. LCMS and ^1H NMR confirmed. LCMS: $m/z = 415.5$ ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, METHANOL-d_4) $\delta = 8.13$ (br s, 1H), 7.78 (br d, $J = 7.2$ Hz, 1H), 7.30 (br d, $J = 2.9$ Hz, 2H), 7.20 - 6.98 (m, 6H), 4.97 (br s, 2H), 4.04 (br d, $J = 5.6$ Hz, 2H), 3.01 (br s, 3H), 2.30 (br s, 3H), 1.35 (br s, 3H).



- Compound **002** was prepared as described for the synthesis of compound **001** with Compound **4** and Compound **B** as the starting materials. Compound **002** (15.4 mg, 33.66 umol, 16.34% yield, 99.126% purity) was obtained as a yellow solid. **LCMS**: $m/z = 454.3$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.51 - 8.02$ (m, 1H), 7.85 (br s, 1H), 7.79 - 7.66 (m, 2H), 7.65 - 7.46 (m, 3H), 7.40 - 7.28 (m, 2H), 7.22 - 7.02 (m, 3H), 4.98 (br s, 2H), 4.08 (br s, 2H), 3.03 (br s, 3H), 1.36 (br s, 3H).

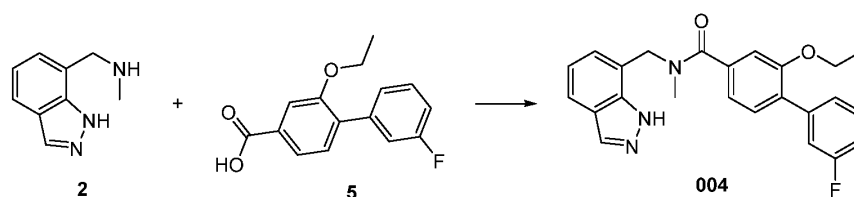


- Compound **003** was prepared as described for the synthesis of Compound **001** with Compound **4** and Compound **D** as the starting materials. Compound **003** (54.3 mg, 114.51 umol, 55.57% yield, 97.112% purity) was obtained as a yellow solid. **LCMS**: $m/z = 461.3$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.33 - 8.12$ (m, 2H), 7.80 (br d, $J = 6.7$ Hz, 1H), 7.68 (br d, $J = 2.1$ Hz, 1H), 7.35 (br d, $J = 4.0$ Hz, 2H), 7.21 - 7.06 (m, 4H), 6.83 - 6.72 (m, 1H), 4.99 (br s, 2H), 4.18 - 3.99 (m, 2H), 3.06 (br d, $J = 4.6$ Hz, 3H), 3.02 (br s, 3H), 1.37 (br s, 3H).



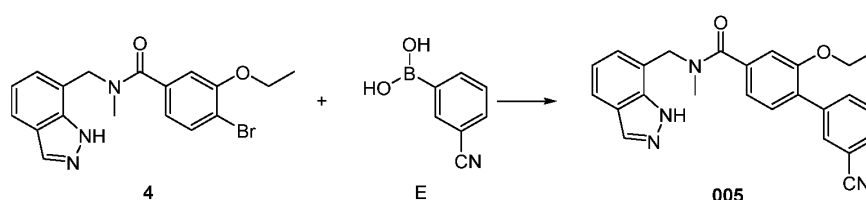
- Compound **004** was prepared as described for the synthesis of Compound **001** with Compound **4** and Compound **F** as the starting materials. Compound **004** (14.8 mg, 36.51 umol, 17.72% yield, 99.518% purity) was obtained as a yellow solid. **LCMS**: $m/z = 404.3$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.35 - 7.99$ (m, 1H), 7.76 (br s, 1H), 7.31 (br d, $J = 6.6$ Hz, 5H), 7.22 - 6.98 (m, 4H), 4.98 (br s, 2H), 4.07 (br d, $J = 2.0$ Hz, 2H), 3.02 (br s, 3H), 1.37 (br s, 3H).

Compound **004** was also prepared by the following protocol.

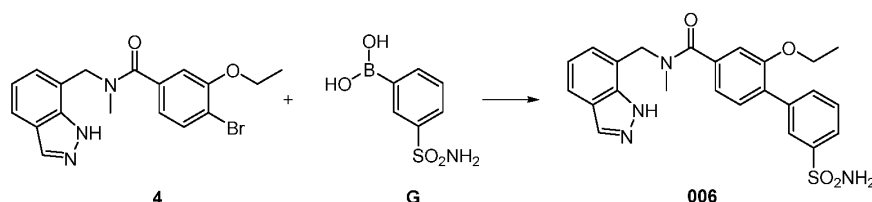


Compound **004** was prepared as described for the synthesis of Compound **4** with Compound **2** and Compound **5** as the starting materials and step 1 at 30 °C for 4 h.

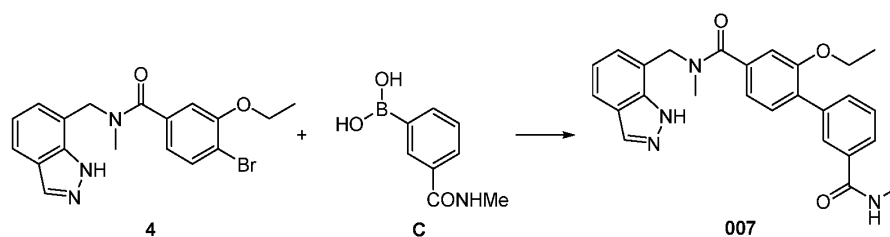
Compound **004** (130.32 mg, 552.74 μmol , 59.40% yield, 100% purity) was obtained as a white solid. **LCMS**: $m/z = 404.0$ ($M+H^+$). **$^1\text{H NMR}$** (400 MHz, CHLOROFORM-d) $\delta = 8.14$ (s, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.30 (s, 5H), 7.18 - 7.11 (m, 1H), 7.07 (br dd, $J = 2.7, 3.9$ Hz, 3H), 4.98 (s, 2H), 4.18 - 3.99 (m, 2H), 3.01 (s, 3H), 1.37 (s, 3H).



Compound **005** was prepared as described for the synthesis of Compound **001** with Compound **4** and Compound **E** as the starting materials, however step 1 was conducted at 100 °C for 12 h and step 2 was conducted at 15 °C for 12 h. Compound **005** (10.0 mg, 24.36 μmol , 11.82% yield, 100% purity) was obtained as a gray solid. **LCMS**: $m/z = 411.0$ ($M+H^+$). **$^1\text{H NMR}$** (400 MHz, CHLOROFORM-d) $\delta = 8.37 - 8.01$ (m, 1H), 7.87 (s, 1H), 7.83 - 7.70 (m, 2H), 7.64 (br d, $J = 7.6$ Hz, 1H), 7.54 (br d, $J = 7.6$ Hz, 1H), 7.32 (br s, 3H), 7.28 - 7.00 (m, 3H), 4.99 (br s, 2H), 4.10 (br d, $J = 5.4$ Hz, 2H), 3.04 (br s, 3H), 1.38 (br s, 3H).

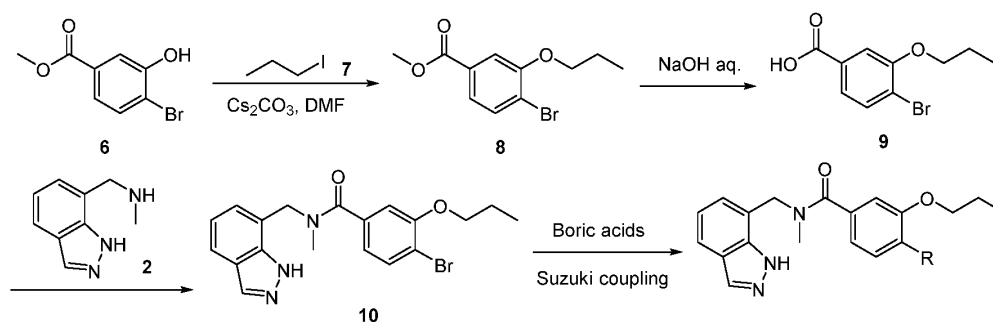


Compound **006** was prepared as described for the synthesis of Compound **001** with Compound **4** and Compound **G** as the starting materials, however, step 1 was conducted at 100 °C for 16 h and step 2 was conducted at 15 °C for 12 h. Compound **006** (34.2 mg, 72.66 μmol , 35.27% yield, 98.7% purity) was obtained as white solid. **LCMS**: $m/z = 465.1$ ($M+H^+$). **$^1\text{H NMR}$** (400 MHz, CHLOROFORM-d) $\delta = 8.34 - 8.10$ (m, 2H), 7.97 - 7.88 (m, 1H), 7.80 (br s, 2H), 7.66 - 7.53 (m, 1H), 7.43 - 7.29 (m, 2H), 7.24 - 7.00 (m, 3H), 5.00 (br s, 4H), 4.26 - 3.90 (m, 2H), 3.03 (br s, 3H), 1.38 (br s, 3H).



Compound **007** was prepared as described for the synthesis of Compound **001** with Compound **4** and Compound **C** as the starting materials. Also, step 1 was conducted at 100 °C for 16 h and step 2 was conducted at 100 °C for 16 h. Compound **007** (13.8 mg, 30.25 umol, 14.68% yield, 97.0% purity) was obtained as a gray solid. LCMS: $m/z = 443.1$ ($M+H^+$). 1H NMR (400 MHz, CHLOROFORM- d) $\delta = 8.20 - 8.08$ (m, 1H), 7.94 (s, 1H), 7.85 - 7.77 (m, 1H), 7.77 - 7.64 (m, 2H), 7.54 - 7.44 (m, 1H), 7.37 (br d, $J = 7.7$ Hz, 1H), 7.31 (br d, $J = 6.6$ Hz, 1H), 7.22 - 7.01 (m, 3H), 6.36 - 6.03 (m, 1H), 4.99 (s, 2H), 4.07 (br d, $J = 6.4$ Hz, 2H), 3.24 - 2.89 (m, 6H), 1.36 (br t, $J = 6.2$ Hz, 3H)

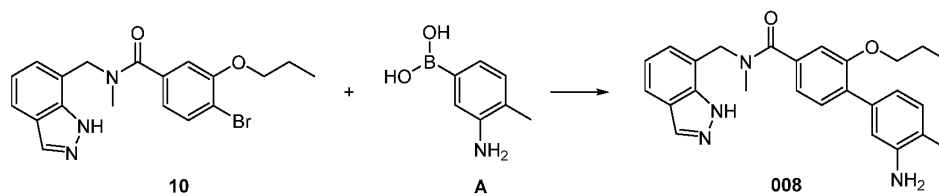
10 Scheme 2.



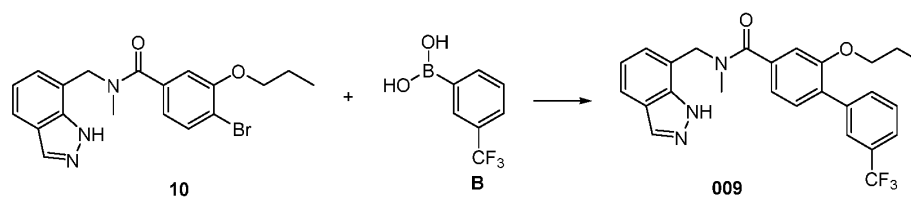
To a solution of compound **6** (5 g, 21.64 mmol, 1 eq) in DMF (50 mL) was added compound **7** (5.52 g, 32.46 mmol, 3.17 mL, 1.5 eq) and Cs_2CO_3 (7.05 g, 21.64 mmol, 1 eq), the mixture was stirred at 50 °C for 1 hr. TLC (PE : EtOAc = 10 : 1, $R_f = 0.5$) showed the starting material was consumed completely and a new point was detected. The mixture was filtered and the filtrate was collected. The filtrate was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mLx3). The combined organic phase was washed with brine (50 mLx 4), dried with anhydrous Na_2SO_4 , filtered and concentrated to give a crude product in vacuum. The crude product used for next step without further purification. Compound **8** (5.14 g, 18.39 mmol, 84.96% yield, 97.7% purity) was obtained as black brown solid, confirmed by LCMS and 1H NMR. LCMS: $m/z = 273.0$ ($M+H^+$). 1H NMR (400 MHz, DMSO- d_6) $\delta = 7.72$ (d, $J = 8.1$ Hz, 1H), 7.50 (d, $J = 1.8$ Hz, 1H), 7.44 (dd, $J = 1.9$, 8.1 Hz, 1H), 4.09 - 4.03 (m, 2H), 3.86 (s, 3H), 1.77 (sxt, $J = 7.0$ Hz, 2H), 1.02 (t, $J = 7.4$ Hz, 3H).

To a solution of methyl compound **8** (5.14 g, 18.39 mmol, 97.7% purity, 1 eq) in MeOH (60 mL) and THF (60 mL) was added NaOH in water (2 M, 60 mL, 6.53 eq), the mixture was stirred at 50 °C for 1 hr. The mixture was adjusted to pH = 2 with HCl (1 mol /L). Then there was a lot of solid separated out, the mixture was filtered and the white solid was collected and dried in vacuo. The crude product used for next step without further purification. Compound **9** (4.37 g, 16.83 mmol, 91.55% yield, 99.8% purity) was obtained as white solid, confirmed by LCMS and ¹H NMR. **LCMS**: m/z = 256.9 (M+H⁺). **¹H NMR** (400 MHz, DMSO-d₆) δ = 13.22 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.52 (s, 1H), 7.47 - 7.42 (m, 1H), 4.07 (t, J = 6.3 Hz, 2H), 1.77 (sxt, J = 6.9 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

Compound **10** was prepared as described for the synthesis of compound **4** with compound **9** and compound **2** as the starting materials. Compound **10** (1 g, 2.49 mmol, 80.51% yield, 100% purity) was obtained as a white solid. **LCMS**: m/z = 401.9 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.13 - 7.96 (m, 1H), 7.81 - 7.63 (m, 1H), 7.53 - 7.37 (m, 1H), 7.22 - 7.15 (m, 1H), 7.08 - 7.00 (m, 1H), 6.92 - 6.87 (m, 1H), 6.83 - 6.76 (m, 1H), 4.85 (s, 2H), 3.91 (s, 2H), 2.86 (s, 3H), 1.88 - 1.69 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).

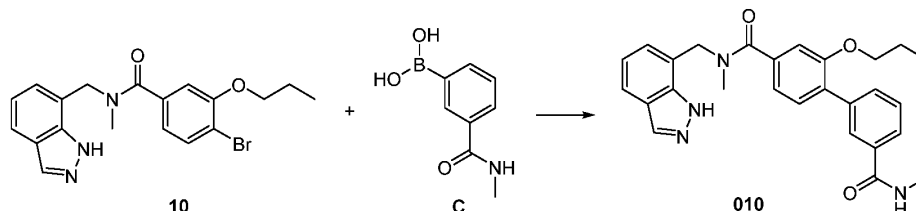


Compound **008** was prepared as described for the synthesis of Compound **001** with Compound **10** and Compound **A** as the starting materials and step 2 at 20 °C for 12 hr. Compound **008** (19.8 mg, 44.91 μmol, 25.81% yield, 97.2% purity) was obtained as a red solid. **LCMS**: m/z = 429.2 (M+H⁺). **¹H NMR** (400 MHz, DMSO-d₆) δ = 12.95 - 12.64 (m, 1H), 8.15 - 8.08 (m, 1H), 7.78 - 7.70 (m, 1H), 7.29 (dd, J = 7.4, 15.2 Hz, 2H), 7.22 - 7.15 (m, 1H), 7.11 - 7.05 (m, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.82 - 6.76 (m, 1H), 6.66 (d, J = 7.3 Hz, 1H), 4.94 (s, 2H), 4.83 - 4.36 (m, 2H), 3.78 (s, 2H), 3.04 (s, 3H), 2.10 (s, 3H), 1.60 (d, J = 7.0 Hz, 2H), 0.87 (t, J = 7.1 Hz, 3H).

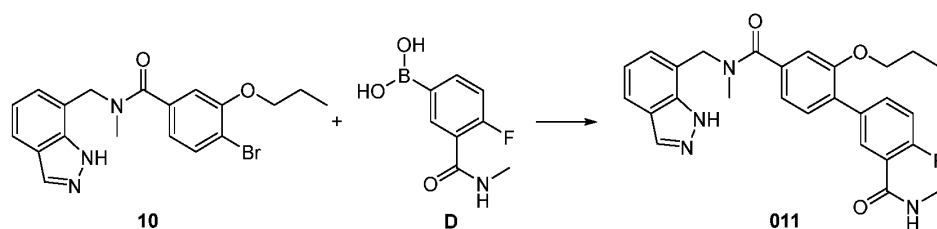


Compound **009** was prepared as described for the synthesis of Compound **001** with Compound **10** and Compound **B** as the starting materials and step 2 at 20 °C for 12 h. Compound **009** (10.2 mg, 21.69 μmol, 12.46% yield, 99.4% purity) was obtained as a white solid. **LCMS**: m/z = 468.2 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.31 - 8.11 (m,

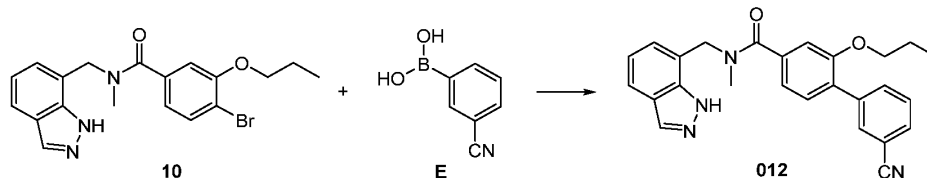
1H), 7.92 - 7.78 (m, 2H), 7.77 - 7.67 (m, 1H), 7.65 - 7.49 (m, 3H), 7.44 - 7.30 (m, 2H), 7.26 - 7.02 (m, 3H), 5.01 (br s, 2H), 4.15 - 3.83 (m, 2H), 3.17 - 2.90 (m, 3H), 1.83 - 1.70 (m, 2H), 0.99 (br s, 3H).



- 5 Compound **010** was prepared as described for the synthesis of Compound **001** with Compound **10** and Compound **C** as the starting materials and step 2 at 20 °C for 12 h. Compound **010** (20.3 mg, 44.33 μ mol, 25.48% yield, 99.7% purity) was obtained as a white solid. LCMS: m/z = 457.2 ($M+H^+$). 1H NMR (400 MHz, CHLOROFORM- d) δ = 11.92 (s, 1H), 8.05 (s, 1H), 7.84 (s, 1H), 7.75 - 7.56 (m, 3H), 7.45 - 7.35 (m, 1H), 7.29 - 7.24 (m, 1H), 7.21 (d, J = 6.9 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 3.1 Hz, 2H), 6.10 (s, 1H), 4.90 (s, 2H), 3.86 (t, J = 6.3 Hz, 2H), 3.06 - 2.84 (m, 6H), 1.74 - 1.61 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

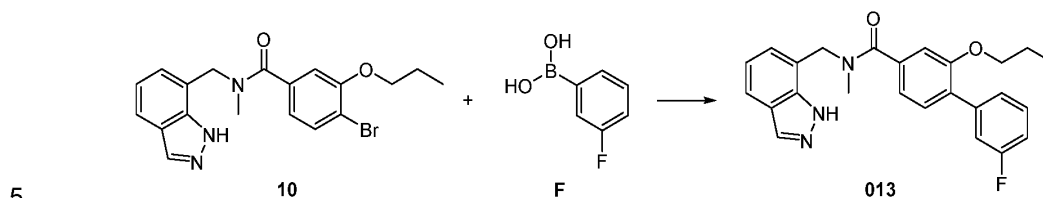


- 15 Compound **011** was prepared as described for the synthesis of Compound **001** with Compound **10** and Compound **D** as the starting materials and step 2 at 20 °C for 12 h. Compound **011** (18.1 mg, 37.00 μ mol, 21.26% yield, 97% purity) was obtained as a white solid. LCMS: m/z = 475.3 ($M+H^+$). 1H NMR (400 MHz, CHLOROFORM- d) δ = 8.26 (d, J =6.97 Hz, 1 H) 8.22 - 8.11 (m, 1 H) 7.80 (d, J =3.55 Hz, 1 H) 7.68 (s, 1 H) 7.35 (s, 1 H) 7.32 (s, 1 H) 7.19 - 7.04 (m, 4 H) 6.78-6.75 (m, 1 H) 4.99 (s, 2 H) 4.04 - 3.88 (m, 2 H) 3.08-3.01(m, 6 H) 1.75 (s, 2 H) 0.97 (s, 3 H).



Compound **012** was prepared as described for the synthesis of compound **001** with compound **10** and compound **E** as the starting materials and step 2 at 20 °C for 12 h. Compound **012** (12.5 mg, 28.86 μ mol, 16.58% yield, 98% purity) was obtained as a white

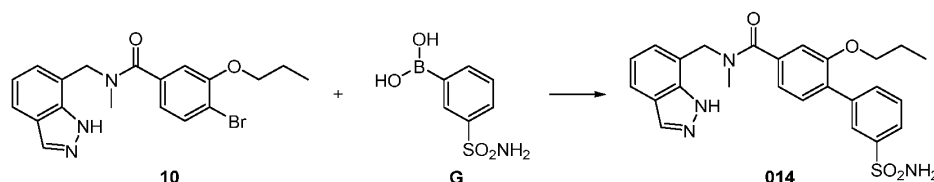
solid. **LCMS**: $m/z = 425.2$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.27 - 8.05$ (m, 1H), 7.85 (s, 1H), 7.77 (d, $J = 7.7$ Hz, 2H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.55 - 7.48 (m, 1H), 7.31 (s, 2H), 7.23 - 6.97 (m, 3H), 5.07 - 4.90 (m, 2H), 4.11 - 3.84 (m, 2H), 3.02 (s, 3H), 1.75 (s, 2H), 0.97 (s, 3H).



Compound **013** was prepared as described for the synthesis of compound **001** with compound **10** and compound **F** as the starting materials and step 2 at 20 °C for 12 h.

Compound **013** (39.8 mg, 94.38 μ mol, 54.24% yield, 99% purity) was obtained as a white solid. **LCMS**: $m/z = 418.2$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.23$ (s, 1 H) 7.80 (d, $J=6.50$ Hz, 1 H) 7.65 7.44m, 1 H) 7.33 (s, 5 H) 7.17 (s, 1 H) 7.09 (s, 3 H) 4.99 (s, 2 H) 3.97 (s, 2 H) 3.03 (s, 3 H) 1.78 (d, $J=5.63$ Hz, 2 H) 1.00 (s, 3 H).

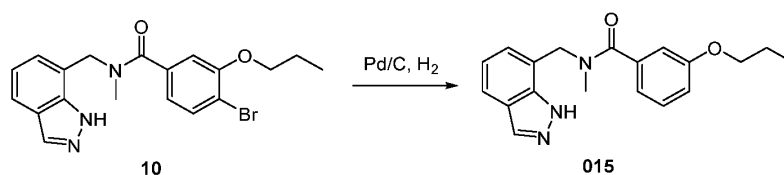
10



Compound **014** was prepared as described for the synthesis of compound **001** with compound **10** and compound **G** as the starting materials and step 2 at 20 °C for 12 h.

15 Compound **014** (21.2 mg, 44.21 μ mol, 25.41% yield, 99.8% purity) was obtained as a white solid. **LCMS**: $m/z = 479.3$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.27 - 8.17$ (m, 1 H) 8.14 (s, 1 H) 7.90 (d, $J=6.72$ Hz, 1 H) 7.81 (d, $J=1.83$ Hz, 1 H) 7.77 (d, $J=7.09$ Hz, 1 H) 7.56 (d, $J=5.99$ Hz, 1 H) 7.44 - 7.30 (m, 2 H) 7.17 (s, 1 H) 7.13- 7.06 (m, 1 H) 5.00 (s, 2 H) 4.39 - 4.75 (m, 2 H) 4.12 - 3.82 (m, 2 H) 3.12 - 2.93 (m, 3 H) 1.83 - 1.64 (m, 2 H) 0.97 (s, 3 H).

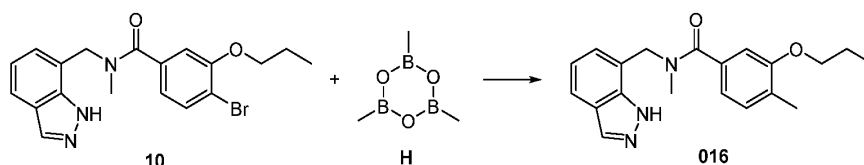
20 H).



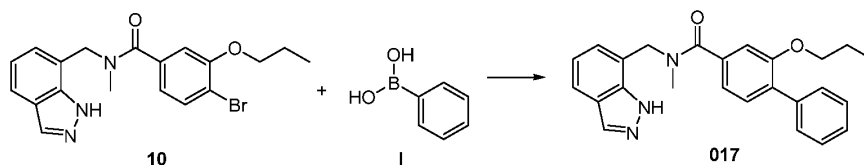
To a solution of compound **10** (50 mg, 124.29 μ mol, 1 eq) in THF (5 mL) was added Pd/C (20 mg, 18.80 μ mol, 10% purity, 1.51e-1 eq) under N_2 atmosphere, the mixture was stirred at 30 °C for 12 hr in H_2 (250.55 μ g, 124.29 μ mol, 1 eq) atmosphere. LCMS showed the starting material was consumed completely and there was 70% desired mass. The reaction mixture was filtered under N_2 atmosphere, the filtrate was concentrated to give a

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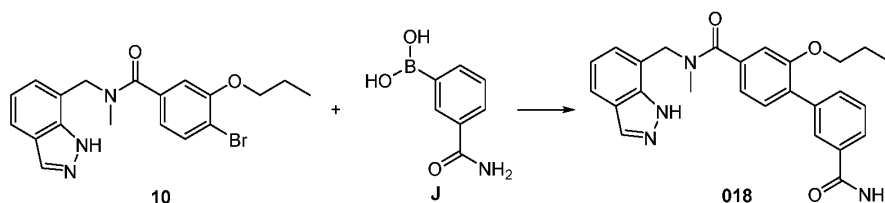
crude product. The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(0.225%FA)-ACN];B%: 46%-76%,10min). The purified solution was lyophilized. Compound **015** (21.5 mg, 66.48 umol, 53.49% yield, 100% purity) was obtained as colorless oil, confirmed by LCMS and ¹H NMR. **LCMS**: m/z = 324.1 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.17 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.21 - 7.12 (m, 1H), 7.04 - 6.94 (m, 3H), 4.97 (s, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.96 (s, 3H), 1.86 - 1.76 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).



Compound **016** was prepared as described for the synthesis of compound **001** with compound **10** and compound **H** as the starting materials and step 2 at 20 °C for 3 hr. Compound **016** (24.7 mg, 72.40 umol, 41.61% yield, 98.9% purity) was obtained as a black brown oil. **LCMS**: m/z = 338.1 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.17 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 6.7 Hz, 1H), 7.15 (d, *J* = 6.6 Hz, 2H), 6.94 (s, 2H), 4.97 (s, 2H), 3.96 (s, 2H), 2.99 (s, 3H), 2.26 (s, 3H), 1.85 (d, *J* = 7.0 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H).



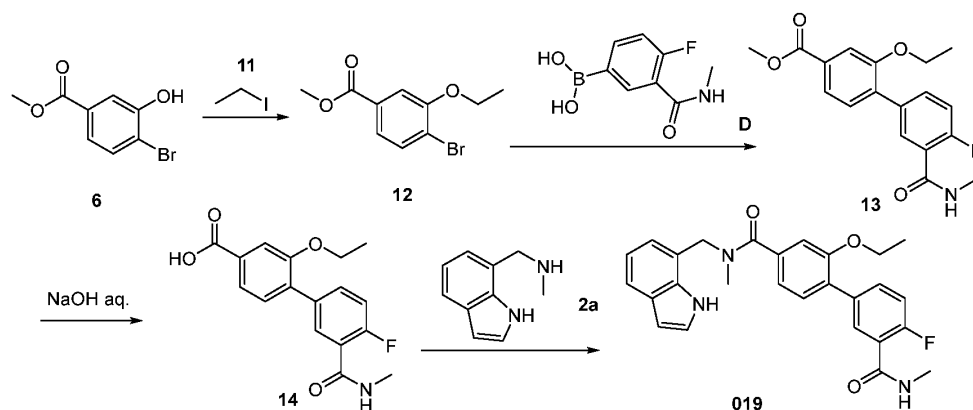
Compound **017** was prepared as described for the synthesis of compound **001** with compound **10** and compound **I** as the starting materials and step 2 at 20 °C for 3 hr. Compound **017** (15.9 mg, 38.81 umol, 22.30% yield, 97.5% purity) was obtained as a yellow solid. **LCMS**: m/z = 400.2 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.37 - 8.02 (m, 1H), 7.92 - 7.75 (m, 1H), 7.59 - 7.53 (m, 2H), 7.45 - 7.40 (m, 2H), 7.39 - 7.30 (m, 3H), 7.24 - 6.99 (m, 3H), 5.17 - 4.89 (m, 2H), 3.99 (td, *J* = 1.3, 2.7 Hz, 2H), 3.07 (s, 3H), 1.77 (d, *J* = 1.2 Hz, 2H), 1.06 - 0.93 (m, 3H).



Compound **018** was prepared as described for the synthesis of compound **001** with compound **10** and compound **J** as the starting materials and step 2 at 20 °C for 12 h.

Compound **018** (17.5 mg, 39.55 μ mol, 22.73% yield, 100% purity) was obtained as a white solid. **LCMS**: $m/z = 443.3$ ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.18$ (s, 1 H) 8.00 (s, 1 H) 7.84 - 7.76 (m, 2 H) 7.73 (d, $J=7.46$ Hz, 1 H) 7.50 (t, $J=7.40$ Hz, 1 H) 7.40 - 7.30 (m, 2 H) 7.17 (t, $J=6.85$ Hz, 1 H) 7.09 (s, 2 H) 6.33 - 6.02 (m, 1 H) 6.01 - 5.72 (m, 1 H) 5.06 - 4.92 (m, 2 H) 3.96 (s, 2 H) 3.03 (s, 3 H) 1.74 (d, $J=5.75$ Hz, 2 H) 0.96 (t, $J=6.91$ Hz, 3 H).

Scheme 3.



Compound **12** was prepared as described for the synthesis of compound **8** with compound **6** and compound **11** as the starting materials. Compound **12** (950 mg, 3.47 mmol, 80.14% yield, 94.6% purity) was obtained as a yellow solid. **LCMS**: $m/z = 260.9$ ($M+H^+$). **1H NMR** (400 MHz, DMSO- d_6) $\delta = 7.78$ (d, $J = 8.3$ Hz, 1H), 7.56 (d, $J = 1.8$ Hz, 1H), 7.50 (dd, $J = 1.9, 8.1$ Hz, 1H), 4.22 (q, $J = 7.0$ Hz, 2H), 3.91 (s, 3H), 1.43 (t, $J = 6.9$ Hz, 3H).

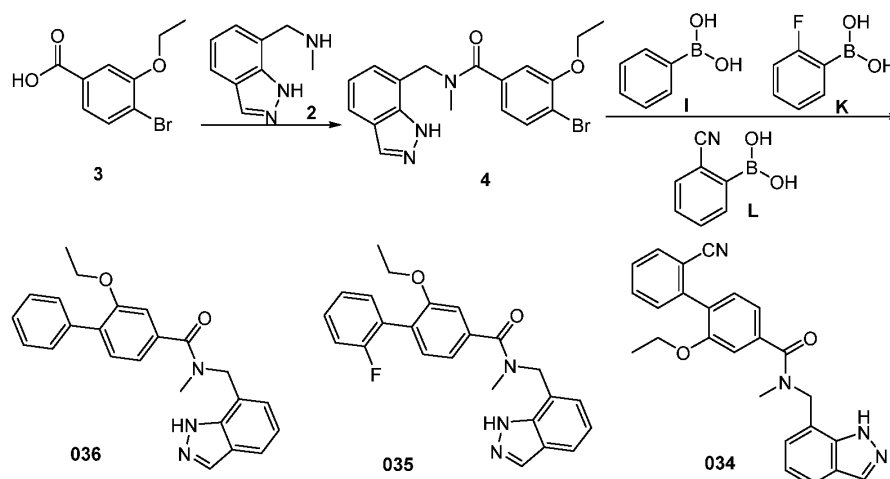
Compound **13** was prepared as described for the synthesis of compound **001** with compound **12** and compound **D** as the starting materials and step 1 at 90 °C for 12 hr. The mixture was poured into water (20ml) and the aqueous phase was extracted with ethyl acetate (20 mLx3). The combined organic phase was washed with brine (20 mLx4), dried with anhydrous Na_2SO_4 , filtered and concentrated to give a crude product in vacuum. The crude product was purified by column chromatography on silica gel eluted with PE: EtOAc = 8:1 to 4:1. Compound **13** (480 mg, 1.43 mmol, 78.24% yield, 98.6% purity) was obtained as yellow solid. **LCMS**: $m/z = 332.1$ ($M+H^+$). **1H NMR** (400 MHz, DMSO- d_6) $\delta = 8.36$ (d, $J = 2.3$ Hz, 1H), 7.83 (dd, $J = 2.3, 6.9$ Hz, 1H), 7.77 (ddd, $J = 2.4, 5.0, 8.5$ Hz, 1H), 7.69 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.64 (d, $J = 1.4$ Hz, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.40 (dd, $J = 8.7, 10.3$ Hz, 1H), 4.18 (q, $J = 6.9$ Hz, 2H), 3.93 (s, 3H), 2.84 (d, $J = 4.5$ Hz, 3H), 1.34 (t, $J = 6.9$ Hz, 3H).

Compound **14** was prepared as described for the synthesis of compound **9** with compound **13** as the starting material and step 1 at 30 °C for 1 h. The crude product used for next step without further purification. Compound **14** (315 mg, 962.94 μ mol, 66.47% yield, 97.0% purity) was obtained as a yellow solid. **LCMS**: $m/z = 318.1$ ($M+H^+$). **1H NMR** (400

MHz, DMSO- d_6) δ = 13.09 (s, 1H), 8.32 (s, 1H), 7.78 (d, J = 5.3 Hz, 1H), 7.72 (d, J = 2.8 Hz, 1H), 7.64 - 7.57 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 9.4 Hz, 1H), 4.12 (q, J = 6.7 Hz, 2H), 2.79 (d, J = 4.3 Hz, 3H), 1.29 (t, J = 6.8 Hz, 3H).

Compound **019** was prepared as described for the synthesis of compound **4** with compound **14** and compound **2a** as the starting materials. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(0.225%FA)-ACN]; B%: 49%-79%, 10min), the purified solution was lyophilized. Compound **019** (21.7 mg, 47.04 μ mol, 21.32% yield, 99.6% purity) was obtained as a white solid. **LCMS**: m/z = 460.2 ($M+H^+$). **¹H** NMR (400 MHz, CHLOROFORM- d) δ = 10.44 (s, 1H), 8.28 (dd, J = 2.3, 7.6 Hz, 1H), 7.75 - 7.65 (m, 2H), 7.39 - 7.32 (m, 2H), 7.21 - 7.15 (m, 1H), 7.15 - 7.07 (m, 2H), 7.06 - 6.98 (m, 2H), 6.84 - 6.72 (m, 1H), 6.65 - 6.58 (m, 1H), 5.06 - 4.93 (m, 2H), 4.13 - 4.00 (m, 2H), 3.14 - 2.97 (m, 6H), 1.37 (t, J = 6.9 Hz, 3H).

Scheme 4



15

To a solution of compound **2** and compound **3** (456.13 mg, 2.32 mmol, 1.2 eq) in dioxane (5 mL) and H₂O (0.6 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (315.19 mg, 385.96 μ mol, 0.2 eq), the mixture stirred at 90 °C for 12 h. LCMS showed most of the starting material was remained, then K₂CO₃ (533.42 mg, 3.86 mmol, 2 eq) was added, the mixture was stirred at 90 °C for 4 h. LCMS (showed the starting material was consumed completely. After the reaction was completed, the mixture was poured into water (100 mL) and extracted with EtOAc (100mL X3), the combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1/1, desired product R_f=0.6). Compound **4** (630 mg, crude) was obtained as yellow oil. **LCMS**: m/z = 331.9 ($M+H^+$)

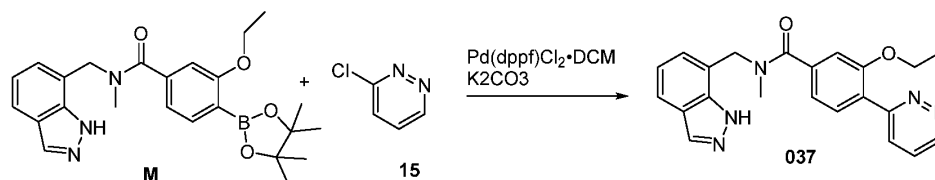
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Compound **036** was prepared as described for the synthesis of compound **001** with compound **4** and compound **I** as the starting materials. Also, step 1 was conducted at 90 °C for 12 hr and step 2 was conducted at 15 °C for 12 h. Compound **036** (16.71 mg, 43.35 umol, 42.08% yield, 100% purity) obtained as a white solid. **LCMS**: $m/z = 386.1$ ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 8.10 - 8.03$ (m, 1H), 7.74 - 7.67 (m, 1H), 7.50 - 7.43 (m, 2H), 7.37 - 7.30 (m, 2H), 7.29 - 7.20 (m, 3H), 7.10 - 6.97 (m, 3H), 4.97 - 4.84 (m, 2H), 4.07 - 3.91 (m, 2H), 3.02 - 2.88 (m, 3H), 1.34 - 1.21 (m, 3H).

Compound **035** was prepared as described for the synthesis of Compound **001** with compound **4** and compound **K** as the starting materials. Also, step 1 was conducted at 90 °C for 12 hr and step 2 was conducted at 15 °C for 12 h. Compound **035** (5.48 mg, 13.58 umol, 13.18% yield, 100% purity) obtained as a white solid. **LCMS**: $m/z = 404.1$ ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 8.11 - 8.03$ (m, 1H), 7.75 - 7.66 (m, 1H), 7.32 - 7.20 (m, 4H), 7.16 - 6.92 (m, 5H), 4.96 - 4.86 (m, 2H), 4.04 - 3.91 (m, 2H), 2.99 - 2.90 (m, 3H), 1.26 - 1.19 (m, 3H)

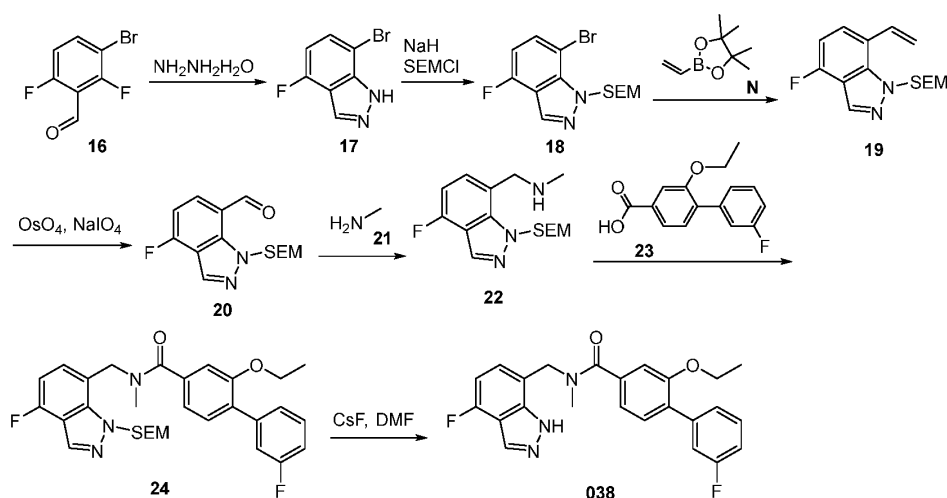
Compound **034** was prepared as described for the synthesis of compound **001** with compound **4** and compound **L** as the starting materials. Also, step 1 was conducted at 90 °C for 12 hr and step 2 was conducted at 15 °C for 12 h. Compound **034** (8.62 mg, 21.00 umol, 20.38% yield, 100% purity) obtained as a white solid. **LCMS**: $m/z = 411.1$ ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 8.28 - 8.04$ (m, 1H), 7.90 - 7.71 (m, 2H), 7.70 - 7.61 (m, 1H), 7.54 - 7.39 (m, 2H), 7.37 - 7.29 (m, 2H), 7.24 - 7.06 (m, 3H), 5.13 - 4.90 (m, 2H), 4.21 - 4.04 (m, 2H), 3.11 - 2.99 (m, 3H), 1.41 - 1.30 (m, 3H).

Scheme 5.



Compound **037** was prepared as described for the synthesis of compound **001** with compound **M** and compound **15** as the starting materials. Also, step 1 was conducted at 90 °C for 12 hr and step 2 was conducted at 15 °C for 12 h. Compound **037** (6.46 mg, 16.67 umol, 18.15% yield, 100% purity) was obtained as a red solid. **LCMS**: $m/z = 388.1$ ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 9.11 - 9.02$ (m, 1H), 8.08 - 8.04 (m, 1H), 8.03 - 7.97 (m, 1H), 7.96 - 7.92 (m, 1H), 7.73 - 7.68 (m, 1H), 7.44 - 7.39 (m, 1H), 7.23 - 7.20 (m, 1H), 7.11 - 7.03 (m, 3H), 4.97 - 4.84 (m, 2H), 4.11 - 3.98 (m, 2H), 2.97 - 2.86 (m, 3H), 1.34 - 1.26 (m, 3H).

Scheme 6.



To a solution of compound **16** (5 g, 22.62 mmol, 1 eq) in DMSO (50 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (4.53 g, 90.50 mmol, 4.40 mL, 4 eq), the mixture was stirred at 130 °C for 12 hr. LCMS showed there was desired mass. The mixture was cooled to room temperature and poured into water (200 mL). The aqueous phase was extracted with ethyl acetate (200 mL*3). The combined organic phase was washed with brine (200 mL*4), dried with anhydrous Na_2SO_4 , filtered and concentrated to give a crude product in vacuum. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate = 6 : 1 to 4 : 1. Compound **17** (1.05 g, 4.51 mmol, 19.94% yield, 92.4% purity) was obtained as white solid, confirmed by LCMS and ^1H NMR. LCMS: m/z = 215.0 ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 13.84 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J = 4.3, 8.2 Hz, 1H), 6.90 (dd, J = 8.5, 9.6 Hz, 1H)

To a solution of compound **17** (1.05 g, 4.88 mmol, 1 eq) in THF (15 mL) was added SEM-Cl (1.22 g, 7.32 mmol, 1.30 mL, 1.5 eq) and NaH (390.62 mg, 9.77 mmol, 60% purity, 2 eq) at 0 °C, the mixture was stirred at 20 °C for 12 hr. LCMS showed there was desired mass. The mixture was neutralized with saturated NH_4Cl solution (50 mL) at 0 °C and extracted with Ethyl acetate (3x50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate = 6 : 1 to 5 : 1. Compound **18** (1.5 g, crude) was obtained as colorless oil, confirmed by LCMS. LCMS: m/z = 347.0 ($\text{M}+2+\text{H}^+$)

Compound **19** was prepared as described for the synthesis of compound **19** with compound **18** and compound **N** as the starting materials and Cs_2CO_3 as the base. The mixture was filtered, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate = 15 : 1 to 14 : 1. Compound **19** was obtained as colorless oil. LCMS: m/z = 293.0 ($\text{M}+\text{H}^+$). ^1H

NMR (400 MHz, CHLOROFORM-*d*) δ = 8.15 - 8.09 (m, 1H), 7.57 - 7.41 (m, 2H), 6.86 (dd, *J* = 8.2, 9.2 Hz, 1H), 5.87 - 5.81 (m, 2H), 5.74 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.46 (dd, *J* = 1.1, 10.9 Hz, 1H), 3.65 (dd, *J* = 7.7, 8.8 Hz, 2H), 0.99 - 0.93 (m, 2H), 0.01 - -0.04 (m, 9H)

To a solution of compound **19** (220 mg, 752.33 μ mol, 1 *eq*) in acetone (10 mL) and
5 H₂O (2 mL) was added OsO₄ (19.13 mg, 75.23 μ mol, 3.90 μ L, 0.1 *eq*) and NaIO₄ (804.58 mg, 3.76 mmol, 208.44 μ L, 5 *eq*), the mixture was stirred at 20 °C for 3 hr. TLC (PE : EtOAc = 5 : 1, *R_f* = 0.6) showed the starting material was consumed completely and there was a new point. The reaction mixture was poured into saturated aqueous Na₂SO₃ (40 mL), the combined mixture was stirred for 2 h, the resulting solution was extracted by
10 dichloromethane (2x20 mL), the organic phase was dried and concentrated under vacuo to give a residue. The crude product was purified by prep-TLC (PE : EtOAc = 5 : 1). Compound **20** (80 mg, 244.57 μ mol, 32.51% yield, 90% purity) was obtained as yellow oil, confirmed by ¹H NMR. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 10.36 (s, 1H), 8.31 (s, 1H), 8.09 (dd, *J* = 5.4, 8.1 Hz, 1H), 7.09 (t, *J* = 8.4 Hz, 1H), 6.25 (s, 2H), 3.60 (t, *J* = 8.1 Hz, 2H), 0.94 (t, *J* =
15 8.1 Hz, 2H), 0.00 (s, 9H)

To a solution of compound **20** (70 mg, 237.77 μ mol, 1 *eq*) in MeOH (2 mL) was added compound **21** in MeOH (2 M, 356.66 μ L, 3 *eq*) and AcOH (1.43 mg, 23.78 μ mol, 1.36 μ L, 0.1 *eq*), the mixture was stirred at 20 °C for 2 hr, then the mixture was added NaBH₄ (13.49 mg, 356.66 μ mol, 1.5 *eq*), the mixture was stirred at 20 °C for 2 hr. LCMS showed
20 there was desired mass. The reaction mixture was poured into NH₄Cl (5 mL), then the mixture was added Na₂CO₃ (0.05 g), the solution was filtered, the filtrate was concentrated under reduced pressure to give a residue. Then the solution was triturated in DCM and MeOH and collected by filtration, the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (HCl, column: 3_Phenomenex
25 Luna C18 75*30mm*3 μ m; mobile phase: [water(0.05% HCl)-ACN]; B%: 26%-46%, 9min), the purified solution was lyophilized. Compound **22** (50 mg, 161.58 μ mol, 67.95% yield, 100% purity) was obtained as white oil, confirmed by LCMS. LCMS: *m/z* = 310.1 (M+H⁺)

Compound **24** was prepared as described for the synthesis of compound **4** with compound **22** and compound **23** as the starting materials and step 1 at 20 °C for 12 hr. The
30 mixture was concentrated to give a crude product. The crude product was purified by prep-TLC (PE : EtOAc = 2 : 1). Compound **24** was obtained as a white oil. LCMS: *m/z* = 574.3 (M+Na). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 8.02 (s, 1H), 7.36 - 7.20 (m, 4H), 7.16 - 6.81 (m, 5H), 5.88 - 5.51 (m, 2H), 5.27 - 5.00 (m, 2H), 3.63 (s, 2H), 3.53 - 3.29 (m, 2H), 3.16 - 2.90 (m, 3H), 1.16 - 1.00 (m, 2H), 0.85 - 0.56 (m, 3H), -0.17 (s, 9H)

35 The solution of compound **24** (15 mg, 26.56 μ mol, 97.7% purity, 1 *eq*) in DMF (1 mL) was added CsF (40.35 mg, 265.63 μ mol, 9.79 μ L, 10 *eq*), the mixture was stirred at 80 °C for 48 hr. LCMS showed there was desired mass. The mixture was filtered and the filtrate

was concentrated in vacuo. The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(0.225%FA)-ACN]; B%: 50%-80%, 10min), the purified solution was lyophilized. Compound **038** (5.2 mg, 12.34 umol, 46.45% yield, 100% purity) was obtained as white solid, confirmed by LCMS and ¹H NMR.

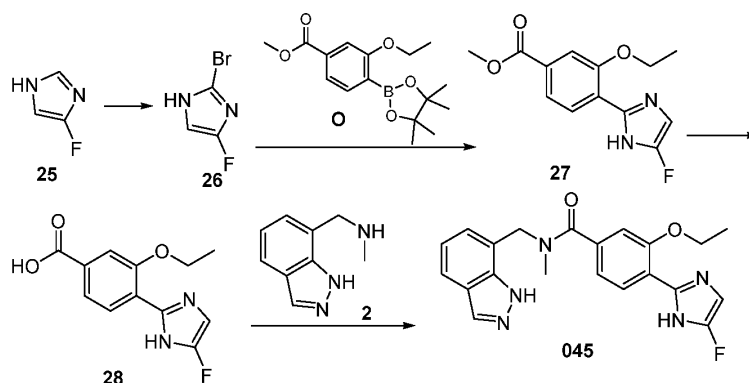
- 5 **LCMS**: m/z = 422.2 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.36 - 11.90 (m, 1H), 8.10 (s, 1H), 7.35 - 7.19 (m, 4H), 7.11 (dd, J = 4.6, 7.6 Hz, 1H), 7.00 - 6.91 (m, 3H), 6.66 (dd, J = 7.8, 9.6 Hz, 1H), 4.83 (s, 2H), 3.98 (q, J = 7.0 Hz, 2H), 2.92 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H).

- Compound 147** was prepared in a similar manner to **038** and was obtained as a
10 white solid (9.3 mg, 20.39 umol, 24.72% yield, 99% purity). **LCMS**: m/z = 452.2 (M+H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.24 - 11.86 (m, 1H), 8.20 - 8.18 (m, 1H), 7.39 - 7.28 (m, 4H), 7.20 (d, J = 7.6 Hz, 1H), 7.07 - 7.02 (m, 3H), 6.73 (d, J = 7.6 Hz, 1H), 5.97 (s, 1H), 5.83 (s, 1H), 4.91 (s, 2H), 4.06 (q, J = 7.0 Hz, 2H), 3.02 - 2.97 (m, 3H), 1.36 (t, J = 7.0 Hz, 3H).

- 15 **Compound 148** was prepared in a similar manner to **038** and was obtained as an off-white solid (11.3 mg, 25.48 umol, 36.55% yield, 100% purity). **LCMS**: m/z = 444.3 (M+H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.60 - 11.41 (m, 1H), 8.24 (s, 1H), 7.32 (br t, J = 7.9 Hz, 4H), 7.17 (br d, J = 7.0 Hz, 1H), 7.09 - 7.00 (m, 3H), 6.71 (br d, J = 7.0 Hz, 1H), 4.92 (s, 2H), 4.12 - 4.02 (m, 2H), 2.99 (s, 3H), 2.29 (br d, J = 4.8 Hz, 1H), 1.36 (br t, J =
20 6.9 Hz, 3H), 1.11 (br d, J = 6.8 Hz, 2H), 0.93 (br d, J = 3.4 Hz, 2H).

- Compound 149** was prepared in a similar manner to **038** and was obtained as brown solid (3.4 mg, 7.46 umol, 21.55% yield, 98.2 % purity). **LCMS**: m/z = 448.2 (M+H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 1.37 (br t, J = 6.88 Hz, 3 H) 2.99 (s, 3 H) 3.48 (s, 3 H) 4.06 (br d, J = 7.00 Hz, 2 H) 4.82 (s, 2 H) 4.96 (s, 2 H) 7.01 - 7.11 (m, 4 H) 7.25 (br d, J = 7.00
25 Hz, 1 H) 7.29 - 7.40 (m, 4 H) 8.23 (s, 1 H) 11.87 - 12.21 (m, 1 H).

Scheme 7.



To a solution of compound **25** (200 mg, 2.32 mmol, 1 eq) in CH₃CN (5 mL) and H₂O (5 mL) was added NaBr (239.10 mg, 2.32 mmol, 74.72 uL, 1 eq) and PhI(OAc)₂ (748.47 mg,

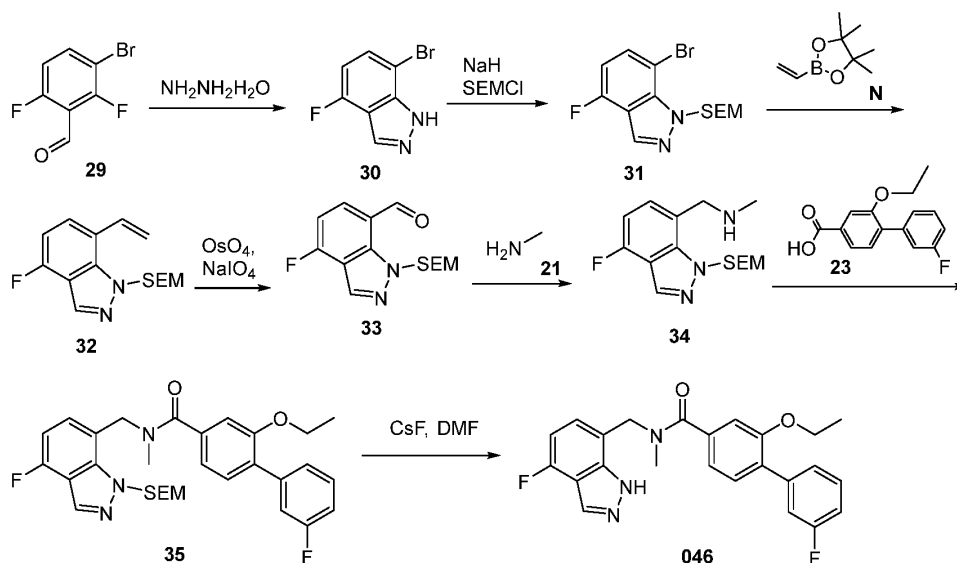
2.32 mmol, 1 eq) at 20°C under N₂. The reaction was poured into water (20 mL), and extracted by EA (20 mL*3). The organic layers was combined and washed by brine (20 ml), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica column (PE:EA=10:1,5:1) to give Compound **26** (350 mg, 2.04 mmol, 87.65% yield, 96% purity) as a light yellow solid, confirmed by LCMS. **LCMS**: m/z = 166.9 (M+H⁺)

Compound **27** was prepared as described for the synthesis of **001** with compound **26** and compound **O** as the starting materials, [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesulfonate as the catalyst, and K₃PO₄ as the base. Also, step 1 was conducted at 100°C for 4 hours. The reaction mixture was concentrated under vacuum. The residue was purified by silica column (PE/EA=10:1, 3:1) to give Compound **27** (32.76% yield, 91.6% purity) as a light yellow solid. **LCMS**: m/z = 265.0 (M+H⁺)

Compound **28** was prepared as described for the synthesis of compound **9** with compound **27** as the starting material, LiOH as the base, and step 1 at 50 °C for 2 hr. Also, the pH of the resulting solution was adjusted to 7. Compound **28** (88.54% yield, 96% purity) was obtained as a white solid. **LCMS**: m/z = 250.9 (M+H⁺)

To a solution of compound **28** (60 mg, 230.53 umol, 96.14% purity, 1 eq) in DMF (4 mL) was added compound **2** (74.32 mg, 461.06 umol, crude purity, 2 eq) and HATU (113.95 mg, 299.69 umol, 1.3 eq); DIEA (59.59 mg, 461.06 umol, 80.31 uL, 2 eq). The mixture was stirred at 20°C for 2 hours. The reaction was poured into water (20 mL), and extracted by EA (20 mL*3), the organic layers was combined and washed by brine (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by Prep-HPLC to give **045** (25.28 mg, 64.26 umol, 27.87% yield, 100% purity) as white solid, confirmed by LCMS and ¹H NMR. **LCMS**: m/z = 250.9 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃) δ ppm 12.00 (s, 1 H), 10.39 (s, 1 H), 8.13 (s, 1 H) 7.75-7.85 (m, 2 H), 7.27 - 7.31 (m, 2 H), 7.05 - 7.19 (m, 3 H), 4.96 (s, 2 H), 4.24 (q, J = 7.2 Hz, 2 H), 3.00 (s, 3 H) 1.54 - 1.57 (m, 3 H).

Scheme 8.



To a solution of compound **29** (5 g, 22.62 mmol, 1 eq) in DMSO (50 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (4.53 g, 90.50 mmol, 4.40 mL, 4 eq), the mixture was stirred at 130 °C for 12 hr. LCMS showed there was desired mass. The mixture was cooled to room temperature and poured into water (200 mL). The aqueous phase was extracted with ethyl acetate (200 mL*3). The combined organic phase was washed with brine (200 mL*4), dried with anhydrous Na_2SO_4 , filtered and concentrated to give a crude product in vacuum. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate = 6 : 1 to 4 : 1. Compound **30** (1.05 g, 4.51 mmol, 19.94% yield, 92.4% purity) was obtained as white solid, confirmed by LCMS and ^1H NMR. LCMS: m/z = 215.0 ($\text{M}+\text{H}^+$), ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 13.84 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J = 4.3, 8.2 Hz, 1H), 6.90 (dd, J = 8.5, 9.6 Hz, 1H)

To a solution of compound **30** (1.05 g, 4.88 mmol, 1 eq) in THF (15 mL) was added SEM-Cl (1.22 g, 7.32 mmol, 1.30 mL, 1.5 eq) and NaH (390.62 mg, 9.77 mmol, 60% purity, 2 eq) at 0 °C, the mixture was stirred at 20 °C for 12 hr. LCMS showed there was desired mass. The mixture was neutralized with saturated NH_4Cl solution (50 mL) at 0 °C and extracted with Ethyl acetate (3x50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate = 6 : 1 to 5 : 1. Compound **31** (1.5 g, crude) was obtained as colorless oil, confirmed by LCMS. LCMS: m/z = 347.0 ($\text{M}+2+\text{H}^+$)

Compound **32** was prepared as described for the synthesis of compound **001** with compound **31** and compound **N** as the starting materials and Cs_2CO_3 as the base. The mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate =

15 : 1 to 14 : 1. Compound **32** was obtained as colorless oil. **LCMS**: m/z = 293.0 ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) δ = 8.15 - 8.09 (m, 1H), 7.57 - 7.41 (m, 2H), 6.86 (dd, J = 8.2, 9.2 Hz, 1H), 5.87 - 5.81 (m, 2H), 5.74 (dd, J = 1.3, 17.2 Hz, 1H), 5.46 (dd, J = 1.1, 10.9 Hz, 1H), 3.65 (dd, J = 7.7, 8.8 Hz, 2H), 0.99 - 0.93 (m, 2H), 0.01 - -0.04 (m, 9H).

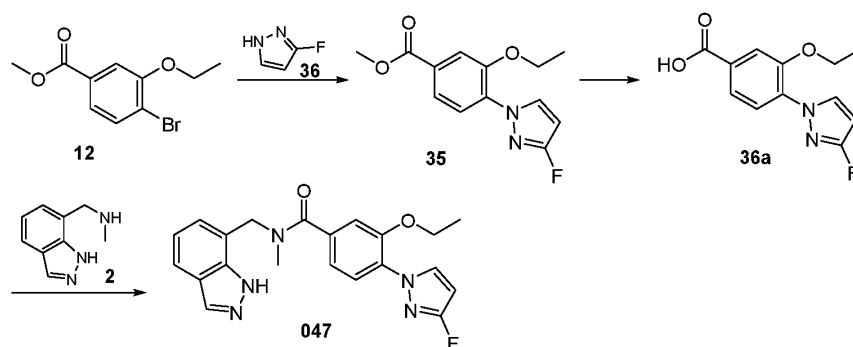
5 Compound **33** was prepared as described for the synthesis of compound **20** with compound **32** as the starting material. Compound **33** (32.51% yield, 90% purity) was obtained as a yellow oil. **1H NMR** (400 MHz, CHLOROFORM- d) δ = 10.36 (s, 1H), 8.31 (s, 1H), 8.09 (dd, J = 5.4, 8.1 Hz, 1H), 7.09 (t, J = 8.4 Hz, 1H), 6.25 (s, 2H), 3.60 (t, J = 8.1 Hz, 2H), 0.94 (t, J = 8.1 Hz, 2H), 0.00 (s, 9H)

10 To a solution of compound **33** (70 mg, 237.77 μ mol, 1 eq) in MeOH (2 mL) was added compound **21** in MeOH (2 M, 356.66 μ L, 3 eq) and AcOH (1.43 mg, 23.78 μ mol, 1.36 μ L, 0.1 eq), the mixture was stirred at 20 °C for 2 hr, then the mixture was added NaBH₄ (13.49 mg, 356.66 μ mol, 1.5 eq), the mixture was stirred at 20 °C for 2 hr. LCMS showed there was desired mass. The reaction mixture was poured into NH₄Cl (5 mL), then the
15 mixture was added Na₂CO₃ (0.05 g), the solution was filtered, the filtrate was concentrated under reduced pressure to give a residue. Then the solution was triturated in DCM and MeOH and collected by filtration, the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (HCl, column: 3_Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: [water(0.05% HCl)-ACN]; B%: 26%-46%, 9min), the
20 purified solution was lyophilized. Compound **34** (50 mg, 161.58 μ mol, 67.95% yield, 100% purity) was obtained as white oil, confirmed by LCMS. **LCMS**: m/z = 310.1 ($M+H^+$)

 Compound **35** was prepared as described for the synthesis of compound **4** with compound **34** and compound **23** as the starting materials and step 1 at 20 °C for 12 hr. The crude product was purified by prep-TLC (PE : EtOAc = 2 : 1). Compound **35** was obtained as
25 a white oil. **LCMS**: m/z = 574.3 ($M+Na$). **1H NMR** (400 MHz, CHLOROFORM- d) δ = 8.02 (s, 1H), 7.36 - 7.20 (m, 4H), 7.16 - 6.81 (m, 5H), 5.88 - 5.51 (m, 2H), 5.27 - 5.00 (m, 2H), 3.63 (s, 2H), 3.53 - 3.29 (m, 2H), 3.16 - 2.90 (m, 3H), 1.16 - 1.00 (m, 2H), 0.85 - 0.56 (m, 3H), -
0.17 (s, 9H)

 Compound **046** was prepared as described for the synthesis of compound **038** with
30 compound **35** as the starting material. Compound **046** (5.2 mg, 12.34 μ mol, 46.45% yield, 100% purity) was obtained as a white solid. **LCMS**: m/z = 422.2 ($M+H^+$) **1H NMR** (400 MHz, CHLOROFORM- d) δ = 12.36 - 11.90 (m, 1H), 8.10 (s, 1H), 7.35 - 7.19 (m, 4H), 7.11 (dd, J = 4.6, 7.6 Hz, 1H), 7.00 - 6.91 (m, 3H), 6.66 (dd, J = 7.8, 9.6 Hz, 1H), 4.83 (s, 2H), 3.98 (q, J = 7.0 Hz, 2H), 2.92 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H).

35 **Scheme 9.**



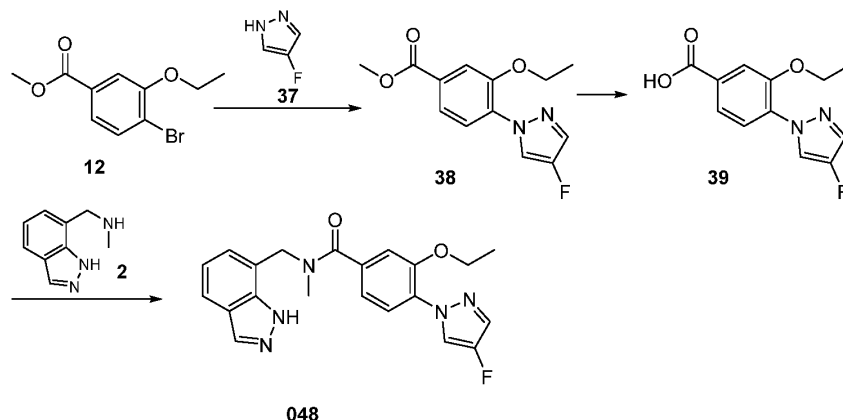
To a solution of compound **12** (200 mg, 764.20 μmol , 99% purity, 1 *eq*) and compound **36** (197.32 mg, 2.29 mmol, 3 *eq*) in DMF (6 mL) was added (1*R*,2*R*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (21.74 mg, 152.84 μmol , 0.2 *eq*) and CuI (14.55 mg, 76.42 μmol , 0.1 *eq*) and K_2CO_3 (211.24 mg, 1.53 mmol, 2 *eq*) under N_2 , the mixture was stirred at 110°C for 12 hours. The reaction solution was poured into water (20 mL), and then extracted by EA (10 mL*3). The organic layers were combined and washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The residue was purified by silica column (PE: EA=20:1, 10:1 UV 254nm) (TLC, PE:EA = 10:1, UV 254nm) to give Compound **35** (50 mg, 189.21 μmol , 24.76% yield, 100% purity) as a white solid, confirmed by LCMS and HNMR and 2D-NMR-LCMS(HMBC-NOE). **LCMS**: m/z = 265.2 ($\text{M}+\text{H}^+$). **^1H NMR** (400 MHz, CDCl_3) δ ppm 8.20-8.19 (m, 1 H), 7.87(d, J = 8.4 Hz, 1 H), 7.70-7.74 (m, 2 H) 6.02-6.00 (m, 1 H), 4.23 (q, J = 6.8 Hz, 3 H), 3.94 (s, 3 H), 1.50 (t, J = 6.8 Hz, 3 H).

Compound **36a** was prepared as described for the synthesis of compound **9** with compound **35** as the starting material, step 1 at 20 °C for 1 h. Also, the pH of the resulting solution was adjusted to 5. Compound **36a** (98.57% yield) was obtained as a white solid. **LCMS**: m/z = 251.1 ($\text{M}+\text{H}^+$).

To a solution of compound **36** (30 mg, 119.89 μmol , 1 *eq*) and compound **2** (38.65 mg, 239.78 μmol , 2 *eq*) in DMF (3 mL) was added DIEA (46.49 mg, 359.68 μmol , 62.65 μL , N/A purity, 3 *eq*) and HATU (68.38 mg, 179.84 μmol , N/A purity, 1.5 *eq*) at 20°C. The mixture was stirred at 20°C for 1 hour. The reaction solution was poured into water (20 mL), then extracted by EA (20 mL*2). The organic layers was combined and washed by brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The residue was purified by prep-HPLC(base): column: Waters Xbridge 150*25mm*5 μm ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 34%-64%, 9min and lyophilization to give **047** (40.03 mg, 101.75 μmol , 84.87% yield, 100% purity) as a white solid, confirmed by LCMS (220nm) and HNMR. **LCMS**: m/z = 394.2 ($\text{M}+\text{H}^+$). **^1H NMR** (400 MHz, CDCl_3) δ ppm 8.14 (s, 1 H) 8.10-8.09 (m, 1H) 7.79(d, J = 8.4 Hz, 2 H) 7.27(d, J = 6.8

Hz, 1 H) 7.12-7.17 (m, 3 H) 5.98 - 6.00 (m, 1 H) 4.96 (s, 2 H) 4.14 - 4.19 (m, 2 H) 2.98 (s, 3 H) 1.46 (t, J = 6.8 Hz, 3 H).

Scheme 10.

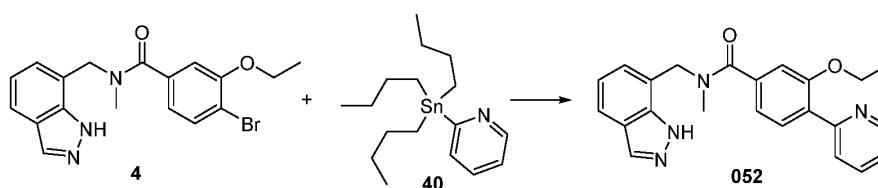


5 Compound **38** was prepared as described for the synthesis of compound **35** with compound **12** and compound **37** as the starting materials. Compound **38** (44.57% yield, 100% purity) was obtained as a white solid. **LCMS**: $m/z = 265.1$ ($M+H^+$). **1H NMR** (400 MHz, $CDCl_3$) δ ppm 8.23 (s, 1 H) 7.92 (d, $J = 8.4$ Hz, 1 H) 7.70 - 7.75 (m, 2 H) 7.60 (d, $J = 4.0$ Hz, 1 H) 4.20 - 4.25 (m, 2 H) 3.94 (s, 3 H) 1.51 (t, $J = 6.8$ Hz, 3 H).

10 Compound **39** was prepared as described for the synthesis of compound **9** with compound **38** as the starting material, step 1 at 20 °C for 1 h. Also, the pH of the resulting solution was adjusted to 5. Compound **39** (79.20% yield) was obtained as a white solid.

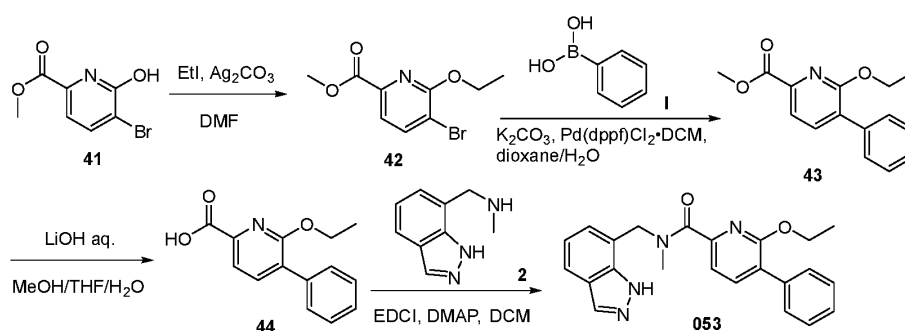
To a solution of compound **39** (50.00 mg, 199.82 μ mol, 1 *eq*) and compound **2** (64.42 mg, 399.64 μ mol, 2 *eq*) in DMF (3 mL) was added DI ETOAC (77.47 mg, 599.46 μ mol, 104.41 μ L, 3 *eq*) and HATU (113.97 mg, 299.73 μ mol, 1.5 *eq*) at 20°C, the mixture was stirred at 20°C. The reaction solution was poured into water (20 mL), then extracted by EtOAc (20 mL*2), the organic layers was combined and washed by brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The residue was purified by prep-HPLC(base): column: Waters Xbridge 150*25mm* 5 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 30%-60%, 9min and lyophilization to give **048** (53.67 mg, 136.42 μ mol, 68.27% yield, 100% purity) as a white solid, confirmed by LCMS and HNMR. **LCMS**: $m/z = 394.2$ ($M+H^+$). **1H NMR** (400 MHz, $CDCl_3-d_6$) δ ppm 8.16 (s, 1 H), 8.13 (d, $J = 4.4$ Hz, 1 H), 7.85-7.78 (m, 2 H), 7.57 (d, $J = 4.0$ Hz, 1 H), 7.28 (d, $J = 13.6$ Hz, 1 H), 7.18-7.14 (m, 3 H), 4.96 (s, 2 H), 4.17 (q, $J = 7.2$ Hz, 2 H), 2.99 (s, 3 H), 1.47 (t, $J = 7.2$ Hz, 3 H).

Scheme 11.



To a mixture of compound **4** (50 mg, 128.78 μmol , 1 *eq*), compound **40** (56.89 mg, 154.54 μmol , 1.2 *eq*), LiCl (54.60 mg, 1.29 mmol, 26.37 μL , 10 *eq*) in DMF (2 mL) was added Pd(PPh₃)₄ (14.88 mg, 12.88 μmol , 0.1 *eq*) under N₂ atmosphere, then the reaction mixture was stirred at 110 °C for 12 hr. LCMS: *m/z* = 387.1 (M+H⁺) showed compound **4** consumed completely and desired mass was detected. The reaction mixture was concentrated to give a residue. The solution was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5 μm ; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 33%-63%, 2min), the purified solution was lyophilized to give a white solid. Compound **052** (15.8 mg, 39.80 μmol , 30.90% yield, 97.342% purity) was obtained as a white solid. LCMS and ¹H NMR confirmed. LCMS: *m/z* = 387.3 (M+H⁺). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 12.29 - 11.70 (m, 1H), 8.78 - 8.70 (m, 1H), 8.16 - 8.09 (m, 1H), 7.98 - 7.91 (m, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 - 7.27 (m, 2H), 7.10 (s, 3H), 4.97 (s, 2H), 4.19 - 4.06 (m, 2H), 2.99 (s, 3H), 1.40 (s, 3H).

15 Scheme 12.



Compound **42** was prepared as described for the synthesis of compound **8** with compound **41** and EtI as the starting materials, Ag₂CO₂ as the base, and step 1 at 60 °C for 12 hr. The residue was purified on silica gel column chromatography (PE: EA=9:1 to 5:1) to give the product. The product compound **42** (35.69% yield) was obtained as yellow solid.

Compound **43** was prepared as described for the synthesis of compound **001** with compound **42** and compound **I** as the starting materials. LCMS: *m/z* = 258.2 (M+H⁺) showed Compound **42** was consumed completely and a main peak with desired mass was detected. The mixture was filtered and the filtrate was poured into water (10mL). The suspension was extracted with EtOAc (10mL x 3). The combined organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by prep-TLC

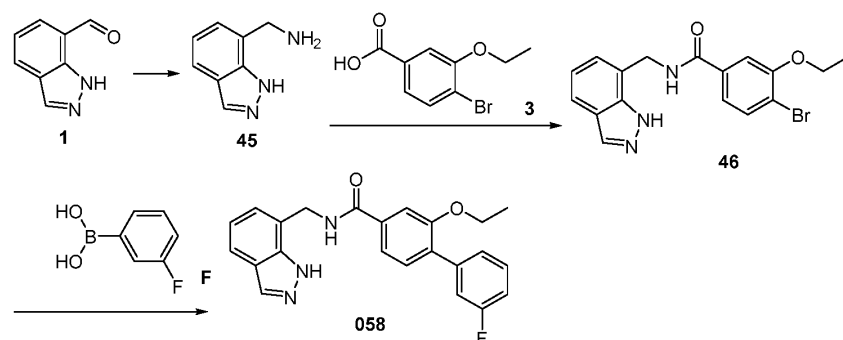
(PE: EA=5:1) to give the product (R_f = 0.7). The product compound **43** (80.49% yield, 98% purity) was obtained as a yellow solid. LCMS: m/z = 258.2 ($M+H^+$)

Compound **44** was prepared as described for the synthesis of compound **9** with compound **43** as the starting material, $LiOH \cdot H_2O$ as the base, and step 1 at 30 °C for 12 h. Also, the pH of the resulting solution was adjusted to 4-5. The crude product compound **44** was obtained as a white solid. LCMS: m/z = 244.1 ($M+H^+$)

Compound **053** was prepared as described for the synthesis of compound **4** with compound **44** and compound **2** as the starting materials. The residue was purified by prep-HPLC (FA:column: Phenomenex luna C18 150*25mm* 10um;mobile phase:

[water(0.225%FA)-ACN];B%: 51%-81%,10min), and the eluent was lyophilized to give the product. The product **053** (20 mg, 49.84 μ mol, 30.31% yield, 96.3% purity) was obtained as a white solid. LCMS: m/z = 387.3 ($M+H^+$). 1H NMR (400 MHz, $CHCl_3$ -d) δ = 8.09 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.60 - 7.51 (m, 2H), 7.46 - 7.37 (m, 3H), 7.37 - 7.32 (m, 1H), 7.28 - 7.20 (m, 1H), 7.14 - 7.06 (m, 1H), 4.96 (s, 2H), 4.39 (q, J = 7.0 Hz, 2H), 3.15 (s, 3H), 1.40 - 1.13 (m, 3H).

Scheme 13.



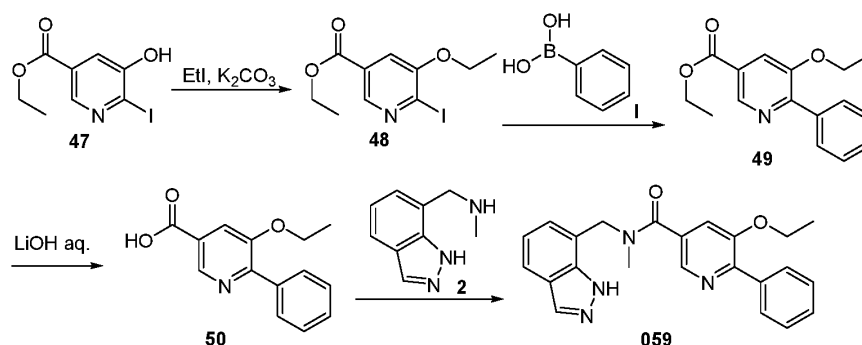
To a solution of compound **1** (100 mg, 684.25 μ mol, 1 eq) in MeOH (3 mL) and $NH_3 \cdot H_2O$ (3 mL) was added nickel (10 mg, 170.38 μ mol, 2.49e-1 eq) under N_2 , the mixture was stirred at 40 °C under H_2 (50 Psi) for 12 h. LCMS showed there was no target mass. After the reaction was completed, the mixture was filtered under N_2 atmosphere, the filtrate was concentrated to give a crude product. The crude product used for next step without further purification. Compound **45** (100 mg, crude) was obtained as yellow solid.

Compound **46** was prepared as described for the synthesis of compound **4** with compound **3** and compound **45** as the starting materials. The crude product was purified by prep-TLC (PE : EtOAc = 1 : 1). Compound **46** (28.76% yield, 97.5% purity) was obtained as a yellow solid. LCMS: m/z = 374.0 ($M+H^+$).

Compound **058** was prepared as described for the synthesis of compound **001** using compound **46** and compound **F** as the starting materials and step to at 20 °C for 12 hr. The crude product was purified by prep-HPLC (Base, column: Waters Xbridge 150*25mm*

5 μm ; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 40%-70%, 8 min). The purified solution was lyophilized. Compound **058** (6.2 mg, 15.92 μmol , 19.86% yield, 100% purity) was obtained as a white solid. LCMS: $m/z = 390.1$ ($M+H^+$). $^1\text{H NMR}$ (400 MHz, CHLOROFORM- d) $\delta = 8.11$ (s, 1H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.57 (s, 1H), 7.44 - 7.29 (m, 5H), 7.15 - 7.10 (m, 1H), 7.09 - 7.02 (m, 1H), 6.89 - 6.81 (m, 1H), 4.97 (d, $J = 6.7$ Hz, 2H), 4.16 (q, $J = 7.0$ Hz, 2H), 1.41 (t, $J = 7.0$ Hz, 3H).

Scheme 14.



10 Compound **48** was prepared as described for the synthesis of compound **8** with compound **47** and EtI as the starting materials, K_2CO_2 as the base, and step 1 at 50 °C for 12 hr. Compound **48** (86.70% yield, 95% purity) was obtained as a white solid and used in the next step. LCMS: $m/z = 321.8$ ($M+H^+$). $^1\text{H NMR}$ (400 MHz, CHLOROFORM- d) $\delta = 8.56$ (d, $J = 1.6$ Hz, 1H), 7.50 (d, $J = 1.7$ Hz, 1H), 4.42 (d, $J = 7.1$ Hz, 2H), 4.18 (d, $J = 7.0$ Hz, 2H), 1.54 (t, $J = 7.0$ Hz, 3H), 1.41 (t, $J = 7.1$ Hz, 3H)

15 Compound **49** was prepared as described for the synthesis of compound **001** with compound **48** and compound **I** as the starting materials. LCMS: $m/z = 272.0$ ($M+H^+$) showed **48** consumed completely and desired mass was detected. The reaction mixture was extracted with ethyl acetate and the organic phase was concentrated to give a residue. The solution was purified by prep-TLC (PE:EA=5:1, $R_f=0.5$) and the purified solution was concentrated to give a white solid. Compound **49** (58.24% yield, 98.418% purity) was obtained as a white solid and used in the next step. LCMS: $m/z = 272.0$ ($M+H^+$)

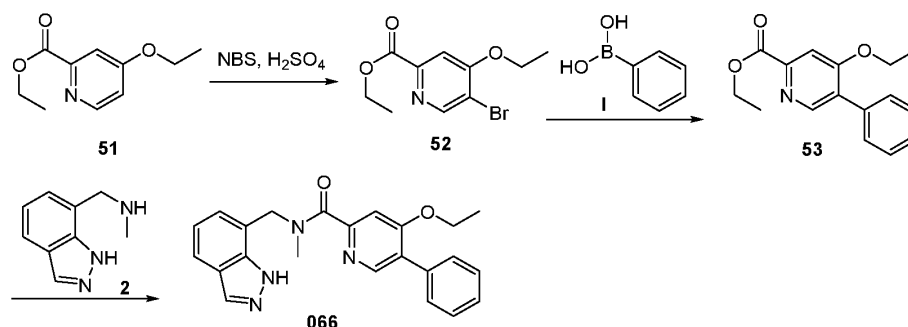
20 Compound **50** was prepared as described for the synthesis of compound **9** with compound **49** as the starting material, LiOH as the base, and step 1 at 20 °C for 2 h. Compound **50** was obtained as a white solid and used to the next step. LCMS: $m/z = 244.2$ ($M+H^+$)

25 Compound **059** was prepared as described for the synthesis of compound **4** with compound **50** and compound **2** as the starting materials and step 1 at 30 °C for 2 hr. The reaction mixture was concentrated to give a residue. The solution was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5 μm ; mobile phase: [water (10mM NH_4HCO_3)-

ACN]; B%: 39%-69%, 8min), the purified solution was lyophilized to give a white solid.

Compound **059** (21.8 mg, 56.41 μ mol, 27.45% yield, 100% purity) was obtained as a white solid. **LCMS**: m/z = 387.0 ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) δ = 12.21 - 11.57 (m, 1H), 8.44 - 8.32 (m, 1H), 8.16 - 8.05 (m, 1H), 7.86 (br s, 2H), 7.81 - 7.71 (m, 1H), 7.48 - 7.34 (m, 4H), 7.26 - 7.21 (m, 1H), 7.15 - 7.08 (m, 1H), 4.96 (s, 2H), 4.09 (d, J = 6.9 Hz, 2H), 3.04 (s, 3H), 1.42 (t, J = 6.9 Hz, 3H).

Scheme 15.



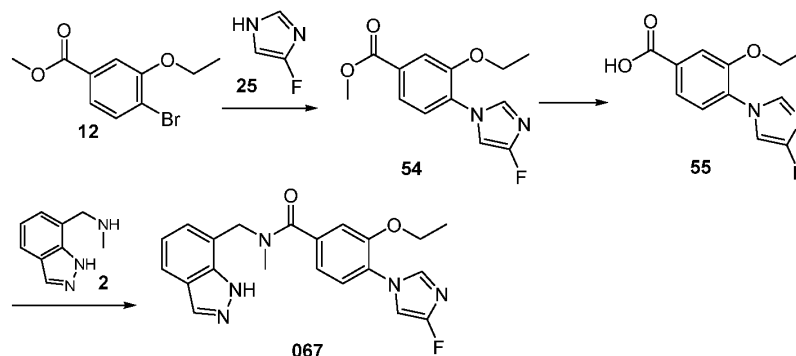
A mixture of compound **51** (230 mg, 1.18 mmol, 1 eq) and NBS (377.46 mg, 2.12 mmol, 1.8 eq) in H_2SO_4 (8 mL) was stirred at 25 °C for 12 hrs. TLC (petroleum ether/ethyl acetate=3/1, UV=254 nm) showed a spot was formed. The reaction mixture was added into saturated $NaHCO_3$ solution (200 mL) dropwisely at 0 °C. The mixture was extracted with ethyl acetate (80 mLx3). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , PE/EA=10/1 to 3/1) to give compound **52** (270 mg, 935.75 μ mol, 79.42% yield, 95% purity) as a white solid. **LCMS**: m/z = 274.1 ($M+H^+$). **1H NMR** (400 MHz, DMSO- d_6) δ = 8.69 (s, 1H), 7.65 (s, 1H), 4.37 - 4.29 (m, 4H), 1.39 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H).

Compound **53** was prepared as described for the synthesis of compound **001** with compound **52** and compound **I** as the starting materials and step 1 at 100 °C for 4 hrs. The mixture was concentrated under vacuum to give a residue. The residue was dissolved into MeOH (10 mL) and filtered. The filtrate was purified by reversed phase (column: spherical C18 20-35 mm 100A 80g; mobile phase: [water (0.5%FA)-ACN]; B%: 45%-53%, 20 min) and concentrated under vacuum to give compound **53** (23.25% yield, 89% purity) as a white solid. **LCMS**: m/z = 244.1 ($M+H^+$).

Compound **066** was prepared as described for the synthesis of compound **4** with compound **53** and compound **2** as the starting materials and step 1 at 25 °C for 12 hrs. The mixture was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water (0.225%FA)-ACN]; B%: 42%-72%, 7min) and lyophilized to give compound **066** (25.3 mg,

65.34 μmol , 35.32% yield, 99.8% purity) as a white solid. **LCMS**: $m/z = 387.1$ ($M+H^+$). **^1H NMR** (400 MHz, $\text{CHLOROFORM-}d$) $\delta = 8.44$ (br s, 1H), 8.15 (s, 1H), 7.80 (br d, $J = 8.0$ Hz, 1H), 7.59 (br d, $J = 7.2$ Hz, 2H), 7.51 - 7.36 (m, 4H), 7.28 - 7.20 (m, 1H), 7.18 - 7.09 (m, 1H), 5.05 - 4.82 (m, 2H), 4.34 - 4.17 (m, 2H), 3.20 - 2.87 (m, 3H), 1.51 - 1.42 (m, 3H).

5 **Scheme 16.**

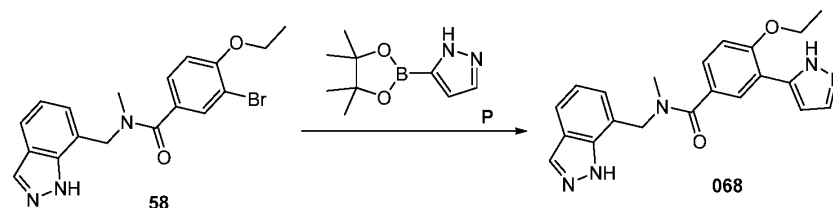


Compound **54** was prepared as described for the synthesis of compound **35** with compound **12** and compound **25** as the starting materials. The residue was purified by silica column (PE: EA = 20:1, 51 UV254nm) (TLC, PE: EA = 5:1, UV254nm) to give compound **54** (12.38% yield, 100% purity) as a white solid. **LCMS**: $m/z = 265.2$ ($M+H^+$). **^1H NMR** (400 MHz, CDCl_3) δ ppm 7.71-7.73 (m, 2 H) 7.54 (d, $J = 1.6$ Hz, 1 H) 7.27-7.34 (m, 1 H) 6.82 - 6.85 (m, 1 H) 4.16-4.21 (m, 2 H) 3.97 (s, 3 H) 1.45 (t, $J = 6.8$ Hz, 3 H).

Compound **55** was prepared as described for the synthesis of compound **9** with compound **54** as the starting material and step 1 at 20 °C for 1 h. Also, the pH of the resulting solution was adjusted to 5. Compound **55** (99.80% yield) was obtained as a white solid. **LCMS**: $m/z = 251.1$ ($M+H^+$).

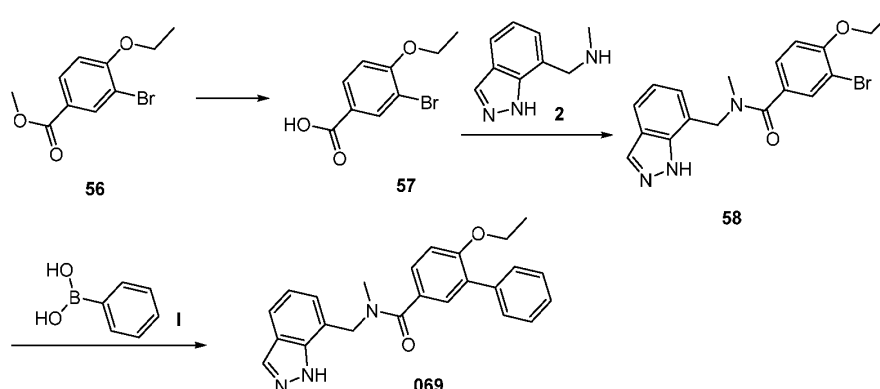
To a solution of compound **55** (20 mg, 79.93 μmol , 1 eq) and compound **2** (25.77 mg, 159.86 μmol , N/A purity, 2 eq) in DMF (3 mL) was added DIEA (51.65 mg, 399.64 μmol , 69.61 μL , 5 eq) and HATU (45.59 mg, 119.89 μmol , 1.5 eq). The mixture was stirred at 20°C for 1 hour. The reaction solution was poured into water (20 mL), then extracted by EA (20 mL*2), the organic layers was combined and washed by brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The residue was purified by prep-HPLC(base): column: Waters Xbridge 150*25mm* 5 μm ;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 32%-62%,9min and lyophilization to give **067** (13.17 mg, 33.48 μmol , 41.88% yield, 100% purity) as a white solid, confirmed by LCMS and HNMR. **LCMS**: $m/z = 394.2$ ($M+H^+$). **^1H NMR** (400 MHz, CDCl_3) δ ppm 8.17 (s, 1 H), 7.81 (d, $J = 8.0$ Hz, 1 H) 7.51 (s, 1 H), 7.34-7.29 (m, 2 H), 7.20-7.17 (m, 2 H), 7.10 (d, $J = 7.6$ Hz, 1 H), 6.79 (d, $J = 8$ Hz, 1 H), 4.97 (s, 2 H), 4.13 (q, $J = 6.8$ Hz, 2 H), 3.00 (s, 3 H) 1.42(t, $J = 6.8$ Hz, 3 H).

Scheme 17.



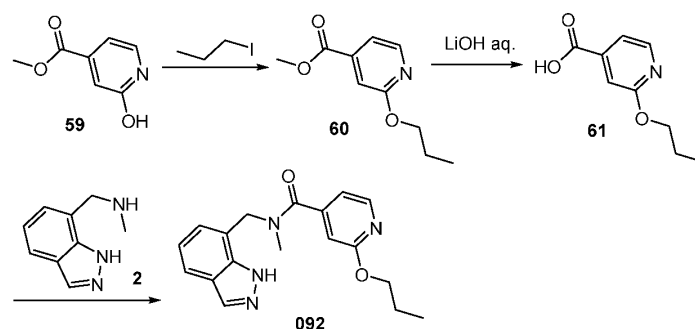
Compound **068** was prepared as described for the synthesis of compound **001** with compound **58** and compound **P** as the starting materials, Cs₂CO₃ as the base, and step 2 at 15 °C for 12 h. Compound **068** (10.34 mg, 27.54 μmol, 21.39% yield, 100% purity) was obtained as a yellow solid. LCMS: *m/z* = 376.0 (M+H⁺). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.14 (s, 1H), 7.97 - 7.86 (m, 1H), 7.84 - 7.76 (m, 1H), 7.73 - 7.59 (m, 1H), 7.47 - 7.42 (m, 1H), 7.30 (s, 1H), 7.18 - 7.11 (m, 1H), 7.07 - 6.99 (m, 1H), 6.89 - 6.53 (m, 1H), 4.98 (s, 2H), 4.39 - 4.22 (m, 2H), 3.02 (s, 4H), 1.60 (s, 3H).

10 Scheme 18.



Compound **069** was prepared as described for the synthesis of compound **001** with compound **58** and compound **I** as the starting materials, K₂CO₃ as the base, step 1 at 90 °C for 12 h, and step 2 at 15 °C for 12 h. The crude product was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5μm; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 40%-70%, 9min), and the purified solution was lyophilized. **069** (11.07 mg, 28.72 μmol, 33.45% yield, 100% purity) was obtained as a white solid. LCMS: *m/z* = 386.1 (M+H⁺). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.12 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.55 (br d, *J* = 7.3 Hz, 2H), 7.50 (s, 2H), 7.42 (s, 2H), 7.38 - 7.31 (m, 1H), 7.28 - 7.25 (m, 1H), 7.17 - 7.08 (m, 1H), 7.03 - 6.95 (m, 1H), 4.97 (s, 2H), 4.18 - 4.02 (m, 2H), 3.03 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H).

Scheme 19.

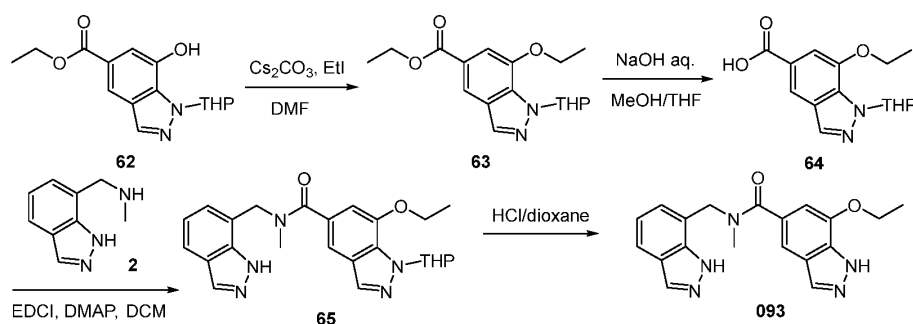


Compound **60** was prepared as described for the synthesis of compound **8** with compound **59** and 1-iodopropane as the starting materials, Ag_2CO_2 as the base, CHCl_3 and DMF as the solvent mixture, and step 1 at 30 °C for 12 hr. The residue was purified by prep-TLC (Petroleum ether: Ethyl acetate= 2: 1) to give Compound **60** (90 mg, 461.03 μmol , 35.30% yield) as a colorless liquid. **¹H NMR** (400 MHz, METHANOL- d_4) δ ppm 8.24 (d, $J=5.13$ Hz, 1 H) 7.39 (d, $J=5.26$ Hz, 1 H) 7.25 (s, 1 H) 4.26 (t, $J=6.54$ Hz, 2 H) 3.92 (s, 3 H) 1.80 (m, $J=7.07$ Hz, 2 H) 1.03 (t, $J=7.46$ Hz, 3 H)

Compound **61** was prepared as described for the synthesis of compound **9** with compound **60** as the starting material and $\text{LiOH}\cdot\text{H}_2\text{O}$ as the base. Also, the reagents were combined at 20 °C and step 1 was conducted at 30 °C for 2 h. Also, the pH of the resulting solution was adjusted to 3. Compound **61** (70 mg, 386.34 μmol , 83.80% yield) was obtained as a white solid and used directly in the next step. **LCMS**: $m/z = 180.0$ ($\text{M}+\text{H}^+$).

Compound **092** was prepared as described for the synthesis of compound **4** with compound **61** and compound **2** as the starting materials. The mixture was concentrated under vacuo to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (0.225%FA)-ACN];B%: 35%-65%,10min) to give a solution. The solution was lyophilized to give **092** (29 mg, 89.40 μmol , 23.14% yield, 100% purity) as a white solid. **LCMS**: $m/z = 325.1$ ($\text{M}+\text{H}^+$). **¹H NMR** (400 MHz, METHANOL- d_4) $\delta = 8.24 - 8.17$ (m, 1H), 8.13 - 8.05 (m, 1H), 7.73 (s, 1H), 7.41 - 7.29 (m, 1H), 7.28 - 7.16 (m, 1H), 6.92 (m, $J = 4.6$ Hz, 1H), 6.74 (s, 1H), 5.02 (s, 1H), 4.79 (s, 1H), 4.29 - 4.07 (m, 2H), 3.22 - 2.89 (m, 3H), 1.85 - 1.65 (m, 2H), 1.06 - 0.90 (m, 3H).

Scheme 20.



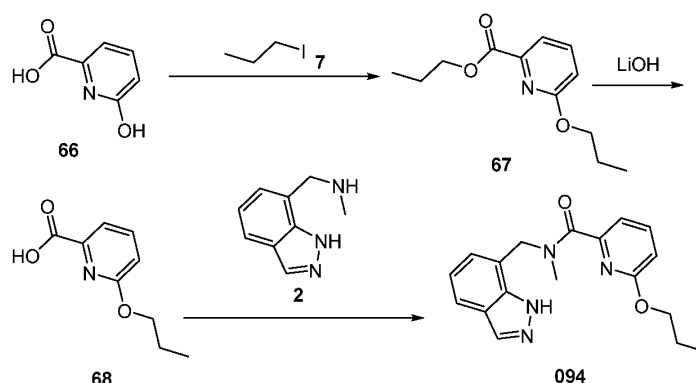
Compound **63** was prepared as described for the synthesis of compound **8** with compound **62** and EtI as the starting materials. The crude product compound **63** was obtained as yellow solid. LCMS: $m/z = 235.2$ ($M+H^+$).

- 5 Compound **64** was prepared as described for the synthesis of compound **9** with compound **63** as the starting material and step 1 at 30 °C for 12 hr. Also, the pH of the resulting solution was adjusted to 4-5. The crude product compound **64** was obtained as a light yellow solid. LCMS: $m/z = 207.1$ ($M+H^+$)

- 10 Compound **65** was prepared as described for the synthesis of compound **4** with compound **64** and compound **2** as the starting materials. The crude product compound **65** was obtained as a light yellow solid. LCMS: $m/z = 434.2$ ($M+H^+$)

- 15 A solution of compound **65** (150 mg, 346.02 μmol , 1 eq) in HCl/dioxane (10 mL) was stirred at 25 °C for 1 hr. LCMS: $R_t = 0.827$ min, $m/z = 350.1$ ($M+H^+$) showed compound **65** was consumed completely and a main peak with desired mass was detected. The mixture was concentrated in vacuo and the residue was basified by TEA until pH=8-9. The mixture was purified by prep-HPLC (column: Waters Xbridge 150*25mm*5 μm ; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 22%-52%, 9min), the eluent was lyophilized to give the product. The product **093** (20.63 mg, 58.15 μmol , 16.81% yield, 98.49% purity) was obtained as white solid. LCMS and ^1H NMR confirmed. LCMS: $m/z = 434.2$ ($M+H^+$). ^1H NMR (400 MHz, CHLOROFORM-d) $\delta = 8.15$ (s, 1H), 8.08 (s, 1H), 7.79 (d, $J = 7.8$ Hz, 1H), 7.44 (s, 1H), 7.31 (br d, $J = 6.2$ Hz, 1H), 7.15 (t, $J = 7.3$ Hz, 1H), 6.89 (s, 1H), 4.99 (s, 2H), 4.26 (q, $J = 6.8$ Hz, 2H), 3.03 (s, 3H), 1.53 (t, $J = 7.0$ Hz, 3H).

Scheme 21.



Compound **67** was prepared as described for the synthesis of compound **8** with compound **66** and 1-iodopropane as the starting materials, Ag_2CO_2 as the base, CHCl_3 as the solvent, and step 1 at 60 °C for 24 hr. The residue was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate (1/0 to 6/1) and concentrated under reduced pressure to give Compound **67** (93.46% yield, 100% purity) as a colorless oil. **LCMS**: $m/z = 224.1$ ($\text{M}+\text{H}^+$)

Compound **68** was prepared as described for the synthesis of compound **9** with compound **67** as the starting material, LiOH as the base, and step 1 at 50 °C for 1 hr. Also, the pH of the resulting solution was adjusted to 6. Compound **68** was obtained as a white solid and used for the next step without further purification. **LCMS**: $m/z = 179.8$ ($\text{M}+\text{H}^+$)

Compound **094** was prepared as described for the synthesis of compound **4** with compound **68** and compound **2** as the starting materials. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 41%-71%, 9min) and lyophilized to give Compound **094** (45.6 mg, 137.63 umol, 49.87% yield, 97.9% purity) as a colorless oil. **LCMS**: $m/z = 179.8$ ($\text{M}+\text{H}^+$). **^1H NMR**: (400 MHz, CHLOROFORM-d) $\delta = 8.03 - 7.98$ (m, 1H), 7.67 - 7.62 (m, 1H), 7.57 - 7.50 (m, 1H), 7.11 (br d, $J = 6.8$ Hz, 2H), 7.05 - 6.97 (m, 1H), 6.76 (br d, $J = 8.4$ Hz, 1H), 4.90 - 4.64 (m, 2H), 4.19 - 3.97 (m, 2H), 2.76 (s, 3H), 1.73 - 1.55 (m, 2H), 0.96 - 0.73 (m, 3H).

Compound **172** was prepared in a similar manner to **094** and isolated as a white solid (8.1 mg, 18.39 umol, 13.67% yield, 100 % purity). **LCMS**: $m/z = 441.0$ ($\text{M}+\text{H}^+$) **^1H NMR** (400 MHz, CHLOROFORM-d) δ ppm 11.62 - 12.36 (m, 1 H) 8.14 (s, 1 H) 8.03 (s, 1 H) 7.78 (br d, $J=8.00$ Hz, 2 H) 7.51 (d, $J=7.88$ Hz, 1 H) 7.37 (d, $J=8.13$ Hz, 1 H) 7.29 (br d, $J=6.88$ Hz, 1 H) 7.14 (br t, $J=7.50$ Hz, 1 H) 7.07 - 7.11 (m, 2 H) 6.86 (br s, 1 H) 4.94 - 5.04 (m, 2 H) 4.45 - 4.56 (m, 2 H) 4.07 (q, $J=6.88$ Hz, 2 H) 2.98 - 3.07 (m, 3 H) 1.35 (t, $J=6.94$ Hz, 3 H).

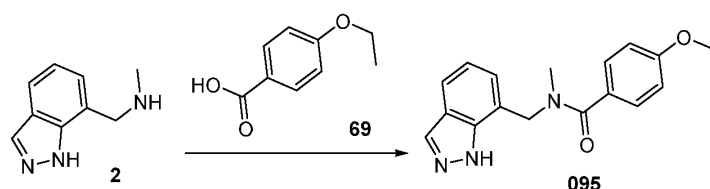
Compound **173** was prepared in a similar manner to **094** and isolated as a yellow solid (2 mg, 4.14 umol, 2.86% yield, 94% purity). **LCMS**: $m/z = 455.2$ ($\text{M}+\text{H}^+$) **^1H NMR** (CHLOROFORM-d , 400 MHz) $\delta = 8.16$ (s, 1H), 8.00 (s, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.73 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.47 (d, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.31 (br d, $J = 6.8$

Hz, 1H), 7.16 (br t, $J = 7.4$ Hz, 1H), 7.11 - 7.07 (m, 2H), 4.98 (s, 2H), 4.42 (s, 2H), 4.07 (q, $J = 7.0$ Hz, 2H), 3.23 (s, 3H), 3.03 (s, 3H), 1.35 (t, $J = 6.9$ Hz, 3H).

Compound 174 was prepared in a similar manner to **094** and isolated as a white solid (21.26 mg, 50.88 μ mol, 17.22% yield, 98% purity). **LCMS**: $m/z = 410.1$ ($M+H$)⁺ **¹H NMR** (CHLOROFORM-*d*, 400 MHz) $\delta = 8.14$ (s, 1 H) 7.79 (d, $J = 8.13$ Hz, 1 H) 7.48 - 7.56 (m, 4 H) 7.31 (br dd, $J = 13.07$, 7.44 Hz, 2 H) 7.14 (br t, $J = 7.50$ Hz, 1 H) 7.05 - 7.10 (m, 2 H) 4.98 (s, 2 H) 4.01 - 4.10 (m, 2 H) 3.12 (s, 1 H) 3.01 (s, 3 H) 1.35 (br t, $J = 6.88$ Hz, 3 H).

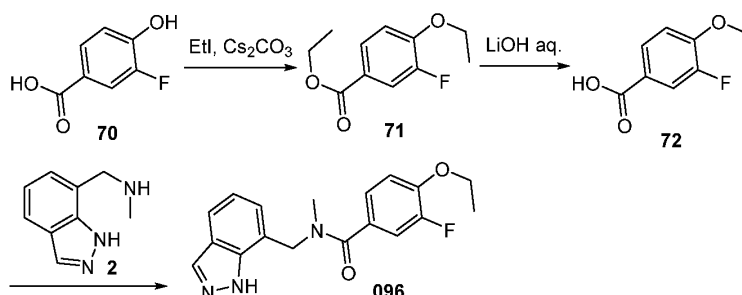
Compound 203 was prepared in a similar manner to **094** and isolated as a white solid (4.04 mg, 9.44 μ mol, 5.88% yield, 99% purity). **LCMS**: $m/z = 424.1$ ($M+H$)⁺ **¹H NMR** (CHLOROFORM-*d*, 400 MHz) $\delta = 8.14$ (br s, 1H), 7.78 (br d, $J = 8.0$ Hz, 1H), 7.50 - 7.40 (m, 4H), 7.35 - 7.29 (m, 2H), 7.14 (br t, $J = 7.5$ Hz, 1H), 7.09 - 7.04 (m, 2H), 4.97 (s, 2H), 4.04 (q, $J = 6.8$ Hz, 2H), 3.01 (s, 3H), 2.08 (s, 3H), 1.35 (br t, $J = 6.9$ Hz, 3H).

Scheme 22



Compound **095** was prepared as described for the synthesis of compound **4** with compound **69** and compound **2** as the starting materials. The crude product was purified by prep-HPLC (FA, column: Phenomenex Luna C18 150*25mm*10 μ m; mobile phase: [water(0.225%FA)-ACN]; B%: 33%-63%, 10min). The purified solution was lyophilized. Compound **095** (62.8 mg, 203.00 μ mol, 67.47% yield, 100% purity) was obtained as a white oil. **LCMS**: $m/z = 310.1$ ($M+H$)⁺. **¹H NMR** (400 MHz, METHANOL-*d*₄) $\delta = 8.11$ (s, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.55 - 7.33 (m, 3H), 7.20 (s, 1H), 6.97 (s, 2H), 5.01 (s, 2H), 4.07 (s, 2H), 3.02 (s, 3H), 1.40 (s, 3H).

Scheme 23.



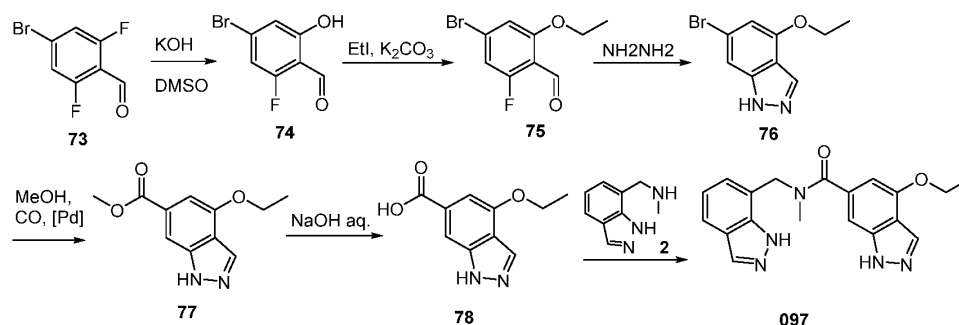
Compound **71** was prepared as described for the synthesis of compound **8** with compound **70** and EtI as the starting materials and step 1 at 50 °C for 12 hr. The crude

product used for next step without further purification. Compound **71** was obtained as a yellow oil. LCMS: $m/z = 212.9(M+H^+)$

Compound **72** was prepared as described for the synthesis of compound **9** with compound **71** as the starting material, LiOH as the base, and step 1 at 30 °C for 12 hr. Also, the pH of the resulting solution was adjusted to 3. The crude product used for next step without further purification. Compound **72** obtained as a white solid. LCMS: $m/z = 183.05(M+H^+)$

Compound **096** was prepared as described for the synthesis of compound **4** with compound **72** and compound **2** as the starting materials. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(0.225%FA)-ACN]; B%: 34%-64%, 10min), and the purified solution was lyophilized. **096** (39.2 mg, 119.75 umol, 44.11% yield, 100% purity) was obtained as a colourless solid. Confirmed by LCMS and 1H NMR. LCMS: $m/z = 328.0 (M+H^+)$. 1H NMR (400 MHz, METHANOL- d_4) $\delta = 8.10$ (s, 1H), 7.80 - 7.71 (m, 1H), 7.41 - 7.06 (m, 5H), 4.93 (br s, 2H), 4.30 - 3.97 (m, 2H), 3.13 - 2.93 (m, 3H), 1.50 - 1.34 (m, 3H).

Scheme 24.



To a solution of compound **74** (900 mg, 4.11 mmol, 1 eq) in DMF (10 mL) was added EtI (1.28 g, 8.22 mmol, 657.36 uL, 2 eq) and K_2CO_3 (1.42 g, 10.27 mmol, 2.5 eq), the mixture was stirred at 60 °C for 16 h. LCMS showed the reaction was completed. The mixture was poured into water (50 mL) and extracted with EtOAc (50mL X3), the combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated to give a crude product. The crude product was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 50/1, desired product $R_f=0.7$). Compound **75** (770 mg, 3.12 mmol, 75.84% yield, 100% purity) was obtained as white solid, confirmed by H-NMR. 1H NMR (400 MHz, CHLOROFORM- d) $\delta = 10.51 - 10.21$ (m, 1H), 6.95 (s, 2H), 4.25 - 4.04 (m, 2H), 1.51 (s, 3H).

Compound **76** was prepared as described for the synthesis of compound **17** with compound **75** as the starting material. The crude product used for next step without further

purification. Compound **76** (99.06% yield) was obtained as a yellow solid. LCMS: m/z =241.0 (M+H+)

To a solution of compound **76** (290 mg, 1.20 mmol, 1 eq) in MeOH (10 mL) was added Pd(OAc)₂ (27.01 mg, 120.29 umol, 0.1 eq), DPPF (133.37 mg, 240.58 umol, 0.2 eq) and TEA (1.22 g, 12.03 mmol, 1.67 mL, 10 eq), the mixture was stirred at 80 °C under CO (50 Psi) for 12 h. LCMS showed the reaction was completed. After the reaction was completed, the mixture was filtered and the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1, desired product Rf=0.4). Compound **77** (220 mg, 998.98 umol, 83.05% yield, 100% purity) was obtained as white solid. LCMS: m/z =220.9 (M+H+). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.36 - 8.18 (m, 1H), 7.88 (s, 1H), 7.17 (s, 1H), 4.29 (d, J = 7.0 Hz, 2H), 3.98 (s, 3H), 1.55 (t, J = 7.0 Hz, 3H)

Compound **78** was prepared as described for the synthesis of compound **9** with compound **77** as the starting material and LiOH as the base. Also, and step 1 was conducted at 15 °C for 1 hr and then at 30 °C for 12 h and the pH of the resulting solution was adjusted to 5. The crude product used for next step without further purification. 4-ethoxy-1H-indazole-6-carboxylic acid (**78**) was obtained as a white solid. LCMS: m/z =206.9 (M+H+).

Compound **097** was prepared as described for the synthesis of compound **4** with compound **78** and compound **2** as the starting materials. The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(0.225%FA)-ACN];B%: 29%-59%,10min) and the purified solution was lyophilized. **097** (15.0 mg, 42.93 umol, 17.71% yield, 100% purity) was obtained as a white solid. LCMS: m/z =350.0 (M+H+). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.26 - 8.05 (m, 2H), 7.87 - 7.68 (m, 1H), 7.35 - 7.29 (m, 1H), 7.13 (s, 2H), 6.65 - 6.41 (m, 1H), 5.00 (s, 2H), 4.42 - 4.09 (m, 2H), 2.98 (s, 3H), 1.53 (s, 3H).

Compound **134** was prepared in a similar manner to **097** and was obtained as a white solid (5.3 mg, 12.55 umol, 16.31% yield, 100% purity). LCMS: m/z = 423.1 (M-H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.04 (s, br., 1H), 8.17 (d, J = 1.5 Hz, 1H), 7.47 - 7.40 (m, 5H), 7.31 - 7.27 (m, 1H), 7.23 - 7.19 (m, 1H), 6.79 - 6.72 (m, 1H), 4.93 (s, 2H), 4.38 (d, J = 7.0 Hz, 2H), 3.18 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

Compound **135** was prepared in a similar manner to **097** and was obtained as an off-white solid (7.8 mg, 17.81 umol, 33.73% yield, 100% purity). LCMS: m/z =438.1 (M-H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.04 (br s, 1H), 8.08 (s, 1H), 7.28 - 7.16 (m, 4H), 7.08 (d, J = 7.4 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.96 - 6.89 (m, 3H), 4.82 (s, 2H), 3.95 (q, J = 6.9 Hz, 2H), 2.89 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H).

Compound 136 was prepared in a similar manner to **097** and was obtained as an off-white solid (2.8 mg, 6.19 μ mol, 27.09% yield, 97% purity). **LCMS**: m/z = 439.2 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.08 - 11.89 (m, 1H), 8.05 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.30 - 7.20 (m, 3H), 7.07 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.96 - 6.91 (m, 1H), 4.81 (s, 2H), 4.28 (q, J = 7.0 Hz, 2H), 3.03 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).

Compound 137 was prepared in a similar manner to **097** and was obtained as an off-white solid (18.4 mg, 42.77 μ mol, 61.28% yield, 99.6% purity). **LCMS**: m/z = 429.3 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.53 - 12.19 (m, 1H), 8.34 (s, 1H), 7.56 (br d, J = 7.4 Hz, 1H), 7.48 - 7.36 (m, 6H), 6.90 - 6.84 (m, 2H), 5.02 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.06 (s, 3H), 1.31 (br t, J = 6.9 Hz, 3H).

Compound 167 was prepared in a similar manner to **097** and was obtained as a white solid (44.9 mg, 101.71 μ mol, 38.77% yield, 100% purity). **LCMS**: m/z = 441.9 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.43 (d, 1H, J=1.5 Hz), 8.27 (s, 1H), 8.2-8.2 (m, 2H), 7.84 (d, 1H, J=1.6 Hz), 7.68 (d, 1H, J=7.8 Hz), 7.5-7.6 (m, 1H), 7.23 (dd, 1H, J=4.5, 7.6 Hz), 6.77 (dd, 1H, J=7.8, 9.6 Hz), 4.95 (s, 2H), 3.86 (td, 1H, J=3.0, 5.8 Hz), 3.08 (s, 3H), 0.8-1.0 (m, 4H).

Compound 194 was prepared in a similar manner to **097** and was obtained as a white solid (1.6mg, 3.60 μ mol, 4.96% yield, 96.7% purity). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.48 (br s, 1H), 8.47 (s, 2H), 7.46 - 7.38 (m, 5H), 6.91 - 6.86 (m, 2H), 5.01 (s, 2H), 4.09 - 4.00 (m, 2H), 3.11 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H), 1.28 - 1.28 (m, 1H).

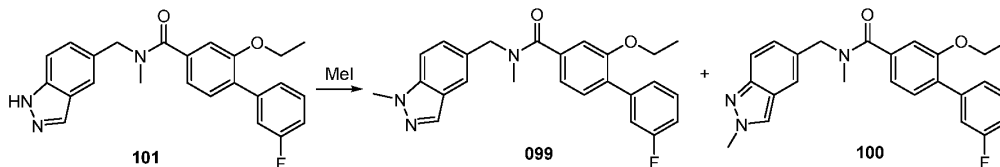
Compound 204 was prepared in a similar manner to **097** and was obtained as an off-white solid (10.97 mg, 21.20 μ mol, 10.68% yield, and 100% purity). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.04 (br s, 1H), 8.22 - 8.16 (m, 1H), 8.09 - 8.05 (m, 1H), 7.84 - 7.79 (m, 1H), 7.63 - 7.57 (m, 1H), 7.31 - 7.26 (m, 1H), 7.11 - 7.04 (m, 1H), 7.02 - 6.99 (m, 1H), 6.99 - 6.97 (m, 1H), 6.76 - 6.63 (m, 1H), 4.79 - 4.74 (m, 2H), 4.48 - 4.39 (m, 1H), 4.02 - 3.95 (m, 2H), 3.00 - 2.97 (m, 3H), 2.97 - 2.93 (m, 3H), 1.31 - 1.26 (m, 3H), 0.86 - 0.81 (m, 4H).

Compound 214 was prepared in a similar manner to **097** and was obtained as a white solid (16.95 mg, 38.19 μ mol, 54.69% yield, 99.7% purity). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 9.26 (br s, 1H), 8.51 (br s, 1H), 8.4-8.5 (m, 2H), 8.16 (s, 1H), 8.01 (br d, 1H, J=9.4 Hz), 7.84 (s, 1H), 7.3-7.4 (m, 1H), 5.03 (s, 2H), 3.88 (br d, 1H, J=2.8 Hz), 3.14 (s, 3H), 0.8-1.0 (m, 4H).

Compound 216 was prepared in a similar manner to **097** and was obtained as a white solid (16.34 mg, 41.88 μ mol, 15.22% yield, 97% purity). **LCMS**: m/z = 378.9 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.12 (br s, 1H), 9.08 (s, 1H), 8.26 (d, J = 16.1 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H), 6.99 - 6.87 (m, 2H), 4.87 (s, 2H), 4.07 (q, J = 6.9 Hz, 2H), 2.92

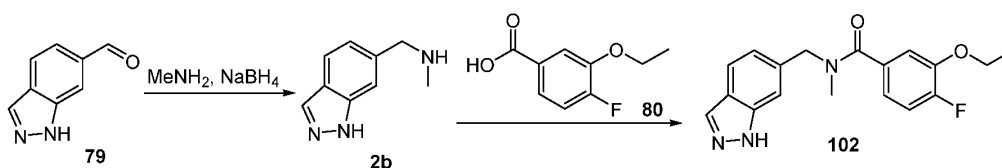
(s, 3H), 2.70 - 2.56 (m, 1H), 1.39 (t, J = 6.9 Hz, 3H), 1.17 (td, J = 3.7, 7.7 Hz, 2H), 0.94 (qd, J = 3.6, 7.5 Hz, 2H).

Scheme 25.



- 5 To a mixture of compound **101** (20 mg, 49.57 μmol , 1 *eq*) in DMF (2 mL) was added NaH (3.97 mg, 99.15 μmol , 60% purity, 2 *eq*) at 0 °C under N₂ atmosphere, then the mixture was stirred at 0 °C for 0.5 hr, CH₃I (10.55 mg, 74.36 μmol , 4.63 μL , 1.5 *eq*) was added, then the mixture was stirred at 20 °C for 12 hr. LCMS: Rt= 0.945, 0.977 min, m/z = 418.1 (M+H⁺) showed **101** consumed completely and desired mass was detected. The reaction mixture
- 10 was quenched by saturated sodium carbonate solution (5 mL) and extracted by ethyl acetate (3*5 mL), the organic phase was concentrated under reduced pressure to give a residue. The solution was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (0.225%FA)-ACN]; B%: 46%-76%, 10min), the solution was lyophilized to give a white solid. Compound **099** (2.2 mg, 5.27 μmol , 10.63% yield, 100% purity) was
- 15 obtained as a white solid. Compound **100** (1.2 mg, 2.75 μmol , 5.54% yield, 95.593% purity) was obtained as a white solid. LCMS: m/z = 418.3 (M+H⁺). LCMS: m/z = 418.3 (M+H⁺). ¹H NMR (400 MHz, DMSO-d₆) δ = 8.11 - 7.96 (m, 1H), 7.63 (br s, 2H), 7.24 (br s, 5H), 7.20 - 7.06 (m, 3H), 4.91 - 4.53 (m, 2H), 4.16 - 3.88 (m, 5H), 2.97 - 2.82 (m, 3H), 1.34 - 1.13 (m, 3H) ¹H NMR (400 MHz, DMSO-d₆) δ = 8.39 - 8.22 (m, 1H), 7.74 - 7.55 (m, 2H), 7.52 - 7.21
- 20 (m, 5H), 7.15 (br s, 3H), 4.80 - 4.52 (m, 2H), 4.16 (s, 3H), 4.09 - 3.84 (m, 2H), 2.95 - 2.84 (m, 3H), 1.42 - 1.26 (m, 3H).

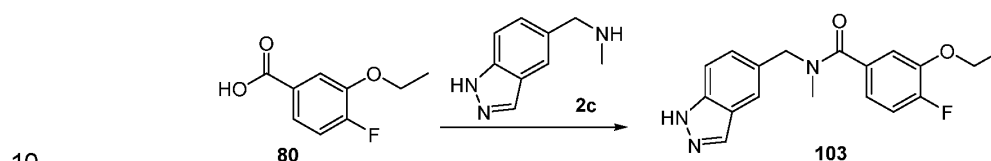
Scheme 26.



- 25 Compound **2b** was prepared as described for the synthesis of compound **2** with compound **79** as the starting material, step 1 at 20 °C for 2 hr, and step 2 at 20 °C for 12 hr. The crude was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5 μm ; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 0%-17%, min), the purified solution was lyophilized to give a white solid. Compound **2b** was obtained as a white solid and used in the next step. LCMS: m/z = 160.2 (M-H⁺). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.05
- 30 (s, 1H), 7.76 - 7.66 (m, 1H), 7.48 (s, 1H), 7.14 (s, 1H), 3.90 (s, 2H), 2.54 (s, 3H)

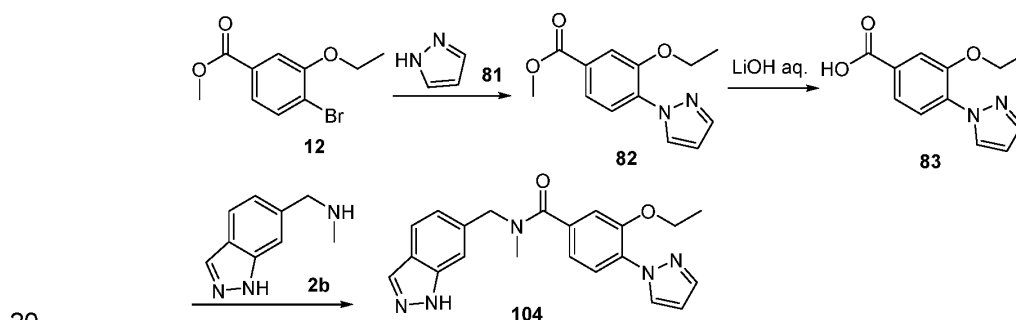
Compound **102** was prepared as described for the synthesis of compound **4** with compound **80** and compound **2b** as the starting materials. The solution was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225%FA)-ACN]; B%: 29%-59%, 10min) and the purified solution was lyophilized to give a white solid. Compound **102** (24.83 mg, 75.85 umol, 46.56% yield, 100% purity) was obtained as a white solid. LCMS: $m/z = 327.9$ ($M+H^+$). 1H NMR (400 MHz, CHLOROFORM- d) $\delta = 7.92 - 7.79$ (m, 1H), 7.43 - 7.31 (m, 1H), 4.05 (s, 2H), 3.17 (br s, 4H), 3.01 (br s, 4H), 2.24 - 2.12 (m, 4H).

Scheme 27.



Compound **103** was prepared as described for the synthesis of compound **4** with compound **80** and compound **2c** as the starting materials. The solution was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225%FA)-ACN]; B%: 28%-58%, 10min) and the purified solution was lyophilized to give a white solid. Compound **103** (30.06% yield, 100% purity) was obtained as a white solid. LCMS: $m/z = 382.0$ ($M+H^+$). 1H NMR (400 MHz, METHANOL- d_4) $\delta = 8.10 - 8.02$ (m, 1H), 7.83 - 7.58 (m, 1H), 7.58 - 7.51 (m, 1H), 7.48 - 6.98 (m, 4H), 4.85 - 4.59 (m, 2H), 4.20 - 3.82 (m, 2H), 3.11 - 2.86 (m, 3H), 1.47 - 1.21 (m, 3H).

Scheme 28.



Compound **82** was prepared as described for the synthesis of compound **35** with compound **12** and compound **81** as the starting materials, N,N'-dimethylethane-1,2-diamine as the ligand, and step 1 at 110 °C for 16 hr. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 5:1) and the solution was concentrated to give a white solid. Compound **82** was obtained as a white solid. LCMS: $m/z = 247.2$ ($M+H^+$). 1H NMR (400 MHz, CHLOROFORM- d) $\delta = 8.58 - 8.19$ (m, 1H), 8.04 - 7.92

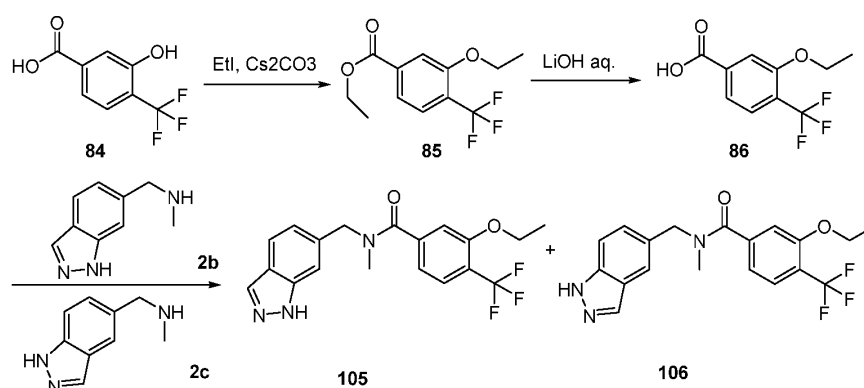
(m, 1H), 7.83 - 7.65 (m, 3H), 6.63 - 6.35 (m, 1H), 4.24 (q, $J = 6.6$ Hz, 2H), 3.95 (s, 3H), 1.49 (t, $J = 6.8$ Hz, 3H)

Compound **83** was prepared as described for the synthesis of compound **9** with compound **82** as the starting material, LiOH·H₂O as the base, and step 1 at 30 °C for 2 hr.

Also, the pH of the resulting solution was adjusted to 6-7. Compound **83** was obtained as a white solid.

Compound **104** was prepared as described for the synthesis of compound **4** with compound **83** and compound **2b** as the starting materials. The residue was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 μ m; mobile phase: [water (0.225%FA)-ACN]; B%: 30%-60%, 10min) and the solution was lyophilized to give a white solid. **104** (45.48% yield, 100% purity) was obtained as a white solid. **LCMS**: $m/z = 376.2$ ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 8.31 - 8.13$ (m, 1H), 8.09 (s, 1H), 7.96 - 7.74 (m, 2H), 7.71 (s, 1H), 7.61 - 7.31 (m, 1H), 7.27 - 6.93 (m, 3H), 6.52 - 6.35 (m, 1H), 5.02 - 4.59 (m, 2H), 4.30 - 3.77 (m, 2H), 3.28 - 2.87 (m, 3H), 1.62 - 1.15 (m, 3H).

Scheme 29.



Compound **85** was prepared as described for the synthesis of compound **8** with compound **84** and EtI as the starting materials and step 1 at 50 °C for 12 hr. The crude product used for next step without further purification. Compound **85** was obtained as a white solid. **LCMS**: $m/z = 262.8$ ($M+H^+$)

Compound **86** was prepared as described for the synthesis of compound **9** with compound **85** as the starting material, LiOH as the base, and step 1 at 30 °C for 12 hr. Also, the pH of the resulting solution was adjusted to 3. The crude product used for next step without further purification. Compound **86** was obtained as a yellow solid. **LCMS**: $m/z = 233.05$ ($M+H^+$)

Compound **105** was prepared as described for the synthesis of compound **4** with compound **86** and compound **2b** as the starting materials. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10 μ m; mobile phase:

[water(0.225%FA)-ACN];B%: 37%-67%,10min) and the purified solution was lyophilized.

Compound **105** (18.7 mg, 49.55 μ mol, 29.01% yield, 100% purity) obtained as a white solid.

LCMS: m/z = 377.9 ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) δ = 8.30 - 7.98 (m, 1H), 7.89 - 7.73 (m, 1H), 7.40 (br s, 1H), 7.43 - 7.29 (m, 1H), 7.25 (br s, 3H), 4.95 - 4.62 (m, 2H),

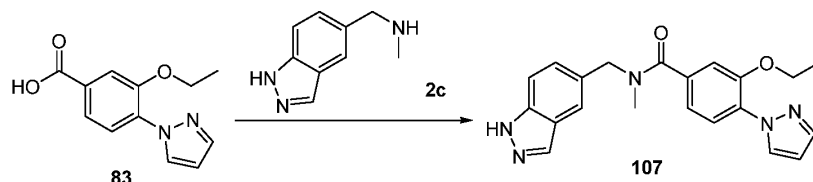
5 4.24 - 3.92 (m, 2H), 3.15 - 2.91 (m, 3H), 1.54 - 1.30 (m, 3H)

Compound **106** was prepared as described for the synthesis of compound **4** with compound **86** and compound **2c** as the starting materials. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10 μ m;mobile phase:

[water(0.225%FA)-ACN];B%: 36%-66%,10min) and the purified solution was lyophilized. **106**

10 (14.7 mg, 38.95 μ mol, 22.81% yield, 100% purity) obtained as white solid. **LCMS**: m/z = 377.9($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) δ = 8.28 - 8.00 (m, 1H), 7.60 (br s, 3H), 7.29 (s, 3H), 5.00 - 4.52 (m, 2H), 4.28 - 3.91 (m, 2H), 2.90 (br s, 3H), 1.63 - 1.16 (m, 3H).

Scheme 30.



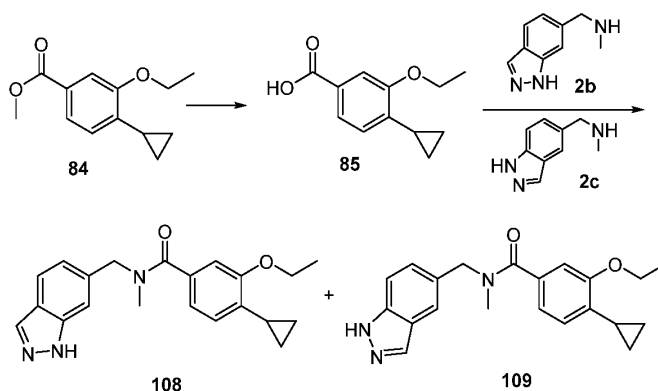
15

Compound **107** was prepared as described for the synthesis of compound **4** with compound **83** and compound **2c** as the starting materials. The residue was purified by prep-HPLC

(column: Phenomenex Synergi C18 150*25mm* 10 μ m; mobile phase: [water (0.225%FA)-ACN]; B%: 25%-55%, 10min) and the solution was lyophilized to give a white solid. **107** (32

20 mg, 85.24 μ mol, 39.59% yield, 100% purity) was obtained as a white solid. **LCMS**: m/z = 376.2 ($M+H^+$). **1H NMR** (400 MHz, CHLOROFORM- d) δ = 8.27 - 8.12 (m, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.66 - 7.42 (m, 2H), 7.27 - 7.06 (m, 3H), 6.44 (s, 1H), 4.98 - 4.58 (m, 2H), 4.25 - 3.90 (m, 2H), 3.16 - 2.88 (m, 3H), 1.49 - 1.23 (m, 3H).

Scheme 31.



25

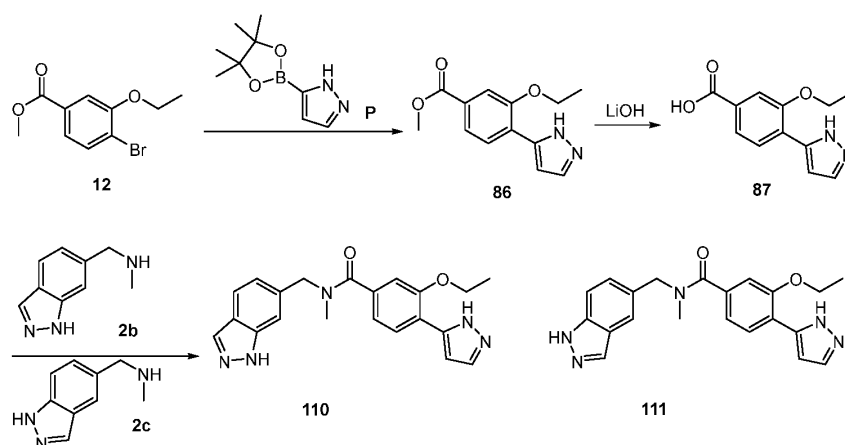
Compound **85** was prepared as described for the synthesis of compound **9** with compound **84** as the starting material, LiOH as the base, and step 1 at 30 °C for 12 hr. Also, the pH of the resulting solution was adjusted to 3. The crude product used for next step without further purification. Compound **85** was obtained as a white solid. LCMS: m/z = 205.1 (M+H⁺).

Compound **108** was prepared as described for the synthesis of compound **4** with compound **85** and compound **2b** as the starting materials. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water(0.225%FA)-ACN]; B%: 38%-68%, 10min) and the purified solution was lyophilized.

Compound **108** (12.57 mg, 35.97 μmol, 12.37% yield, 100 % purity) was obtained as a white solid. LCMS m/z = 350.0(M+H⁺). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.18 - 8.00 (m, 1H), 7.84 - 7.70 (m, 1H), 7.60 - 7.34 (m, 1H), 6.98 (br s, 3H), 6.89 - 6.70 (m, 1H), 4.98 - 4.59 (m, 2H), 4.22 - 3.77 (m, 2H), 3.19 - 2.83 (m, 3H), 2.30 - 2.13 (m, 1H), 1.54 - 1.24 (m, 3H), 1.07 - 0.85 (m, 2H), 0.74 - 0.57 (m, 2H).

Compound **109** was prepared as described for the synthesis of compound **4** with compound **85** and compound **2c** as the starting materials. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water(0.225%FA)-ACN]; B%: 37%-67%, 10min) and the purified solution was lyophilized. **109** (43.01 mg, 123.09 μmol, 42.31% yield, 100% purity) obtained as a white solid. LCMS: m/z = 350.0(M+H⁺). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.01 (s, 1H), 7.76 - 7.50 (m, 1H), 7.43 (br d, J = 7.4 Hz, 1H), 7.19 (s, 1H), 6.89 (s, 2H), 6.77 - 6.61 (m, 1H), 4.85 - 4.51 (m, 2H), 4.11 - 3.75 (m, 2H), 3.12 - 2.73 (m, 3H), 2.26 - 2.05 (m, 1H), 1.48 - 1.15 (m, 3H), 0.87 (br d, J = 7.4 Hz, 2H), 0.59 (br s, 2H).

Scheme 32.



Compound **86** was prepared as described for the synthesis of compound **001** with compound **12** and compound **P** as the starting materials. The mixture was filtered and the

filtrate was concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 20/1, desired product R_f = 0.3). Compound **86** (84.17% yield) was obtained as a yellow oil. **LCMS**: m/z = 246.9 (M+H⁺)

Compound **87** was prepared as described for the synthesis of compound **9** with
5 compound **86** as the starting material, LiOH as the base, and step 1 at 30 °C for 12 hr. Also, the pH of the resulting solution was adjusted to 3. The crude product used for next step without further purification. Compound **87** (30.73% yield, 61% purity) was obtained as a white solid. **LCMS**: m/z = 231.1 (M+H⁺)

Compound **110** was prepared as described for the synthesis of compound **4** with
10 compound **87** and compound **2b** as the starting materials. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(0.225%FA)-ACN];B%: 24%-54%,10min) and the purified solution was lyophilized. **110** (13.94 mg, 36.39 umol, 16.90% yield, 98% purity) obtained as a white solid. **LCMS**: m/z = 376.0 (M+H⁺). ¹H NMR (400 MHz, METHANOL-d₄) δ = 8.12 - 8.01 (m, 1H), 7.91 - 7.73 (m,
15 2H), 7.69 - 7.38 (m, 2H), 7.28 - 7.18 (m, 1H), 7.02 (br d, J = 7.4 Hz, 2H), 6.93 - 6.72 (m, 1H), 4.76 (br s, 2H), 4.30 - 4.14 (m, 1H), 3.98 - 3.86 (m, 1H), 3.20 - 2.96 (m, 3H), 1.58 - 1.22 (m, 3H)

Compound **111** was prepared as described for the synthesis of compound **4** with
compound **87** and compound **2c** as the starting materials. The crude product was purified by
20 prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(0.225%FA)-ACN];B%: 22%-52%,10min) and the purified solution was lyophilized. Compound **111** (23.70% yield, 100% purity) was obtained as a white solid. **LCMS**: m/z = 376.0(M+H⁺). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.06 - 7.97 (m, 1H), 7.77 - 7.33 (m, 4H), 7.19 (s, 1H), 7.16 - 6.95 (m, 2H), 6.74 - 6.51 (m, 1H), 4.91 - 4.51 (m, 2H), 4.30 - 3.89
25 (m, 2H), 3.10 - 2.78 (m, 3H), 1.64 - 1.22 (m, 3H).

Compound **150** was prepared in a similar manner to **111** and was obtained as a
white solid (4.83 mg, 9.74 umol, 12.37% yield, 96.7% purity). **LCMS**: m/z=480.0 (M-H⁺) ¹H
NMR (400 MHz, CHLOROFORM-d) δ = 12.31 - 12.04 (m, 1H), 8.50 - 8.28 (m, 1H), 8.19 (s,
1H), 7.75 (s, 2H), 7.53 - 7.39 (m, 1H), 7.24 - 7.12 (m, 2H), 6.84 - 6.66 (m, 2H), 4.95 (s, 2H),
30 4.50 - 4.28 (m, 2H), 3.17 (s, 3H), 3.08 (dd, J = 0.9, 4.8 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

Compound **151** was prepared in a similar manner to **111** and was obtained as a
white solid (5.96 mg, 12.28 umol, 15.43% yield, 100% purity). **LCMS**: m/z=486.41 (M-H⁺) ¹H
NMR (400 MHz, CHLOROFORM-d) δ = 12.59 - 12.20 (m, 1H), 8.40 - 8.19 (m, 2H), 7.74 -
7.62 (m, 1H), 7.59 - 7.48 (m, 1H), 7.40 - 7.31 (m, 2H), 7.20 - 7.10 (m, 1H), 7.10 - 7.02 (m,
35 2H), 6.83 - 6.69 (m, 1H), 5.01 (br s, 2H), 4.11 - 4.02 (m, 2H), 3.09 - 3.00 (m, 6H), 1.36 (td, J
= 3.6, 6.9 Hz, 3H).

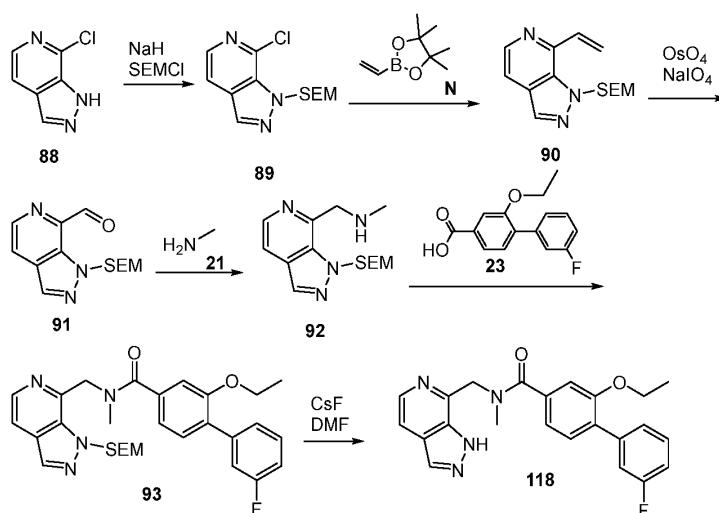
Compound 152 was prepared in a similar manner to **111** and was obtained as a white solid (4.5 mg, 8.70 μ mol, 28.23% yield, 94% purity). **LCMS**: m/z = 487.1 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.65 - 12.04 (m, 1H), 8.42 - 8.22 (m, 2H), 7.90 - 7.68 (m, 2H), 7.58 - 7.53 (m, 1H), 7.52 - 7.47 (m, 1H), 7.39 - 7.35 (m, 1H), 7.23 - 7.16 (m, 1H), 6.88 - 6.58 (m, 1H), 5.04 (s, 2H), 4.52 - 4.16 (m, 2H), 3.29 - 3.14 (m, 3H), 3.08 (s, 3H), 1.43 - 1.35 (m, 3H).

Compound 153 was prepared in a similar manner to **111** and was obtained as a white solid (23.50 mg, 47.47 μ mol, 41.82% yield, 98.27% purity). **LCMS**: m/z = 487.4 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.52 - 12.19 (m, 1H), 8.86 (dd, J = 2.4, 7.8 Hz, 1H), 8.44 - 8.31 (m, 2H), 8.20 - 8.11 (m, 1H), 7.57 (d, J = 7.1 Hz, 1H), 7.46 - 7.34 (m, 2H), 7.22 (dd, J = 8.7, 11.6 Hz, 1H), 6.84 - 6.70 (m, 1H), 5.05 (s, 2H), 4.17 (q, J = 6.9 Hz, 2H), 3.16 - 3.02 (m, 6H), 1.52 (t, J = 7.0 Hz, 3H).

Compound 170 was prepared in a similar manner to **111** and was obtained as a white solid (4.37 mg, 10.42 μ mol, 7.38% yield, 100% purity). **LCMS**: m/z = 420.0 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.22 - 8.17 (m, 1H), 7.40 - 7.35 (m, 1H), 7.35 - 7.29 (m, 3H), 7.11 (br d, J = 7.5 Hz, 1H), 7.08 - 7.04 (m, 2H), 7.04 - 7.00 (m, 1H), 6.44 (d, J = 7.4 Hz, 1H), 4.88 (s, 2H), 4.06 (q, J = 6.9 Hz, 2H), 2.99 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H).

Compound 199 was prepared in a similar manner to **111** and was obtained as a white solid (6.82 mg, 13.40 μ mol, 15.03% yield, 95% purity). **LCMS**: m/z = 487.2 (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.50 - 8.40 (m, 2H), 8.30 - 8.25 (m, 1H), 7.71 - 7.64 (m, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.19 - 7.13 (m, 1H), 7.11 - 7.05 (m, 2H), 6.84 - 6.72 (m, 1H), 5.03 - 4.97 (m, 2H), 4.11 - 4.03 (m, 2H), 3.09 - 3.04 (m, 6H), 1.39 - 1.34 (m, 3H).

Scheme 33.



Compound 89 was prepared as described for the synthesis of compound **18** with compound **88** as the starting material. The crude product was purified by prep-TLC (PE :

EtOAc = 2 : 1). Compound **89** was obtained as a yellow oil. **LCMS**: m/z = 284.0 ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.20 - 8.10 (m, 2H), 7.61 (d, J = 5.4 Hz, 1H), 6.09 (s, 2H), 3.68 - 3.56 (m, 2H), 0.99 - 0.87 (m, 2H), -0.05 (s, 9H).

Compound **90** was prepared as described for the synthesis of compound **001** with compound **89** and compound **N** as the starting materials and Cs_2CO_3 as the base. The mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate = 14 : 1 to 12 : 1. Compound **90** was obtained as a yellow oil. **LCMS**: m/z = 276.1 ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.41 (d, J = 5.4 Hz, 1H), 8.09 (s, 1H), 7.73 - 7.58 (m, 2H), 6.59 (dd, J = 1.8, 16.8 Hz, 1H), 5.94 (s, 2H), 5.75 (dd, J = 1.9, 10.8 Hz, 1H), 3.70 - 3.55 (m, 2H), 1.00 - 0.87 (m, 2H), 0.02 - -0.06 (m, 9H).

Compound **91** was prepared as described for the synthesis of compound **20** with compound **90** as the starting material. Compound **91** was obtained as a colorless oil. **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 10.29 (s, 1H), 8.62 (d, J = 5.3 Hz, 1H), 8.26 (s, 1H), 7.95 (d, J = 5.3 Hz, 1H), 6.32 (s, 2H), 3.54 - 3.44 (m, 2H), 0.87 - 0.77 (m, 2H), -0.09 (s, 9H).

Compound **92** was prepared as described for the synthesis of compound **2** with compound **91** as the starting material, step 1 at 20 °C for 2 hr, and step 2 at 20 °C for 2 hr. The crude product was purified by prep-HPLC (HCl, column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [water(0.05%HCl)-ACN]; B%: 23%-43%, 9min) and the purified solution was lyophilized. Compound **92** (33.73% yield, 100% purity, HCl) was obtained as a white solid. **LCMS**: m/z = 293.1 ($M+H^+$).

Compound **93** was prepared as described for the synthesis of compound **4** with compound **92** and compound **23** as the starting materials and step 1 at 20 °C for 12 hr. The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water(0.225%FA)-ACN]; B%: 63%-93%, 10min) and the purified solution was lyophilized. Compound **93** (15 mg, 24.80 umol, 40.78% yield, 88.4% purity) was obtained as a black oil. **LCMS**: m/z = 535.3 ($M+H^+$).

Compound **118** was prepared as described for the synthesis of compound **038** with compound **93** as the starting material and step 1 at 80 °C for 12 hr. The crude product was purified by prep-HPLC (FA, column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water(0.225%FA)-ACN]; B%: 32%-62%, 10min) and the purified solution was lyophilized. Compound **118** (2.4 mg, 5.93 umol, 23.93% yield, 100% purity) was obtained as a yellow solid. **LCMS**: m/z = 405.2 ($M+H^+$). **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.10 (d, J = 5.6 Hz, 1H), 8.06 - 8.00 (m, 1H), 7.53 (d, J = 5.6 Hz, 1H), 7.25 - 7.12 (m, 4H), 6.99 - 6.87 (m, 3H), 5.01 (s, 2H), 3.92 (q, J = 6.9 Hz, 2H), 2.96 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H).

Compound **158** was prepared in a similar manner to **038** and was obtained as a white solid (5.27 mg, 10.97 umol, 31.68% yield, 93.12% purity). **LCMS**: m/z = 448.1 ($M+H^+$).

¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.50 - 8.24 (m, 1H), 7.36 (br dd, J = 8.9, 16.7 Hz, 6H), 7.14 - 7.01 (m, 3H), 5.02 (s, 2H), 4.18 - 4.01 (m, 2H), 3.07 (s, 3H), 1.42 - 1.35 (m, 3H).

Compound 159 was prepared in a similar manner to **038** and was obtained as a white solid (7.71 mg, 17.15 μ mol, 24.78% yield, 99.56% purity). **LCMS**: m/z = 448.1 (M+H⁺)

5 ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.68 (s, 1H), 8.00 (d, J = 7.3 Hz, 1H), 7.40 - 7.34 (m, 3H), 7.31 (br d, J = 7.6 Hz, 2H), 7.09 - 7.02 (m, 3H), 5.05 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 3.03 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H).

Compound 191 was prepared in a similar manner to **038** and was obtained as a white solid (9.7 mg, 22.19 μ mol, 62.66% yield, 99.4% purity). **LCMS**: m/z = 435.2 (M-H⁺)

10 ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.27 - 11.78 (m, 1H), 8.17 (s, 1H), 7.81 (s, 1H), 7.39 - 7.28 (m, 4H), 7.08 - 7.00 (m, 3H), 4.83 (s, 2H), 4.12 (s, 3H), 4.06 (q, J = 7.0 Hz, 1H), 4.03 - 4.02 (m, 1H), 3.02 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H).

Compound 192 was prepared in a similar manner to **038** and was obtained as a white solid (21.8 mg, 49.37 μ mol, 58.82% yield, 98.4% purity). **LCMS**: m/z = 435.2 (M-H⁺)

15 ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.18 - 11.95 (m, 1H), 8.17 (s, 1H), 7.82 (s, 1H), 7.41 - 7.28 (m, 4H), 7.11 - 7.00 (m, 3H), 4.84 (s, 2H), 4.12 (s, 3H), 4.07 (q, J = 6.9 Hz, 2H), 3.03 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H).

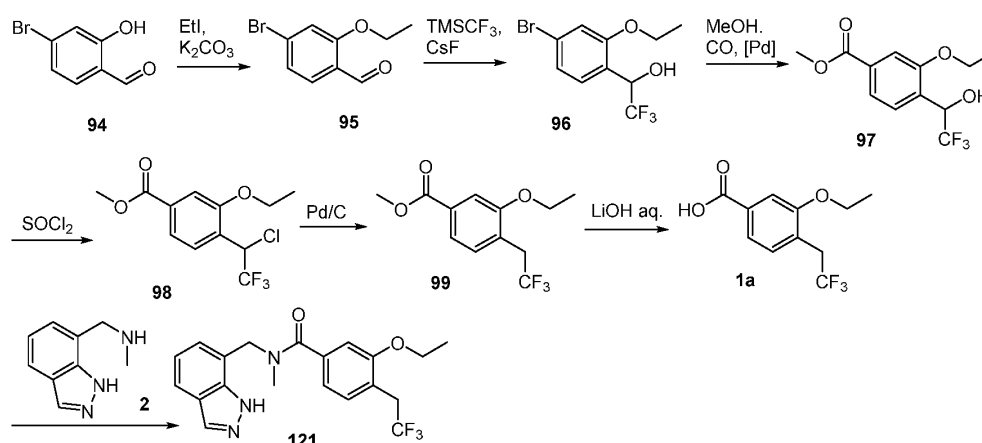
Compound 193 was prepared in a similar manner to **038** and was obtained as a white solid (20 mg, 45.17 μ mol, 51.65% yield, 99.7% purity). **LCMS**: m/z = 442.1 (M-H⁺)

20 ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.08 - 11.98 (m, 1H), 8.17 (s, 1H), 7.85 (t, J = 1.5 Hz, 1H), 7.81 (s, 1H), 7.76 (td, J = 1.4, 7.9 Hz, 1H), 7.62 (td, J = 1.3, 7.8 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.10 - 7.06 (m, 2H), 4.83 (s, 2H), 4.12 (s, 3H), 4.07 (q, J = 6.9 Hz, 2H), 3.02 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H).

Compound 208 was prepared in a similar manner to **038** and was obtained as a

25 white solid (2.4 mg, 4.83 μ mol, 21.29% yield, 97.94 % purity). **LCMS**: m/z = 487.3 (M-H⁺) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 13.14 - 12.94 (m, 1H), 9.47 - 8.45 (m, 1H), 8.28 (dd, J = 2.4, 7.6 Hz, 1H), 7.71 - 7.65 (m, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.16 (dd, J = 8.6, 11.7 Hz, 1H), 7.12 - 7.08 (m, 1H), 7.06 (s, 1H), 6.83 - 6.73 (m, 1H), 4.97 (s, 2H), 4.07 (q, J = 6.9 Hz, 2H), 3.10 (s, 3H), 3.06 (d, J = 4.5 Hz, 3H), 1.38 (s, 3H).

30 **Scheme 34.**



Compound **97** was prepared as described for the synthesis of compound **77** with compound **96** as the starting material. The crude product was purified by column on silica (petroleum ether:ethyl acetate=2:1, R_f =0.6) and concentrated under reduced pressure to give a yellow solid. Compound **97** (34.83% yield, 90% purity) was obtained as a yellow solid and used to the next step. LCMS: $m/z = 277.0$ ($\text{M}-\text{H}^+$)

To a mixture of compound **97** (180 mg, 646.96 μmol , 1 eq), Py (5.12 mg, 64.70 μmol , 5.22 μL , 0.1 eq) in toluene (5 mL) was added SOCl_2 (153.94 mg, 1.29 mmol, 93.86 μL , 2 eq) at 0 °C, then the mixture was stirred at 70 °C for 12 hr. TLC (PE:EA=5:1, R_f =0.6) showed compound **97** consumed completely and new spot observed. The solution was extracted by ethyl acetate (3*10 mL), the organic phase was concentrated to give a residue. The solution was purified by column on silica (petroleum ether:ethyl acetate=5:1, R_f =0.6) and concentrated under reduced pressure to give a yellow oil. Compound **98** (130 mg, 394.38 μmol , 60.96% yield, 90% purity) was obtained as a yellow oil. $^1\text{H NMR}$ (400 MHz, $\text{CHLOROFORM}-d$) $\delta = 7.70$ (s, 2H), 7.61 - 7.54 (m, 1H), 6.06 - 5.74 (m, 1H), 4.26 - 4.07 (m, 2H), 3.94 (s, 3H), 1.47 (s, 3H).

Compound **99** was prepared as described for the synthesis of compound **10** with compound **98** as the starting material, MeOH as the solvent, and step 1 at 45 °C for 12 hr. The reaction mixture was purified by prep-TLC (PE:EA=5:1, R_f =0.6), the purified solution was concentrated to give a white solid. Compound **99** (77.54% yield, 99% purity) was obtained as a white solid. LCMS: $m/z = 262.8$ ($\text{M}+\text{H}^+$)

Compound **1a** was prepared as described for the synthesis of compound **9** with compound **99** as the starting material, LiOH as the base, and step 1 at 30 °C for 1 hr. Also, the pH of the resulting solution was adjusted to 1. Compound **1a** (64.56% yield, 100% purity) was obtained as a white solid. LCMS: $m/z = 247.1$ ($\text{M}-\text{H}^+$)

Compound **121** was prepared as described for the synthesis of compound **4** with compound **1a** and compound **2** as the starting materials. The solution was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 44%-74%, 9min) and the purified solution was lyophilized to give a brown solid.

5 Compound **121** (46.89 mg, 116.26 umol, 64.12% yield, 97.04% purity) was obtained as a brown solid. **LCMS**: m/z = 392.0 (M+H⁺). **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.49 - 8.33 (m, 1H), 8.11 - 8.00 (m, 1H), 7.63 - 7.52 (m, 2H), 7.47 - 7.37 (m, 1H), 7.31 - 7.23 (m, 2H), 5.24 (s, 2H), 4.45 - 4.27 (m, 2H), 3.87 - 3.68 (m, 2H), 3.24 (s, 3H), 1.71 (s, 3H).

10 **Compound 178** was prepared in a similar manner to **121** and was obtained as a white solid (8 mg, 17.40 umol, 6.23% yield, 93.4% purity). **LCMS**: m/z = 430.1 (M+H⁺) **¹H NMR**: (400 MHz, CHLOROFORM-d) δ 8.18 - 8.07 (m, 1H), 8.02 - 7.97 (m, 1H), 7.95 (d, J = 1.1 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.73 - 7.67 (m, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.18 - 7.11 (m, 1H), 5.00 (s, 2H), 4.47 - 4.21 (m, 1H), 3.23 (s, 3H), 0.88 - 0.62 (m, 4H).

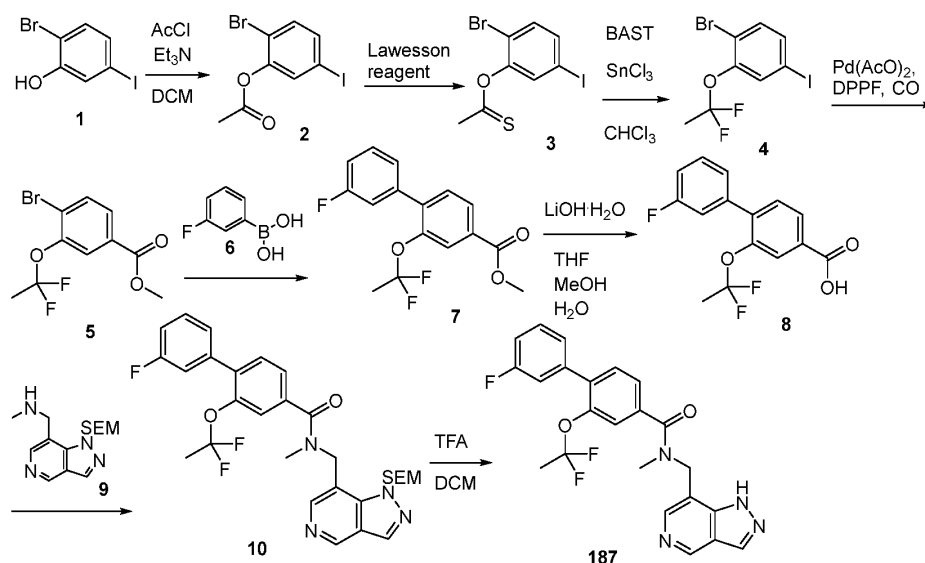
15 **Compound 179** was prepared in a similar manner to **121** and was obtained as a white solid (35 mg, 84.03 umol, 57.42% yield, 100% purity). **LCMS**: m/z = 443.2 (M+H⁺) **¹H NMR**: (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.98 (d, J = 1.4 Hz, 1H), 7.90 (d, J = 1.3 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.30 - 7.28 (m, 1H), 7.17 - 7.12 (m, 1H), 7.09 - 7.05 (m, 2H), 4.97 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 2.99 (s, 3H), 1.46 (t, J = 6.9 Hz, 3H)

20 **Compound 180** was prepared in a similar manner to **121** and was obtained as a white solid (12 mg, 28.30 umol, 12.94% yield, 98.451% purity). **LCMS**: m/z = 418.1 (M+H⁺) **¹H NMR**: (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.02 (d, J = 4.8 Hz, 2H), 7.86 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 6.8 Hz, 1H), 7.16 - 7.11 (m, 1H), 4.98 (s, 2H), 4.48 (q, J = 7.0 Hz, 2H), 3.15 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H).

Compound 181 was prepared in a similar manner to **121** and was obtained as a white solid (13.11 mg, 33.40 umol, 16.01% yield, 100% purity). **LCMS**: m/z = 393.1 (M+H⁺).

30 **Compound 182** was prepared in a similar manner to **121** and was obtained as a white solid (14.8 mg, 37.33 umol, 17.23% yield, and 99% purity). **LCMS**: m/z = 418.1 (M+H⁺) **¹H NMR**: (400 MHz, CHLOROFORM-d) δ 8.97 - 8.95 (m, 1H), 8.92 - 8.89 (m, 1H), 8.21 - 8.16 (m, 1H), 7.85 - 7.78 (m, 1H), 7.61 - 7.55 (m, 1H), 7.36 - 7.30 (m, 1H), 7.22 - 7.14 (m, 1H), 7.14 - 7.08 (m, 2H), 5.02 - 4.97 (m, 2H), 4.21 - 4.12 (m, 2H), 3.06 - 2.98 (m, 3H), 1.51 - 1.46 (m, 3H)

Scheme 35.



To a solution of compound 1 in DCM (35 mL) was added Et₃N (1.40 g, 13.85 mmol, 1.93 mL, 1.2 eq) and acetyl chloride (1.09 g, 13.85 mmol, 988.40 uL, 1.2 eq), the reaction mixture was stirred at 0 °C for 12 hours under N₂. TLC (PE:EtOAc=10:1, product R_f=0.8) showed the starting material was consumed completely. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate=100/1 to 20/1(desired product R_f=0.8). Compound 2 was obtained as white solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.42 - 7.34 (m, 2H), 7.28 - 7.20 (m, 1H), 2.37 - 2.21 (m, 3H).

To a solution of compound 2 (2.5 g, 7.33 mmol, 1 eq) in 108-67-8 (30 mL) was added Lawesson's reagent (8.90 g, 22.00 mmol, 3 eq), the mixture was stirred at 180 °C for 4 h. TLC (PE:EtOAc=10:1) showed most of the starting material was remained, and a new point was detected. After the reaction was completed, the mixture was cooled to room temperature, then the mixture was poured into water (80 mL), and extracted with EtOAc (80mL X 3), the combined organic phase was washed with brine (50 mL X 3), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 80/1, desired product R_f=0.6). Compound 3 was obtained as yellow solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.41 - 7.34 (m, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.26 - 7.21 (m, 1H), 2.71 (s, 3H).

To a solution of compound 3 (600 mg, 1.68 mmol, 1 eq) in CHCl₃ (10 mL) was added SbCl₃ (1.15 g, 5.04 mmol, 3 eq) and BAST (1.12 g, 5.04 mmol, 1.10 mL, 3 eq) at 0 °C, the mixture was stirred at 20 °C for 12 h. TLC (PE, starting material R_f=0.6, desired product R_f=0.9) showed the reaction was completed. After the reaction was completed, the mixture

was poured into water (50 mL), and extracted with EtOAc (50 mL X 3), the combined organic phase was washed with brine (50 mL X 3), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound **4** (170 mg, 468.40 umol, 27.87% yield, N/A purity) was obtained as colorless oil. ¹H NMR: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.68 (d, *J* = 1.3 Hz, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 1.99 (t, *J* = 13.4 Hz, 3H).

To a solution of compound **4** (110 mg, 303.08 umol, 1 eq) in MeOH (20 mL) was added Pd(OAc)₂ (6.80 mg, 30.31 umol, 0.1 eq) and DPPF (33.60 mg, 60.62 umol, 0.2 eq), and TEA (153.34 mg, 1.52 mmol, 210.93 uL, 5 eq), the mixture was stirred at 40 °C for 12 hr under CO (50 Psi). After the reaction was completed, the mixture was filtered under N₂ and the filtrate was concentrated to give a crude product. The crude product was purified by prep-TLC (PE:EtOAc=10:1, desired product R_f=0.7). Compound **5** (70 mg, 237.23 umol, 78.27% yield, N/A purity) was obtained as colorless oil.

To a solution of compound **5** (30 mg, 101.67 umol, 1 eq) and compound **6** (21.34 mg, 152.50 umol, 1.5 eq) in 1,4-dioxane (2 mL) was added K₂CO₃ (28.10 mg, 203.34 umol, 2 eq) and Pd(dppf)Cl₂·CH₂Cl₂ (4.15 mg, 5.08 umol, 0.05 eq), the mixture was stirred at 100 °C for 12 hr under N₂. The mixture was filtered and the filtrate was concentrated to give a crude product. The crude product was purified by prep-TLC (Petroleum ether : Ethyl acetate = 10:1, desired product R_f=0.6). Compound **7** (26 mg, 83.00 umol, 81.63% yield, 99.043% purity) was obtained as colorless oil. LCMS: *m/z*=311.1 (M+H⁺).

To a solution of compound **7** (26 mg, 83.80 umol, 1 eq) in H₂O (2 mL), THF (2 mL) and MeOH (2 mL) was added LiOH·H₂O (17.58 mg, 418.99 umol, 5 eq), the mixture was stirred at 25 °C for 12 hr. The reaction mixture was adjusted to pH=5 with HCl (1 M), then extracted with ethyl acetate (10 mL X 3), and the combined organic phase was washed with saturated salt (10 mL X 1), dried over sodium sulphate anhydrous. The organic phase was concentrated to give a crude product. The crude product was used for next step without purification. Compound **8** acid (20 mg, 67.51 umol, 80.57% yield) was obtained as white solid. LCMS: *m/z*=295.1 (M-H⁺).

To a solution of compound **8** (20 mg, 67.51 umol, 1 eq) and compound **9** (29.62 mg, 101.27 umol, 1.5 eq) in DCM (2 mL) was added EDCI (19.41 mg, 101.27 umol, 1.5 eq) and DMAP (824.79 ug, 6.75 umol, 0.1 eq), the mixture was stirred at 20 °C for 3 hr. The reaction mixture was concentrated to give a crude product. The crude product was purified by prep-TLC (Petroleum ether : Ethyl acetate = 0:1, desired product R_f=0.7). Compound **10** (45 mg, crude) was obtained as colorless oil. LCMS: *m/z*=571.2 (M+H⁺).

A solution of compound **10** (45 mg, 78.85 umol, 1 eq) in TFA (2 mL) and DCM (2 mL) was stirred at 20 °C for 1 hr. The mixture was concentrated to give a crude product, the

crude product was dissolved in MeOH (10 mL), and Na₂CO₃ (500 mg) was added to the mixture, the mixture was filtered and the filtrate was concentrated to give a crude product.

The crude product was purified by prep-HPLC (FA, column: Phenomenex luna C18

150*25mm* 10um; mobile phase: [water (FA)-ACN];B%: 15%-45%,9min), the purified

5 solution was lyophilized. **Compound 187** (5.32 mg, 11.92 umol, 15.11% yield, 98.643% purity) was obtained as white solid. **LCMS**: m/z = 441.1(M+H)⁺ **¹H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.29 - 9.17 (m, 1H), 8.47 - 8.37 (m, 2H), 7.58 - 7.50 (m, 1H), 7.48 - 7.35 (m, 3H), 7.24 - 7.15 (m, 2H), 7.13 - 7.06 (m, 1H), 5.04 - 4.95 (m, 2H), 4.95 - 4.89 (m, 1H), 3.08 (s, 3H), 1.73 (s, 3H).

10 **Compound 126** was prepared in a similar manner to **187** and was obtained as a white solid (3 mg, 6.84 umol, 12.87% yield, 99% purity). **LCMS**: m/z = 435.3 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.0-12.3 (m, 1H), 8.1-8.2 (m, 1H), 7.7-7.8 (m, 1H), 7.4-7.6 (m, 1H), 7.3-7.4 (m, 1H), 7.3-7.3 (m, 1H), 7.1-7.3 (m, 2H), 7.0-7.1 (m, 1H), 6.7-6.8 (m, 1H), 4.8-5.0 (m, 2H), 4.1-4.4 (m, 1H), 3.1-3.4 (m, 2H), 2.8-2.9 (m, 1H), 0.5-0.8 (m, 4H).

15 **Compound 133** was prepared in a similar manner to **187** and was obtained as a white solid (17 mg, 40.34 umol, 89.02% yield, 100% purity). **LCMS**: m/z = 422.2 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.01 (br s, 1H), 8.11 (s, 1H), 7.37 - 7.32 (m, 4H), 7.31 - 7.26 (m, 1H), 7.12 (dd, J = 4.6, 7.6 Hz, 1H), 6.77 (t, J = 3.9 Hz, 2H), 6.68 (dd, J = 7.8, 9.4 Hz, 1H), 4.83 (s, 2H), 3.94 (q, J = 7.0 Hz, 2H), 2.94 (s, 3H), 1.21 (t, J = 6.9 Hz, 3H).

20 **Compound 160** was prepared in a similar manner to **187** and was obtained as a white solid. **LCMS**: m/z=461.2 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.36 - 11.98 (m, 1H), 8.52 (s, 1H), 8.59 - 8.39 (m, 1H), 7.41 - 7.33 (m, 2H), 7.30 (br d, J = 5.5 Hz, 2H), 7.06 (s, 3H), 6.27 - 6.18 (m, 1H), 5.01 (s, 2H), 4.07 (q, J = 6.8 Hz, 2H), 3.13 (d, J = 4.9 Hz, 3H), 3.00 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H).

25 **Compound 161** was prepared in a similar manner to **187** and was obtained as a white solid. **LCMS**: m/z=475.2 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.32 - 11.98 (m, 1H), 8.21 (s, 1H), 7.50 - 7.38 (m, 5H), 7.28 (d, J = 7.0 Hz, 1H), 7.18 - 7.12 (m, 3H), 5.09 (s, 2H), 4.17 (q, J = 6.9 Hz, 2H), 3.34 (br s, 3H), 3.11 (s, 6H), 1.47 (t, J = 6.9 Hz, 3H).

30 **Compound 165** was prepared in a similar manner to **187** and was obtained as colorless oil (5.16 mg, 11.65 umol, 16.66% yield, 99.7% purity). **LCMS**: m/z = 442.2 (M+H)⁺ **¹H NMR**: (400 MHz, CHLOROFORM-d) δ = 8.65 - 8.21 (m, 1H), 7.88 - 7.71 (m, 4H), 7.65 - 7.53 (m, 1H), 7.34 - 7.28 (m, 1H), 7.24 - 7.17 (m, 1H), 6.76 (br t, J = 7.7 Hz, 1H), 5.04 - 4.74 (m, 2H), 3.98 (br s, 1H), 3.28 - 2.88 (m, 3H), 1.00 - 0.82 (m, 4H)

35 **Compound 171** was prepared in a similar manner to **187** and was obtained as a white solid (13.42 mg, 31.38 umol, 12.48% yield, 99.7% purity). **LCMS**: m/z = 427.2 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.57 - 11.40 (m, 1H), 8.15 (s, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.71 - 7.65 (m, 1H), 7.65 - 7.58 (m, 1H), 7.54 - 7.45 (m,

1H), 7.39 - 7.33 (m, 1H), 7.33 - 7.28 (m, 1H), 7.22 - 7.16 (m, 1H), 6.92 - 6.82 (m, 1H), 6.77 - 6.68 (m, 1H), 4.95 - 4.87 (m, 2H), 3.89 - 3.82 (m, 1H), 0.94 - 0.85 (m, 2H), 0.78 - 0.70 (m, 2H).

Compound 188 was prepared in a similar manner to **187** and was obtained as
5 colorless oil (5.76 mg, 12.82 μ mol, 13.63% yield, 94.046% purity). **LCMS**: m/z = 423.1 (M+H)⁺ **¹H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.20 (s, 1H), 8.40 (d, J = 11.3 Hz, 2H), 7.52 (s, 1H), 7.55 - 7.50 (m, 1H), 7.46 (s, 5H), 7.43 - 7.41 (m, 1H), 7.41 - 7.37 (m, 1H), 4.99 (s, 2H), 3.09 (s, 3H), 1.77 (br s, 3H).

Compound 189 was prepared in a similar manner to **187** and was obtained as a white
10 solid (2.8 mg, 6.38 μ mol, 8.45% yield, 91% purity). **LCMS**: m/z = 400.0 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 9.1-9.2 (m, 1H), 8.3-8.4 (m, 1H), 8.2-8.3 (m, 1H), 7.7-7.8 (m, 1H), 7.6-7.6 (m, 1H), 7.5-7.5 (m, 1H), 7.5-7.5 (m, 1H), 7.5-7.5 (m, 1H), 7.4-7.4 (m, 3H), 4.9-5.0 (m, 2H), 4.1-4.3 (m, 1H), 3.2-3.4 (m, 3H), 0.7-0.8 (m, 4H).

Compound 201 was prepared in a similar manner to **187** and was obtained as a
15 white solid. **LCMS**: m/z = 456.1 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 9.2-9.3 (m, 1H), 8.4-8.5 (m, 2H), 8.3-8.4 (m, 2H), 8.2-8.3 (m, 1H), 7.68 (d, 1H, J = 7.9 Hz), 7.5-7.6 (m, 1H), 7.4-7.5 (m, 1H), 4.9-5.1 (m, 2H), 4.1-4.2 (m, 2H), 3.13 (s, 3H), 1.49 (t, 3H, J = 6.9 Hz).

Compound 202 was prepared in a similar manner to **187** and was obtained as a
white solid (8.34 mg, 19.15 μ mol, 33.73% yield, 99.50% purity). **LCMS**: m/z = 434.2 (M+H)⁺
20 **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.07 (br dd, J = 6.6, 9.6 Hz, 1H), 9.18 (s, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 9.9 Hz, 1H), 7.45 (dt, J = 6.1, 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 5.30 (t, J = 5.7 Hz, 1H), 5.03 (t, J = 6.9 Hz, 2H), 4.97 (s, 2H), 4.79 (dd, J = 5.1, 7.8 Hz, 2H), 3.11 (s, 3H).

Compound 203 was prepared in a similar manner to **187** and was obtained as a
25 white solid (20 mg, 44.30 μ mol, 25.77% yield, 100% purity). **LCMS**: m/z = 451.1 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 13.08 - 11.63 (m, 1H), 9.33 - 9.19 (m, 1H), 8.52 - 8.46 (m, 1H), 8.46 - 8.43 (m, 1H), 8.43 - 8.39 (m, 1H), 8.02 - 7.89 (m, 1H), 7.88 - 7.78 (m, 1H), 7.30 (br s, 1H), 7.01 - 6.96 (m, 1H), 5.41 - 5.22 (m, 1H), 5.10 - 5.03 (m, 2H), 5.03 - 4.97 (m, 30 2H), 4.83 - 4.76 (m, 2H), 3.20 - 3.06 (m, 3H).

Compound 204 was prepared in a similar manner to **187** and was obtained as a
white solid (6.9 mg, 14.60 μ mol, 25.28% yield, 97% purity). **LCMS**: m/z = 459.1 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 11.9-12.0 (m, 1H), 9.1-9.2 (m, 1H), 8.4-8.5 (m, 1H), 8.3-8.4 (m, 1H), 8.3-8.3 (m, 1H), 8.2-8.3 (m, 1H), 8.1-8.1 (m, 1H), 7.4-7.5 (m, 1H), 7.02 (d, 35 1H, J = 1.6 Hz), 5.34 (quin, 1H, J = 5.4 Hz), 5.05 (t, 2H, J = 6.9 Hz), 4.9-5.0 (m, 2H), 4.7-4.8 (m, 2H), 3.1-3.1 (m, 3H).

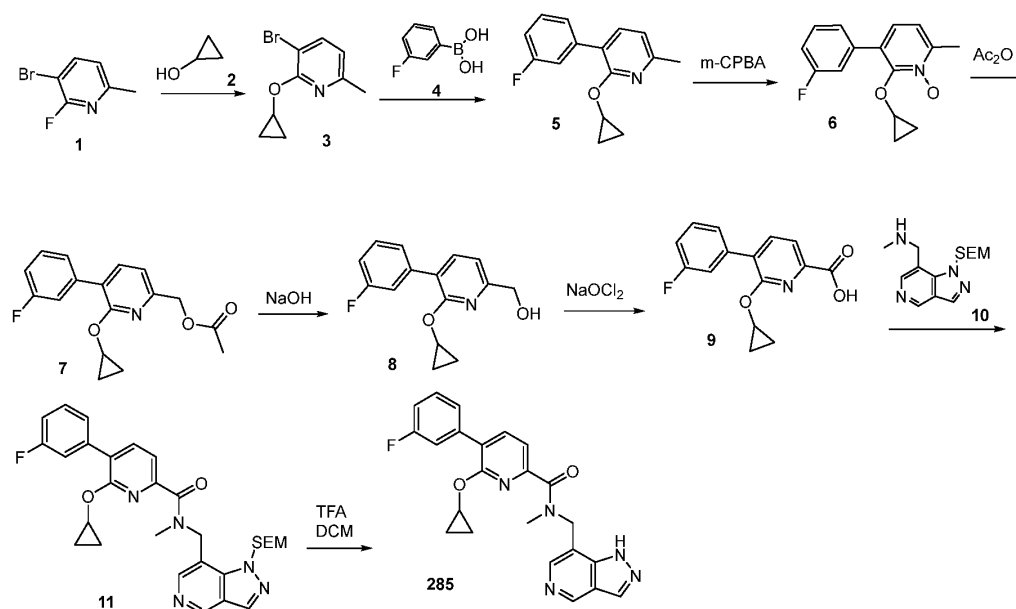
Compound 205 was prepared in a similar manner to **187** and was obtained as a white solid (64 mg, 156.92 μ mol, 93.22% yield, and 99.16 % purity). **LCMS**: m/z = 405.0 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 13.01 - 11.99 (m, 1H), 9.41 - 9.03 (m, 1H), 8.52 - 8.30 (m, 2H), 7.29 (td, J = 2.9, 7.8 Hz, 2H), 7.26 - 7.20 (m, 2H), 7.06 - 6.94 (m, 3H), 4.93 (s, 2H), 4.00 (d, J = 6.9 Hz, 2H), 3.02 (s, 3H), 1.31 (t, J = 6.9 Hz, 3H).

Compound 215 was prepared in a similar manner to **187** and was obtained as a white solid (2.87 mg, 6.85 μ mol, 24.91% yield, 99.1% purity). **LCMS**: m/z = 416.1 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 13.16 - 11.40 (m, 1H), 8.42 (s, 1H), 8.40 (s, 1H), 7.55 (d, J = 1.3 Hz, 1H), 7.39 - 7.29 (m, 4H), 7.09 - 7.03 (m, 2H), 4.99 (d, J = 6.6 Hz, 2H), 4.16 (q, J = 6.9 Hz, 2H), 1.41 (t, J = 6.9 Hz, 3H).

Compound 217 was prepared in a similar manner to **187** and was obtained as a white solid (5.8 mg, 13.46 μ mol, 15.01% yield, 99.2% purity). **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 13.04 - 11.82 (m, 1H), 8.40 (d, J = 6.9 Hz, 2H), 7.92 (s, 1H), 7.41 - 7.37 (m, 1H), 7.36 - 7.32 (m, 1H), 7.26 - 7.12 (m, 3H), 7.08 - 7.01 (m, 1H), 5.00 (d, J = 6.6 Hz, 2H), 3.85 (tt, J = 3.0, 5.9 Hz, 1H), 0.93 - 0.84 (m, 2H), 0.83 - 0.72 (m, 2H).

Compound 218 was prepared in a similar manner to **187** and was obtained as a white solid (9.8 mg, 21.56 μ mol, 22.93% yield, 100% purity). **LCMS**: m/z = 455.2 (M+H)⁺ **¹H NMR** (CHLOROFORM-d, 400 MHz) δ 12.33 - 11.77 (m, 1H), 8.14 - 8.05 (m, 1H), 7.82 - 7.71 (m, 2H), 7.70 - 7.63 (m, 2H), 7.58 (br d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.50 - 7.43 (m, 1H), 4.85 - 4.64 (m, 2H), 4.30 - 3.99 (m, 4H), 3.22 - 2.78 (m, 3H), 0.88 - 0.50 (m, 4H).

Scheme 36.



To a solution of compound **1** (2 g, 10.53 mmol, 1 eq) and compound **2** (916.97 mg, 15.79 mmol, 1.5 eq) in THF (20 mL) was added t-BuOK (2.36 g, 21.05 mmol, 2 eq) at 0 °C, and then stirred at 50 °C for 2 h. The reaction was stirred at 50 °C for another 10h. Cooled to room temperature, poured into 100 mL of water and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to give crude product. The crude product was purified by silica gel column chromatography eluted with PE to give product. Compound **3** (2.17 g, 9.51 mmol, 90.39% yield) was obtained as colourless oil. **LCMS**: m/z = 226.9 (M+H⁺) **¹H NMR**: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.62-7.64 (d, J = 7.8 Hz, 1H), 6.65-6.32 (d, J = 7.8 Hz, 1H), 4.41 - 4.38 (m, 1H), 2.44 (s, 3H), 0.80 - 0.78 (m, 4H)

To a solution of compound **3** (2.17 g, 9.51 mmol, 1 eq) and compound **4** (1.60 g, 11.42 mmol, 1.2 eq) in dioxane (25 mL) /H₂O (2.5 mL) was added K₂CO₃ (2.63 g, 19.03 mmol, 2 eq) and Pd(dppf)Cl₂·CH₂Cl₂ (388.47 mg, 475.70 μmol, 0.05 eq), and then the reaction was stirred at 100 °C for 12 h under N₂. After cooled to room temperature, 50 mL was added and extracted with EtOAc (50 mL x 3). The combined organic layers was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography eluted with PE:EtOAc=1:0 to 20:1 to give product. Compound **5** (1.56 g, 6.41 mmol, 67.40% yield) was obtained as colourless oil. **LCMS**: m/z = 244.0 (M+H⁺) **¹H NMR**: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.41 (d, J = 7.4 Hz, 1H), 7.28 - 7.22 (m, 1H), 7.18-7.12 (m, 2H), 6.94 - 6.88 (m, 1H), 6.76 (d, J = 7.5 Hz, 1H), 4.39 - 4.34(m, 1H), 2.44 (s, 3H), 0.71 - 0.63 (m, 4H)

To a solution of compound **5** (800 mg, 3.29 mmol, 1 eq) in DCM (8 mL) was added m-CPBA (2.00 g, 9.87 mmol, 85% purity, 3 eq) at 0°C, the reaction mixture was stirred at 25°C for 12 hours under N₂. After the reaction was completed, the mixture was poured into saturated Na₂SO₃ solution (100 mL), and extracted with EtOAc (50 mLX3), the combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 1/5, desired product R_f=0.3). Compound **6** (350 mg, 1.35 mmol, 41.05% yield, N/A purity) was obtained as yellow oil. **LCMS**: m/z = 260.1 (M+H⁺)

A solution of compound **6** (338.68 mg, 1.31 mmol, 1 eq) in Ac₂O (5.45 g, 53.38 mmol, 5.00 mL, 40.87 eq) was stirred at 120 °C for 12 hours under N₂. The reaction mixture was partitioned between EtOAc (150 ml) and water (150ml). The separated organic layer was dried over (Na₂SO₄) and evaporated to dryness to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether:ethyl acetate=100/0 to 100/10 (desired mass R_f=0.4). Compound **7** (1.2 g, crude) was obtained as yellow liquid. **LCMS**: m/z=302.0 (M+H⁺) **¹H NMR** (400 MHz, CHLOROFORM-d)

δ = 7.57 - 7.50 (m, 1H), 7.32 - 7.24 (m, 1H), 7.22 - 7.14 (m, 2H), 7.00 - 6.92 (m, 2H), 5.19 - 5.09 (m, 2H), 4.38 - 4.30 (m, 1H), 2.13 - 2.11 (m, 3H), 0.72 - 0.62 (m, 4H).

To a solution of compound **7** (1.2 g, 3.98 mmol, 1 eq) in THF (12 mL), MeOH (12 mL) and H₂O (12 mL) was added NaOH (1.59 g, 39.83 mmol, 10 eq), the reaction mixture was stirred at 25°C for 12 hours under N₂. The reaction mixture was partitioned between EtOAc (250 mL) and water (250 mL), the combined organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and evaporated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether:ethyl acetate = 100/0 to 100/20 (desired product R_f = 0.2). Compound **8** (169 mg, 644.00 μ mol, 16.17% yield, 98.8% purity) was obtained as yellow oil. **LCMS**: m/z = 260.1 (M+H⁺)

To a solution of compound **8** (140 mg, 539.97 μ mol, 1 eq) in ACN (5 mL) was added NaH₂PO₄ (2 M, 404.98 μ L, 1.5 eq) and TEMPO (169.82 mg, 1.08 mmol, 2 eq), the mixture was stirred at 20 °C for 1 h, then sodium chlorite (146.51 mg, 1.62 mmol, 3 eq) and NaClO (1.21 g, 1.62 mmol, 996.60 μ L, 10% purity, 3 eq) was added, the mixture was stirred at 20 °C for 12 h. After the reaction was completed, the mixture was poured into saturated Na₂SO₃ solution (100 mL), and extracted with EtOAc (50 mL x 3), the combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. **LCMS**: m/z = 274.0 (M+H⁺)

To a solution of compound **1** (40 mg, 146.38 μ mol, 1 eq) and compound **2** (42.81 mg, 146.38 μ mol, 1 eq) in DCM (2 mL) was added EDCI (42.09 mg, 219.57 μ mol, 1.5 eq) and DMAP (1.79 mg, 14.64 μ mol, 0.1 eq), the mixture was stirred at 20 °C for 12 h. Evaporate the solution on a water bath under reduced pressure using a rotary evaporator. The crude product was purified by Prep-TLC (Ethyl acetate, desired product R_f = 0.8). Compound **3** (10 mg, 17.36 μ mol, 11.86% yield, 95.1% purity) was obtained as a colorless oil. **LCMS**: m/z = 548.2 (M+H⁺)

To a solution of compound **3** (10 mg, 18.26 μ mol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 739.72 eq), the mixture was stirred at 20 °C for 1 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (FA, column: Phenomenex Luna C18 150*25mm* 10 μ m; mobile phase: [water (FA)-ACN]; B%: 14%-44%, 9 min), the purified solution was lyophilized. Compound **285** (2.2 mg, 4.83 μ mol, 26.44% yield, 91.6% purity) was obtained as yellow solid. **LCMS**: m/z = 418.2 (M+H⁺) **¹H NMR**: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.47 - 11.95 (m, 1H), 9.40 - 8.87 (m, 1H), 8.20 (s, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.39 (br s, 1H), 7.21 (s, 1H), 7.16 (br s, 1H), 7.05 - 6.95 (m, 1H), 5.16 - 4.77 (m, 2H), 4.43 - 3.95 (m, 1H), 3.23 (s, 3H), 0.81 - 0.59 (m, 4H).

Compound 127 was prepared in a similar manner to **285** and was obtained as a light yellow solid (10.08 mg, 21.44 μ mol, 29.19% yield, 93.90% purity). **LCMS**: m/z = 440.6 (M+H⁺)

¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.30 - 11.88 (m, 1H), 8.22 - 8.13 (m, 1H), 7.84 - 7.76 (m, 1H), 7.72 (s, 2H), 7.69 - 7.64 (m, 1H), 7.63 - 7.57 (m, 1H), 7.57 - 7.51 (m, 1H), 7.24 - 7.13 (m, 1H), 6.83 - 6.69 (m, 1H), 5.05 - 4.83 (m, 2H), 4.40 - 4.26 (m, 1H), 3.33 - 3.16 (m, 3H), 0.87 - 0.64 (m, 4H).

5 **Compound 128** was prepared in a similar manner to **285** and was obtained as an off white solid (3.5 mg, 8.02 μ mol, 11.32% yield, 99.5% purity). **LCMS**: m/z = 435.1 (M-H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.47 - 11.38 (m, 1H), 8.31 (s, 1H), 8.09 (s, 1H), 7.75 - 7.68 (m, 1H), 7.66 - 7.60 (m, 1H), 7.59 - 7.52 (m, 1H), 7.35 - 7.24 (m, 1H), 7.17 - 7.10 (m, 1H), 7.05 - 6.96 (m, 1H), 6.72 - 6.61 (m, 1H), 4.85 (s, 2H), 3.74 (br s, 1H), 3.03 - 2.93 (m, 10 3H), 0.88 - 0.77 (m, 2H), 0.76 - 0.64 (m, 2H).

Compound 129 was prepared in a similar manner to **285** and was obtained as a white solid (4 mg, 8.52 μ mol, 19.33% yield, 97.9% purity). **LCMS**: m/z = 460.2 (M-H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.12 - 11.94 (m, 1H), 8.44 - 8.40 (m, 1H), 8.21 - 8.15 (m, 2H), 8.04 - 7.99 (m, 1H), 7.86 - 7.82 (m, 1H), 7.41 - 7.36 (m, 1H), 7.26 - 7.20 (m, 15 1H), 6.83 - 6.74 (m, 1H), 4.99 - 4.91 (m, 2H), 3.91 - 3.85 (m, 1H), 3.11 - 3.03 (m, 3H), 0.99 - 0.89 (m, 2H), 0.88 - 0.80 (m, 2H).

Compound 130 was prepared in a similar manner to **285** and was obtained as a white solid (3.4mg, 7.21 μ mol, 16.81% yield, 96% purity). **LCMS**:m/z = 453.3 (M-H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.12 - 12.03 (m, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.20 (s, 1H), 7.82 (d, J = 1.8 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.23 (dd, J = 4.5, 7.6 Hz, 1H), 6.85 (tt, J = 2.4, 8.7 Hz, 1H), 6.77 (dd, J = 7.8, 9.6 Hz, 1H), 4.96 (s, 2H), 3.86 (tt, J = 3.0, 5.9 Hz, 1H), 3.07 (s, 3H), 0.94 - 0.90 (m, 2H), 0.87 - 0.83 (m, 2H).

Compound 131 was prepared in a similar manner to **285** and was obtained as a white solid (13.1 mg, 29.68 μ mol, 24.20% yield, 99.8% purity). **LCMS**:m/z = 441.2 (M-H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.48 (br s, 1H), 8.28 (s, 1H), 7.49 - 7.32 (m, 8H), 7.10 (br d, J = 7.8 Hz, 1H), 5.11 (s, 2H), 3.76 (br s, 1H), 3.13 (s, 3H), 0.88 - 0.69 (m, 4H).

Compound 143 was prepared in a similar manner to **285** and was obtained as an off-white solid (2.9 mg, 6.69 μ mol, 11.34% yield, 100% purity). **LCMS**: m/z = 434.2 (M+H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.11 - 11.61 (m, 1H), 7.90 - 7.80 (m, 1H), 7.40 - 7.33 (m, 2H), 7.30 (br d, J = 7.6 Hz, 3H), 7.21 - 7.11 (m, 1H), 7.09 - 7.00 (m, 3H), 5.11 (br s, 30 2H), 5.02 - 4.91 (m, 2H), 4.11 - 4.00 (m, 2H), 3.08 - 2.93 (m, 3H), 1.45 - 1.28 (m, 3H).

Compound 144 was prepared in a similar manner to **285** and was obtained as an off-white solid (10 mg, 23.93 μ mol, 32.77% yield, 99.9% purity). **LCMS**: m/z =418.3 (M+H+) ¹H NMR (400 MHz, CHLOROFORM-d) δ = 11.62 - 11.54 (m, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.41 - 7.31 (m, 4H), 7.15 - 7.01 (m, 5H), 4.97 (s, 2H), 4.07 (q, J = 7.0 Hz, 2H), 3.00 (s, 3H), 35 2.65 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H).

Compound 145 was prepared in a similar manner to **285** and was obtained as a white solid (7.6 mg, 17.48 umol, 16.42% yield, 99.7% purity). **LCMS**: m/z = 434.2 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.15 - 11.72 (m, 1H), 8.17 (s, 1H), 7.39 - 7.28 (m, 4H), 7.17 (d, J = 7.6 Hz, 1H), 7.07 - 6.99 (m, 3H), 6.41 (d, J = 7.6 Hz, 1H), 4.88 (s, 2H), 4.05 (q, J = 7.0 Hz, 2H), 3.99 (s, 3H), 2.99 - 2.97 (m, 3H), 1.35 (t, J = 6.9 Hz, 3H).

Compound 146 was prepared in a similar manner to **285** and was obtained as a white solid (11.4 mg, 26.24 umol, 37.04% yield, 100 % purity). **LCMS**: m/z = 435.1 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 1.38 (t, J =7.00 Hz, 3 H) 3.14 (s, 3 H) 3.99 (s, 3 H) 4.39 - 4.45 (m, 2 H) 4.90 (s, 2 H) 6.42 (d, J =7.63 Hz, 1 H) 7.04 - 7.10 (m, 1 H) 7.18 (d, J =7.63 Hz, 1 H) 7.35 (br d, J =7.38 Hz, 2 H) 7.38 - 7.43 (m, 1 H) 7.45 (d, J =7.63 Hz, 1 H) 7.72 (d, J =7.50 Hz, 1 H) 8.17 (s, 1 H) 11.76 - 12.08 (m, 1 H).

Compound 156 was prepared in a similar manner to **285** and was obtained as a white solid (4.79 mg, 10.30 umol, 24.35% yield, 99.048% purity). **LCMS**: m/z =613.3 (M+Na⁺) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.23 (br d, J = 7.5 Hz, 1H), 7.54 - 7.21 (m, 6H), 7.18 - 6.83 (m, 3H), 5.21 - 4.95 (m, 2H), 4.67 - 4.47 (m, 1H), 4.23 - 3.49 (m, 2H), 3.27 - 2.90 (m, 6H), 1.46 - 1.22 (m, 3H), 1.09 (br s, 1H).

Compound 157 was prepared in a similar manner to **285** and was obtained as a white solid (15.6 mg, 32.87 umol, 50.98% yield, 100% purity). **LCMS**: m/z =475.2 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.25 - 12.07 (m, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.39 - 7.20 (m, 5H), 7.17 - 7.10 (m, 2H), 7.05 - 6.77 (m, 3H), 5.05 - 4.75 (m, 2H), 4.13 - 3.73 (m, 2H), 3.51 - 3.32 (m, 3H), 3.21 - 3.10 (m, 3H), 2.93 (s, 3H), 1.29 (s, 3H).

Compound 164 was prepared in a similar manner to **285** and was obtained as a white solid (7.67 mg, 18.10 umol, 19.90% yield, 99% purity). **LCMS**: m/z = 420.1 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 7.98 (s, 1H), 7.40 - 7.33 (m, 2H), 7.33 - 7.28 (m, 2H), 7.12 - 7.01 (m, 4H), 6.97 (s, 1H), 4.92 (s, 2H), 4.05 (q, J = 6.8 Hz, 2H), 3.02 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H).

Compound 168 was prepared in a similar manner to **285** and was obtained as a white solid (44.42 mg, 96.68 umol, 50.21% yield, 100% purity). **LCMS**: m/z = 460.1 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.28 - 11.94 (m, 1H), 8.29 - 8.06 (m, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.66 - 7.56 (m, 2H), 7.52 - 7.47 (m, 1H), 7.40 - 7.34 (m, 1H), 7.17 (br d, J = 2.3 Hz, 1H), 6.76 (dd, J = 7.8, 9.6 Hz, 1H), 4.85 (s, 2H), 4.44 - 4.05 (m, 1H), 3.24 (s, 3H), 0.92 - 0.45 (m, 4H).

Compound 169 was prepared in a similar manner to **285** and was obtained as a white solid (2.54mg, 4.59 umol, 32.63% yield, 90% purity). **LCMS**: m/z =453.0 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.31 - 11.74 (m, 1H), 8.09 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.44 - 7.24 (m, 1H), 7.14 (dd, J = 4.5, 7.6 Hz, 1H), 7.16 -

7.11 (m, 1H), 7.01 - 6.93 (m, 1H), 7.04 - 6.90 (m, 1H), 6.81 - 6.61 (m, 2H), 4.89 - 4.77 (m, 1H), 4.95 - 4.68 (m, 1H), 4.29 - 4.07 (m, 1H), 3.16 (s, 3H), 0.68 (br d, $J = 12.4$ Hz, 4H).

Compound 190 was prepared in a similar manner to **285** and was obtained as a white solid (5.16 mg, 11.63 μ mol, 10.74% yield, 99.7% purity). **LCMS**: $m/z = 443.1$ (M+H+)

5 **^1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 8.49 - 8.45$ (m, 1H), 8.44 - 8.42 (m, 1H), 7.81 - 7.76 (m, 1H), 7.66 - 7.61 (m, 1H), 7.45 - 7.37 (m, 1H), 7.31 - 7.29 (m, 1H), 7.27 - 7.24 (m, 1H), 7.13 - 7.07 (m, 1H), 5.08 - 5.05 (m, 2H), 4.38 - 4.30 (m, 1H), 3.38 - 3.35 (m, 3H), 0.81 - 0.75 (m, 4H).

10 **Compound 195** was prepared in a similar manner to **285** and was obtained as a white solid (12mg, 27.26 μ mol, 43.13% yield, 96.2% purity). **LCMS**: $m/z = 424.3$ (M-H+) **^1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 12.62 - 12.52$ (m, 1H), 8.44 (d, $J = 4.6$ Hz, 2H), 7.47 - 7.42 (m, 3H), 7.42 - 7.37 (m, 2H), 7.36 - 7.33 (m, 2H), 7.13 - 7.08 (m, 1H), 5.01 (s, 2H), 3.78 - 3.74 (m, 1H), 3.10 (s, 3H), 0.79 (br t, $J = 5.3$ Hz, 2H), 0.81 - 0.74 (m, 1H), 0.75 (dd, $J = 3.5, 4.3$ Hz, 1H).

15 **Compound 200** was prepared in a similar manner to **285** and was obtained as a white solid (12.9 mg, 26.25 μ mol, 36.26% yield, 100 % purity). **LCMS**: $m/z = 492.1$ (M-H+) **^1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 1.36$ (t, $J=6.94$ Hz, 3 H) 3.02 (s, 3 H) 3.06 (d, $J=4.25$ Hz, 3 H) 4.07 (q, $J=7.00$ Hz, 2 H) 4.13 (s, 3 H) 4.84 (s, 2 H) 6.77 (dt, $J=7.63, 4.57$ Hz, 1 H) 7.04 - 7.10 (m, 2 H) 7.15 (dd, $J=11.76, 8.63$ Hz, 1 H) 7.36 (d, $J=7.50$ Hz, 1 H) 7.65 - 7.70 (m, 1 H) 7.81 - 7.84 (m, 1 H) 8.18 (s, 1 H) 8.27 (dd, $J=7.69, 2.44$ Hz, 1 H) 11.91 - 12.31 (m, 1 H).

25 **Compound 213** was prepared in a similar manner to **285** and was obtained as a white solid (2.34 mg, 5.24 μ mol, 5.70% yield, 95% purity). **LCMS**: $m/z = 425.0$ (M-H+) **^1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 12.31 - 11.74$ (m, 1H), 8.09 (s, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.44 - 7.24 (m, 1H), 7.14 (dd, $J = 4.5, 7.6$ Hz, 1H), 7.16 - 7.11 (m, 1H), 7.01 - 6.93 (m, 1H), 7.04 - 6.90 (m, 1H), 6.81 - 6.61 (m, 2H), 4.89 - 4.77 (m, 1H), 4.95 - 4.68 (m, 1H), 4.29 - 4.07 (m, 1H), 4.29 - 4.01 (m, 1H), 3.16 (s, 3H), 0.68 (br d, $J = 12.4$ Hz, 4H).

30 **Compound 232** was prepared in a similar manner to **285** and was obtained as a white solid (6 mg, 14.37 μ mol, 19.68% yield, 100% purity). **LCMS**: $m/z = 418.1$ (M-H+) **^1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 12.54 - 12.40$ (m, 1H), 9.20 (br s, 1H), 8.44 (br s, 1H), 8.39 (s, 1H), 7.99 (d, $J = 1.4$ Hz, 1H), 7.91 (d, $J = 1.4$ Hz, 1H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.11 - 7.08 (m, 2H), 4.99 (s, 2H), 4.15 (q, $J = 6.9$ Hz, 2H), 3.06 (s, 3H), 1.48 (t, $J = 6.9$ Hz, 3H)

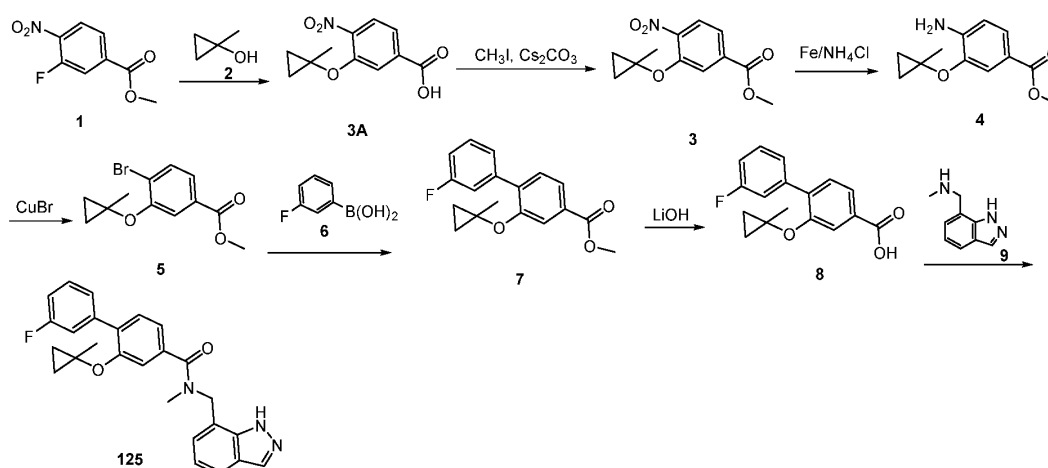
35 **Compound 233** was prepared in a similar manner to **285** and was obtained as a white solid (7 mg, 17.70 μ mol, 15.42% yield, 99% purity). **LCMS**: $m/z = 393.1$ (M-H+) **^1H NMR** (400 MHz, CHLOROFORM- d) $\delta = 12.26$ (br s, 1H), 9.15 (br s, 1H), 8.46 - 8.17 (m, 2H),

7.74 (dd, $J = 1.3, 3.0$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.48 (dd, $J = 1.3, 5.0$ Hz, 1H), 7.36 (dd, $J = 3.0, 5.0$ Hz, 1H), 7.10 - 7.02 (m, 2H), 4.95 (s, 2H), 4.13 (q, $J = 7.0$ Hz, 2H), 3.05 (s, 3H), 1.48 (t, $J = 6.9$ Hz, 3H)

Compound 234 was prepared in a similar manner to **285** and was obtained as a yellow solid (34 mg, 86.41 μ mol, 43.10% yield, 100% purity). **LCMS**: $m/z = 394.1$ (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 13.40 - 12.56$ (m, 1H), 9.66 - 9.07 (m, 1H), 8.61 - 8.39 (m, 2H), 8.06 - 7.77 (m, 2H), 7.57 - 7.46 (m, 2H), 7.40 (dd, $J = 3.1, 5.1$ Hz, 1H), 5.23 - 4.85 (m, 2H), 4.47 (q, $J = 6.4$ Hz, 2H), 3.39 - 3.18 (m, 3H), 1.67 - 1.36 (m, 3H)

Compound 235 was prepared in a similar manner to **285** and was obtained as a white solid (8 mg, 19.12 μ mol, 29.97% yield, 100% purity). **LCMS**: $m/z = 419.0$ (M-H⁺) **¹H NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 12.63 - 12.25$ (m, 1H), 9.21 (br s, 1H), 8.45 (br s, 1H), 8.38 (s, 1H), 8.03 (d, $J = 0.9$ Hz, 2H), 7.89 (d, $J = 7.6$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 1H), 5.00 (s, 2H), 4.48 (q, $J = 7.1$ Hz, 2H), 3.24 (s, 3H), 1.46 (t, $J = 7.1$ Hz, 3H)

15 **Scheme 37.**



To a solution of compound **1** (800 mg, 4.02 mmol, 1 eq) and compound **2** (579.35 mg, 8.03 mmol, 2 eq) in DMF (10 mL) was added NaH (482.04 mg, 12.05 mmol, 60% purity, 3 eq) at 0 °C, the mixture was stirred at 20 °C for 12h. The mixture was poured into saturated NH₄Cl (50 mL) solution, and extracted with EtOAc (50 mL X3), the combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product used for next step without further purification. Compound **3A** (2 g, crude) was obtained as red oil. **LCMS**: $m/z = 236.1$ (M+H⁺)

To a solution of compound **3A** (2 g, 8.43 mmol, 1 eq) in DMF (20 mL) was added Cs₂CO₃ (5.49 g, 16.86 mmol, 2 eq) and CH₃I (3.59 g, 25.29 mmol, 1.57 mL, 3 eq), the reaction mixture was stirred at 70 °C for 2 hours under N₂. TLC (petroleum: ethyl acetate=10:1, desired product R_f=0.4) showed the starting material was consumed completely. The

- reaction mixture was partitioned between EtOAc (150ml) and water (150ml). The separated organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and evaporated to give a crude product. The crude product was purified by column chromatography on silica gel eluted by petroleum: ethyl acetate=100:0 to 100/10(desired product R_f=0.4). Compound
- 5 **3** (362 mg, crude) was obtained as yellow solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.00 - 7.95 (m, 1H), 7.73 - 7.67 (m, 1H), 7.62 - 7.57 (m, 1H), 3.92 - 3.89 (m, 3H), 1.58 - 1.54 (m, 3H), 1.25 - 1.14 (m, 1H), 1.05 - 0.99 (m, 2H), 0.79 - 0.74 (m, 2H).
- To a solution of compound **3** (420 mg, 1.67 mmol, 1 eq) in H₂O (10 mL) and MeOH (10 mL) was added Fe (933.58 mg, 16.72 mmol, 10 eq) and NH₄Cl (894.24 mg, 16.72 mmol, 10 eq),
- 10 the reaction mixture was stirred at 70°C for 2 hours under N₂. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The product was purified by column chromatography on silica gel eluted by petroleum ether: ethyl acetate=100/0 to 100/10 (desired product R_f= 0.4).Compound **4** (256 mg, 1.12 mmol, 66.84% yield, 96.57% purity) was obtained as white solid. LCMS: m/z =222.0 (M+H+)
- 15 To a solution of compound **4** (120 mg, 542.37 umol, 1 eq) in MeCN (5 mL) and CuBr (155.61 mg, 1.08 mmol, 33.04 uL, 2 eq)was added isopentyl nitrite (127.07 mg, 1.08 mmol, 146.06 uL, 2 eq) under N₂, the reaction mixture was stirred at 70°C for 12 hours under N₂. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The crude product was purified by prep-TLC (petroleum ether: ethyl acetate=10:1, desired mass R_f
- 20 =0.8).Compound **5** (85 mg, 288.39 umol, 53.17% yield, 96.74% purity) was obtained as white solid. LCMS: m/z =284.9 (M+H+)
- To a solution of compound **5** (85 mg, 298.11 umol, 1 eq) in dioxane (1 mL) was added compound **6** (50.05 mg, 357.73 umol, 1.2 eq), K₂CO₃ (82.40 mg, 596.21 umol, 2 eq) and Pd (dppf) Cl₂. CH₂Cl₂ (24.34 mg, 29.81 umol, 0.1 eq), the reaction mixture was stirred at 100°C
- 25 for 12 hours under N₂. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The crude product was purified by prep-TLC (petroleum ether: ethyl acetate=10:1, desired mass R_f=0.7) Compound **7** (85 mg, 279.07 umol, 93.61% yield, 98.60% purity) was obtained as colorless oil. LCMS: m/z =301.1 (M+H+)
- To a solution of compound **7** (85 mg, 283.03 umol, 1 eq) in H₂O (1 mL), THF (1 mL) and
- 30 MeOH (1 mL) was added LiOH·H₂O (59.38 mg, 1.42 mmol, 5 eq), the reaction mixture was stirred at 30°C for 2 hours under N₂. Acidify the reaction mixture by adding 1mol/L HCl to pH=5, the precipitated brown solid was collected and dried. The crude product was used directly to the next step without purification. Compound **8** (54 mg, 185.26 umol, 65.46% yield, 98.22% purity) was obtained as white solid. LCMS: m/z =287.0 (M+H+)
- 35 To a solution of compound **8** (20 mg, 69.86 umol, 1 eq) in DCM (2 mL) was added compound **9** (13.51 mg, 83.83 umol, 1.2 eq), EDCI (20.09 mg, 104.79 umol, 1.5 eq) and DMAP (853.44 ug, 6.99 umol, 0.1 eq), the reaction mixture was stirred at 25°C for 12 hours

under N₂. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 51%-81%, 9min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give white solid. **125** (22.58 mg, 52.57 umol, 75.26% yield, 100% purity) was obtained as white solid. **LCMS**: m/z =430.1(M+H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.07 - 11.90 (m, 1H), 8.15 (s, 1H), 7.83 - 7.78 (m, 1H), 7.41 - 7.39 (m, 1H), 7.38 - 7.35 (m, 1H), 7.35 - 7.33 (m, 1H), 7.26 - 7.13 (m, 4H), 7.10 - 7.03 (m, 2H), 5.01 (s, 2H), 3.06 - 3.04 (m, 3H), 1.59 - 1.58 (m, 3H), 1.03 - 0.96 (m, 2H), 0.78 - 0.72 (m, 2H).

Compound 138 was prepared in a similar manner to **125** and was obtained as a white solid (6.51 mg, 14.58 umol, 15.57% yield, 100% purity). **LCMS**: m/z=447.3 (M-H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.36 (m, 1H), 8.36 - 8.32 (m, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.37 - 7.33 (m, 2H), 7.13 - 7.06 (m, 4H), 6.84 - 6.76 (m, 1H), 5.03 (s, 2H), 4.10 (q, J = 6.9 Hz, 2H), 1.43 - 1.38 (m, 3H), 1.28 (s, 1H).

Compound 139 was prepared in a similar manner to **125** and was obtained as a white solid (4.7 mg, 10.50 umol, 18.39% yield, 100% purity). **LCMS**: m/z = 448.2 (M-H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.31 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.1 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.1 Hz, 1H), 7.14 (br d, J = 6.5 Hz, 2H), 6.84 (s, 1H), 5.03 (s, 2H), 4.43 (d, J = 7.0 Hz, 2H), 3.20 (s, 3H), 1.55 (br s, 1H), 1.39 (t, J = 7.1 Hz, 3H).

Compound 140 was prepared in a similar manner to **125** and was obtained as a white solid (12.21 mg, 30.11 umol, 26.22% yield, 99% purity). **LCMS**: 0.552 min, m/z = 405.1 (M-H+).

Compound 141 was prepared in a similar manner to **125** and was obtained as a white solid (13 mg, 30.77 umol, 41.28% yield, 97.4% purity). **LCMS**: m/z = 412.2 (M-H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 11.92 (br s, 1H), 8.98 (d, J = 2.1 Hz, 1H), 8.85 (d, J = 1.9 Hz, 1H), 8.18 (t, J = 2.0 Hz, 1H), 8.15 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 6.9 Hz, 1H), 7.18 - 7.11 (m, 3H), 5.00 (s, 2H), 4.16 - 4.08 (m, 2H), 3.02 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H).

Compound 142 was prepared in a similar manner to **125** and was obtained as a white solid (9 mg, 20.62umol, 22.47% yield, 100% purity). **LCMS**: m/z =437.2 (M-H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.25 (br d, J = 1.0 Hz, 1H), 8.89 - 8.88 (m, 1H), 8.77 (d, J = 1.9 Hz, 1H), 8.26 - 8.24 (m, 1H), 8.09 (t, J = 2.1 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.29 (dd, J = 2.6, 7.4 Hz, 2H), 7.07 - 7.01 (m, 2H), 4.95 (s, 2H), 4.03 (q, J = 7.0 Hz, 2H), 2.95 (s, 3H), 1.34 - 1.27 (m, 4H).

Compound 154 was prepared in a similar manner to **125** and was obtained as a white solid (2.7 mg, 5.17 μ mol, 4.34% yield, 96.5% purity).

Compound 183 was prepared in a similar manner to **125** and was obtained as a white solid (12.9 mg, 32.41 μ mol, 19.70% yield, 98.6% purity). **LCMS**: m/z = 393.1 (M-H+)
5 **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.47 (d, J = 1.6 Hz, 1H), 8.13 (s, 1H), 7.80 (t, J = 8.8 Hz, 2H), 7.65 (d, J = 1.5 Hz, 1H), 7.29 (s, 1H), 7.18 - 7.08 (m, 3H), 4.97 (s, 2H), 4.28 (q, J = 7.0 Hz, 2H), 2.98 (s, 3H), 1.62 (t, J = 6.9 Hz, 3H).

Compound 184 was prepared in a similar manner to **125** and was obtained as a white solid (23.9 mg, 60.46 μ mol, 50.24% yield, 99.28% purity). **LCMS**: m/z = 393.0 (M-H+)
10 **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.76 (br d, J = 1.0 Hz, 1H), 8.47 - 8.27 (m, 1H), 8.20 - 8.07 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.30 (s, 1H), 7.20 - 7.04 (m, 3H), 5.16 - 4.80 (m, 2H), 4.37 - 4.01 (m, 2H), 3.08 - 2.90 (m, 3H), 1.69 - 1.39 (m, 3H)

Compound 185 was prepared in a similar manner to **125** and was obtained as a white solid (35 mg, 104.98 μ mol, 28.52% yield, 100% purity). **LCMS**: m/z = 344.1 (M-H+) **¹H**
15 **NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.14 (s, 1H), 7.81 - 7.76 (m, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.31 - 7.28 (m, 1H), 7.17 - 7.11 (m, 1H), 6.98 - 6.93 (m, 2H), 4.95 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.34 (s, 1H), 2.94 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H).

Compound 196 was prepared in a similar manner to **125** and was obtained as a white solid (2.6 mg, 5.77 μ mol, 33.00% yield, 98% purity). **LCMS**: m/z = 442.2 (M-H+) **¹H**
20 **NMR** (400 MHz, CHLOROFORM-*d*) δ = 12.66 - 12.50 (m, 1 H) 8.53 - 8.40 (m, 2 H) 7.48 (d, J = 1.38 Hz, 1 H) 7.43 - 7.35 (m, 2 H) 7.28 - 7.20 (m, 1 H) 7.28 - 7.19 (m, 1 H) 7.14 (dd, J = 7.75, 1.50 Hz, 1 H) 7.07 (td, J = 8.47, 1.81 Hz, 1 H) 5.10 - 5.00 (m, 2 H) 3.83 - 3.74 (m, 1 H) 3.13 (s, 3 H) 0.87 - 0.78 (m, 4 H).

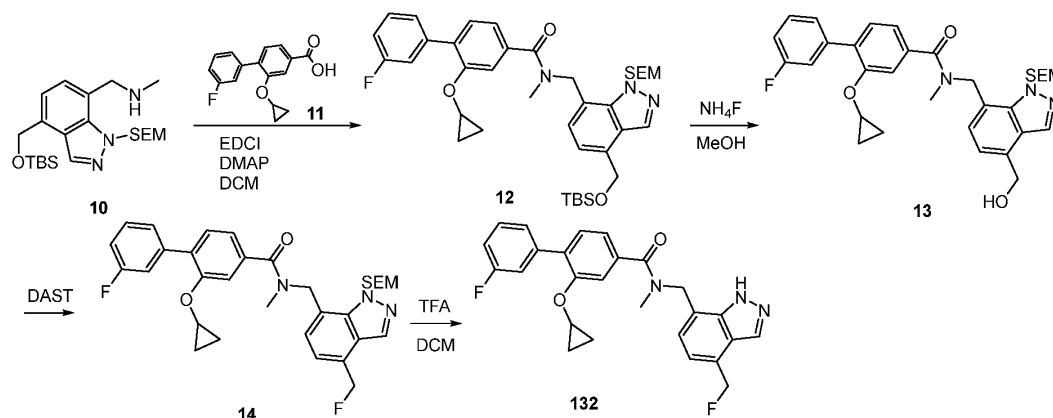
Compound 197 was prepared in a similar manner to **125** and was obtained as a
25 white solid (2.4 mg, 4.93 μ mol, 19.01% yield, 92% purity). **LCMS**: m/z = 448.2 (M-H+) **¹H**
NMR (400 MHz, CHLOROFORM-*d*) δ = 8.44 (d, 2H, J = 2.0 Hz), 7.35 (d, 1H, J = 7.8 Hz), 7.1 - 7.1 (m, 4H), 6.80 (tt, 1H, J = 2.3, 8.9 Hz), 5.01 (s, 2H), 4.08 (q, 2H, J = 6.9 Hz), 3.07 (s, 3H), 1.39 (t, 3H, J = 6.9 Hz).

Compound 198 was prepared in a similar manner to **125** and was obtained as a
30 white solid (15.3 mg, 36.84 μ mol, 66.64% yield, 99.30% purity). **LCMS**: m/z = 413.2 (M-H+)
¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 12.10 (br s, 1H), 9.21 - 9.14 (m, 1H), 8.98 (d, J = 2.1 Hz, 1H), 8.88 - 8.84 (m, 1H), 8.36 (s, 1H), 8.29 (s, 1H), 8.18 (t, J = 2.1 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.18 - 7.10 (m, 2H), 5.02 - 4.92 (m, 2H), 4.19 - 4.08 (m, 2H), 3.06 (s, 4H), 1.40 (t, J = 7.0 Hz, 4H).

35 **Compounds 163 and 259** were prepared in a similar manner to **125** and were separated using an SFC column. Both compounds were obtained as a white solid (9 mg, 20.62 μ mol, 22.47% yield, 100% purity). **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 13.19 -

11.87 (m, 1H), 8.33 - 8.23 (m, 1H), 7.92 - 7.85 (m, 1H), 7.81 - 7.77 (m, 1H), 7.77 - 7.69 (m, 1H), 7.69 - 7.63 (m, 1H), 7.60 - 7.52 (m, 2H), 7.51 - 7.34 (m, 2H), 6.59 - 5.53 (m, 1H), 4.69 - 4.22 (m, 2H), 3.00 - 2.57 (m, 3H), 1.95 - 1.70 (m, 3H), 1.40 - 1.28 (m, 3H).

Scheme 38.



5

The solution of compound **10** (160.04 mg, 367.28 μmol , 2 eq) and compound **11** (50 mg, 183.64 μmol , 1 eq) in DCM (1 mL) was added in EDCI (52.81 mg, 275.46 μmol , 1.5 eq) and DMAP (2.24 mg, 18.36 μmol , 0.1 eq). Then stirred at 20°C for 2hrs. Evaporate the solution on a water bath under reduced pressure using a rotary evaporator. The residue was purified by prep-TLC (SiO₂, PE: EtOAc = 10: 1, R_f = 0.1), filtered and filtrate was concentrated in vacuo to give colourless oil. The compound of **12** (53 mg, 76.81 μmol , 41.83% yield) was obtained as yellow oil. **LCMS**: m/z = 572.2 (M+H) +

10

The solution of compound **12** (53 mg, 76.81 μmol , 1 eq) in MeOH (4 mL) was added in NH₄F (28.45 mg, 768.11 μmol , 10 eq). Then the mixture was stirred at 60°C for 2.5 hrs. The mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-TLC (PE:EtOAc=2:1, desired product R_f=0.3), the purified solution was concentrated. 3-(cyclopropoxy)-4-(3-fluorophenyl)-N-[[4-(hydroxymethyl)-1-(2-trimethylsilylethoxymethyl) indazol-7-yl] methyl]-N-methyl-benzamide (30 mg, 52.11 μmol , 67.84% yield) was obtained as white solid. **LCMS**: m/z = 458.1 (M+H) +

15

The mixture of compound **13** (30 mg, 52.11 μmol , 1 eq) in DCM (1 mL) was added in DAST (12.60 mg, 78.16 μmol , 10.33 μL , 1.5 eq). The mixture was stirred at 0°C for 0.5hrs under N₂. The reaction mixture was cooled in an ice water bath and quenched by addition of saturated NaHCO₃. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (20 mL×2). The combined organic solutions were dried over Na₂SO₄ and evaporated to give the residue. The crude product was purified by prep-TLC (SiO₂, Petroleum ether: EtOAc = 1:1). The compound of **14** (20 mg, 34.62 μmol , 66.44% yield, N/A purity) was obtained as colourless solid. **LCMS**: m/z = 460.1 (M+H)+ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 9.62 - 9.56 (m, 1H), 8.75 - 8.51 (m, 3H), 7.27 (s, 2H), 7.21 (d, J = 6.0

25

Hz, 1H), 7.09 (d, J = 6.1 Hz, 1H), 6.62 (br d, J = 14.4 Hz, 2H), 5.58 (q, J = 7.1 Hz, 4H), 5.46 - 5.30 (m, 2H), 5.22 - 5.10 (m, 2H), 5.02 - 4.91 (m, 3H), 4.56 - 4.42 (m, 4H), 4.30 (s, 1H), 3.71 (s, 2H), 3.59 - 3.54 (m, 2H), 2.87 (qd, J = 8.1, 11.8 Hz, 2H), 2.40 - 2.23 (m, 3H), 1.56 - 1.44 (m, 2H)

- 5 The mixture of compound **14** (20 mg, 34.62 μ mol, 1 eq) in DCM (1 mL) was added in TFA (770.00 mg, 6.75 mmol, 0.5 mL, 195.07 eq). The mixture was stirred at 20°C for 2hrs.

Evaporate the solution on a water bath under reduced pressure using a rotary evaporator.

The residue product was purified by prep HPLC. Column: Welch Xtimate C18

150*25mm*5 μ m; mobile phase: [water (NH₃H₂O)-ACN]; B%: 55%-85%, 8 min. lyophilized.

- 10 The compound **132** (4.29 mg, 9.59 μ mol, 27.69% yield, 100% purity) was obtained as white solid **LCMS**: m/z = 448.3 (M+H) + **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.26 - 8.21 (m, 1H), 7.47 - 7.32 (m, 4H), 7.25 - 7.16 (m, 3H), 7.15 - 7.08 (m, 2H), 7.06 - 7.00 (m, 1H), 5.83 - 5.66 (m, 2H), 5.00 (s, 2H), 3.81 - 3.72 (m, 1H), 3.03 (s, 3H), 0.75 (br s, 4H).

Compound 155 was prepared in a similar manner to **132**. **LCMS**: m/z = 493.4 (M-

- 15 H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.30 - 8.19 (m, 2H), 7.71 - 7.64 (m, 1H), 7.37 - 7.33 (m, 1H), 7.30 - 7.27 (m, 1H), 7.19 - 7.00 (m, 4H), 5.82 - 5.79 (m, 1H), 5.69 (s, 1H), 5.00 - 4.97 (m, 2H), 4.11 - 4.01 (m, 2H), 3.01 (s, 6H), 1.40 - 1.32 (m, 4H).

Compound 162 was prepared in a similar manner to **132** and isolated as a yellow

- solid. **LCMS**: m/z = 436.2 (M-H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.26 - 11.95 (m, 1H), 8.17 - 7.47 (m, 1H), 7.38 - 7.30 (m, 4H), 7.23 - 7.17 (m, 2H), 7.11 - 7.01 (m, 3H), 5.94 - 5.70 (m, 2H), 4.97 (s, 2H), 4.21 - 3.95 (m, 2H), 3.01 (s, 3H), 1.40 - 1.34 (m, 3H).

Compound 166 was prepared in a similar manner to **132** and isolated as a white

- solid (4.82 mg, 10.75 μ mol, 44.27% yield, 97.160% purity). **LCMS**: m/z = 436.4 (M-H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.17 (s, 1H), 7.80 (d, J = 2.3 Hz, 1H), 7.42 - 7.28 (m, 5H), 7.17 - 6.97 (m, 3H), 5.63 - 5.36 (m, 2H), 4.99 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.29 - 2.92 (m, 3H), 1.42 - 1.32 (m, 3H).

Compound 175 was prepared in a similar manner to **132** and isolated as a white

- solid (4.8 mg, 9.73 μ mol, 12.75% yield, 96% purity). **LCMS**: m/z = 474.2 (M+H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.26 - 8.18 (m, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.54 - 7.48 (m, 1H), 7.41 - 7.35 (m, 1H), 7.31 (br d, J = 6.9 Hz, 1H), 7.13 (dd, J = 2.5, 7.0 Hz, 1H), 5.91 - 5.58 (m, 2H), 5.01 (s, 2H), 4.48 - 4.27 (m, 1H), 3.37 - 3.16 (m, 3H), 0.81 - 0.70 (m, 4H).

Compound 176 was prepared in a similar manner to **132** and isolated as a gray solid

- 35 (4.8 mg, 10.14 μ mol, 23.90% yield, 100% purity). **LCMS**: m/z = 474.2 (M+H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.43 - 8.38 (m, 1H), 8.25 - 8.22 (m, 1H), 8.17 - 8.13 (m, 1H), 8.03 - 7.97 (m, 1H), 7.84 - 7.81 (m, 1H), 7.40 - 7.34 (m, 1H), 7.32 - 7.28 (m, 1H), 7.13 (dd, J

= 2.4, 6.9 Hz, 1H), 5.81 - 5.67 (m, 2H), 5.02 - 4.98 (m, 2H), 3.90 - 3.84 (m, 1H), 3.06 (s, 3H), 0.95 - 0.82 (m, 4H).

Compound 177 was prepared in a similar manner to **132** and isolated as a white solid (10 mg, 22.39 μ mol, 41.77% yield, 96.144% purity). LCMS: m/z = 430.1 (M+H)⁺ ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.51 - 12.20 (m, 1H), 9.25 - 9.17 (m, 1H), 8.42 (br s, 1H), 8.36 (s, 1H), 7.93 (s, 1H), 7.66 - 7.63 (m, 2H), 7.49 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 4.99 (s, 2H), 3.96 - 3.88 (m, 1H), 3.07 (s, 3H), 0.93 - 0.89 (m, 4H).

Compound 206 was prepared in a similar manner to **132** and isolated as a yellow solid (4.14 mg, 9.21 μ mol, 3.56% yield, 100% purity). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.38 - 12.09 (m, 1H), 8.41 (br s, 1H), 8.33 - 8.20 (m, 1H), 7.75 (br d, J = 7.4 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.60 (br d, J = 7.6 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.31 - 7.29 (m, 1H), 7.25 - 7.22 (m, 1H), 7.26 - 7.22 (m, 1H), 7.08 (br t, J = 7.8 Hz, 1H), 5.77 (s, 1H), 5.04 - 4.95 (m, 2H), 4.39 - 4.25 (m, 1H), 3.38 - 3.23 (m, 3H), 0.82 - 0.69 (m, 4H).

Compound 211 was prepared in a similar manner to **132** and isolated as a yellow solid (7.2 mg, 15.35 μ mol, 45.64% yield, 99% purity). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.43 - 12.00 (m, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.28 (s, 1H), 7.45 - 7.36 (m, 2H), 7.36 - 7.29 (m, 2H), 7.17 - 7.05 (m, 2H), 6.62 (s, 1H), 5.93 - 5.76 (m, 2H), 5.27 - 5.20 (m, 1H), 4.99 - 4.92 (m, 4H), 4.75 - 4.69 (m, 2H), 3.04 (s, 3H).

Compound 212 was prepared in a similar manner to **132** and isolated as a yellow solid (24 mg, 52.58 μ mol, 49.76% yield, 100% purity). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.71 - 8.67 (m, 1H), 8.57 (s, 1H), 7.84 (s, 1H), 7.77 (t, J = 8.2 Hz, 2H), 7.72 - 7.65 (m, 2H), 7.60 - 7.54 (m, 1H), 6.26 - 6.09 (m, 2H), 5.13 - 5.03 (m, 2H), 4.36 - 4.31 (m, 1H), 3.40 (s, 3H), 0.83 - 0.72 (m, 4H).

Compound 219 was prepared in a similar manner to **132** and isolated as a yellow solid (4 mg, 8.76 μ mol, 10.26% yield, 99.71% purity). LCMS: m/z = 456.2 (M+H)⁺ ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.56 (d, J = 2.5 Hz, 1H), 8.44 (br d, J = 1.9 Hz, 1H), 7.77 (s, 1H), 7.71 - 7.68 (m, 1H), 7.66 - 7.61 (m, 1H), 7.54 - 7.46 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.14 (dd, J = 1.0, 7.8 Hz, 1H), 6.04 (s, 1H), 5.93 (s, 1H), 5.01 (s, 2H), 3.79 (qd, J = 3.0, 5.9 Hz, 1H), 3.10 (s, 3H), 0.87 - 0.82 (m, 2H), 0.77 - 0.72 (m, 2H).

Compound 220 was prepared in a similar manner to **132** and isolated as a yellow solid (9.1 mg, 20.23 μ mol, 23.42% yield, 99.7% purity). LCMS: m/z = 449.1 (M+H)⁺ ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.45 (d, J = 6.5 Hz, 2H), 7.79 - 7.75 (m, 1H), 7.72 - 7.60 (m, 2H), 7.55 - 7.45 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.16 - 7.11 (m, 1H), 5.05 - 5.00 (m, 2H), 3.83 - 3.75 (m, 1H), 3.10 (s, 3H), 2.66 - 2.62 (m, 1H), 0.90 - 0.73 (m, 4H).

Compound 221 was prepared in a similar manner to **132** and isolated as a white solid (20.81 mg, 47.79 μ mol, 31.07% yield, 100% purity). LCMS: m/z = 436.1 (M+H)⁺ ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.20 (br s, 1H), 8.78 (br s, 1H), 8.17 (br d, J = 1.8

Hz, 1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.46 - 7.34 (m, 4H), 7.08 (br t, $J = 7.7$ Hz, 1H), 5.04 (s, 2H), 4.43 (q, $J = 7.1$ Hz, 2H), 4.20 (s, 3H), 3.25 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H).

Compound 222 was prepared in a similar manner to **132** and isolated as a white solid (37.10 mg, 82.67 μ mol, 39.46% yield, 98.6% purity). LCMS: $m/z = 443.0$ (M+H)⁺ ¹H

5 **NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 11.95$ (br s, 1H), 8.76 (s, 1H), 8.16 (s, 1H), 7.92 (s, 1H), 7.81 (br d, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.46 (d, $J = 7.5$ Hz, 1H), 5.04 (s, 2H), 4.44 (q, $J = 7.0$ Hz, 2H), 4.18 (s, 3H), 3.24 (s, 3H), 1.41 - 1.35 (m, 3H).

Compound 223 was prepared in a similar manner to **132** and isolated as a white
10 solid (11.7 mg, 25.49 μ mol, 18.63% yield, 99% purity). ¹H **NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 11.94$ (br s, 1H), 8.74 (s, 1H), 8.14 (s, 1H), 7.83 (s, 1H), 7.77 - 7.71 (m, 2H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.59 - 7.52 (m, 2H), 5.06 (s, 2H), 4.37 (tt, $J = 3.1, 6.1$ Hz, 1H), 4.14 (s, 3H), 3.32 (s, 3H), 0.81 - 0.70 (m, 4H).

Compound 224 was prepared in a similar manner to **132** and isolated as a white
15 solid (3.2 mg, 6.74 μ mol, 20.39% yield, 100% purity). LCMS: $m/z = 475.2$ (M+H)⁺ ¹H **NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 12.26$ - 12.09 (m, 1H), 8.41 (d, $J = 2.8$ Hz, 1H), 8.31 - 8.24 (m, 1H), 7.78 - 7.73 (m, 1H), 7.65 - 7.63 (m, 1H), 7.62 - 7.58 (m, 1H), 7.53 - 7.48 (m, 1H), 7.37 (dd, $J = 1.2, 7.7$ Hz, 1H), 5.91 - 5.75 (m, 2H), 5.01 - 4.97 (m, 2H), 4.37 - 4.31 (m, 1H), 3.31 - 3.26 (m, 3H), 0.83 - 0.77 (m, 2H), 0.76 - 0.70 (m, 2H).

Compound 225 was prepared in a similar manner to **132** and isolated as a white
20 solid (3.1 mg, 6.55 μ mol, 39.53% yield, 100% purity). LCMS: $m/z = 474.1$ (M+H)⁺ ¹H **NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 12.31$ - 12.09 (m, 1H), 8.44 (d, $J = 2.5$ Hz, 1H), 8.28 (s, 1H), 7.58 (t, $J = 1.4$ Hz, 1H), 7.48 - 7.43 (m, 2H), 7.35 - 7.30 (m, 2H), 7.13 (dd, $J = 1.4, 7.8$ Hz, 1H), 5.92 - 5.76 (m, 2H), 4.99 - 4.94 (m, 2H), 3.83 - 3.76 (m, 1H), 3.08 - 3.04 (m, 3H),
25 0.89 - 0.82 (m, 2H), 0.80 - 0.72 (m, 2H).

Compound 226 was prepared in a similar manner to **132** and isolated as a yellow solid (4.9 mg, 9.81 μ mol, 19.78% yield, 95% purity). LCMS: $m/z = 475.1$ (M+H)⁺ ¹H **NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 8.49$ - 8.41 (m, 2H), 8.30 (s, 1H), 8.21 - 8.15 (m, 1H), 8.12 - 7.99 (m, 1H), 7.88 - 7.82 (m, 1H), 7.44 - 7.35 (m, 1H), 5.95 - 5.75 (m, 2H), 4.99 (s, 2H),
30 3.89 (dt, $J = 3.0, 5.9$ Hz, 1H), 3.17 - 3.09 (m, 3H), 0.99 - 0.92 (m, 2H), 0.89 - 0.81 (m, 2H).

Compound 227 was prepared in a similar manner to **132** and isolated as a white solid (39.8 mg, 99.18 μ mol, 86.41% yield, 97.8% purity). LCMS: $m/z = 393.3$ (M+H)⁺ ¹H **NMR** (400 MHz, CHLOROFORM-*d*) $\delta = 12.91$ - 11.51 (m, 1H), 9.20 - 9.12 (m, 1H), 8.39 - 8.25 (m, 2H), 7.73 - 7.68 (m, 1H), 7.62 - 7.58 (m, 1H), 7.40 - 7.37 (m, 1H), 7.13 - 7.05 (m, 3H), 4.95 (s, 2H), 4.19 (q, $J = 7.0$ Hz, 2H), 3.05 (s, 3H), 1.55 (t, $J = 6.9$ Hz, 3H).

Compound 228 was prepared in a similar manner to **132** and isolated as a white solid (14.3 mg, 34.25 μ mol, 46.90% yield, 100% purity). LCMS: $m/z = 418.2$ (M+H)⁺ ¹H **NMR**

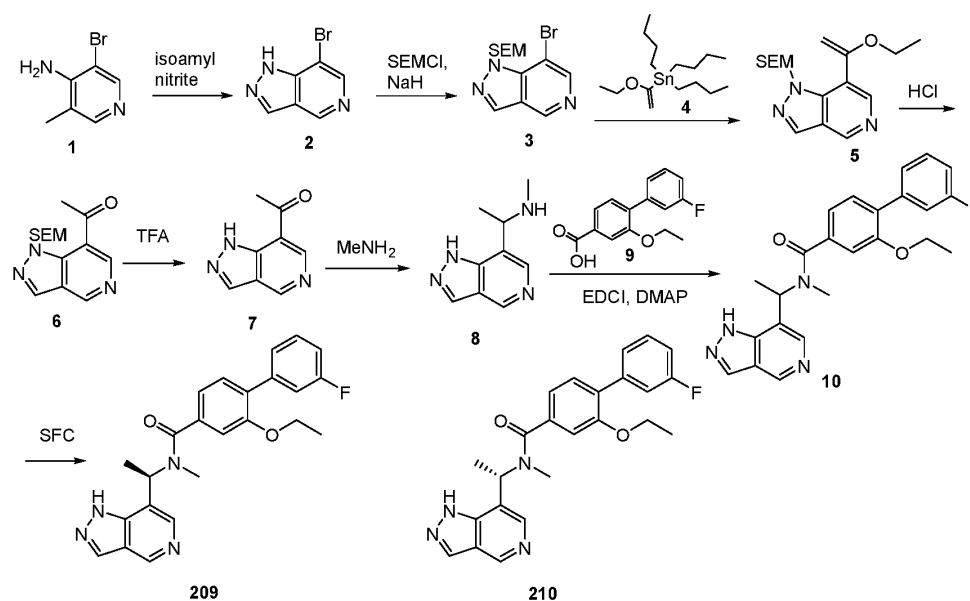
(400 MHz, CHLOROFORM-d) δ = 12.23 - 12.43 (m, 1 H) 9.14 - 9.21 (m, 1 H) 8.33 - 8.42 (m, 2 H) 7.94 (s, 1 H) 7.65 - 7.71 (m, 2 H) 7.08 - 7.12 (m, 2 H) 4.93 - 5.00 (m, 2 H) 4.19 - 4.26 (m, 2 H) 3.02 - 3.07 (m, 3 H) 1.56 (t, J =6.94 Hz, 3 H).

Compound 229 was prepared in a similar manner to **132** and isolated as a light yellow solid (7.8 mg, 18.93 μ mol, 20.25% yield, 98.167% purity). LCMS: m/z =405.2 (M+H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.82 - 12.21 (m, 1H), 9.35 - 8.96 (m, 1H), 8.52 - 8.27 (m, 2H), 7.76 - 7.63 (m, 1H), 7.54 (br d, J = 3.6 Hz, 1H), 7.50 - 7.44 (m, 1H), 7.41 - 7.34 (m, 1H), 7.16 - 7.04 (m, 2H), 5.06 - 4.85 (m, 2H), 3.90 (br d, J = 3.4 Hz, 1H), 3.12 - 2.98 (m, 3H), 0.97 - 0.83 (m, 4H).

Compound 230 was prepared in a similar manner to **132** and isolated as a white solid (6.4 mg, 15.78 μ mol, 60.40% yield, 100% purity). LCMS: m/z =406.1 (M+H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.45 - 12.32 (m, 1H), 9.22 - 9.11 (m, 1H), 8.42 - 8.27 (m, 2H), 8.03 (d, J = 7.8 Hz, 1H), 7.65 - 7.56 (m, 2H), 7.41 (dd, J = 0.9, 5.1 Hz, 1H), 7.12 (dd, J = 3.9, 5.0 Hz, 1H), 4.99 (s, 2H), 4.45 - 4.38 (m, 1H), 3.77 - 3.70 (m, 1H), 3.38 - 3.28 (m, 3H), 2.02 (s, 1H), 1.28 - 1.23 (m, 1H), 0.91 - 0.86 (m, 2H), 0.86 - 0.80 (m, 2H).

Compound 231 was prepared in a similar manner to **132** and isolated as a white solid (35 mg, 77.13 μ mol, 43.25% yield, 94.866% pur). LCMS: m/z =443.2 (M+H+) **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 9.20 (br s, 1H), 8.43 (s, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 0.9 Hz, 1H), 7.72 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 5.00 (s, 2H), 4.48 - 4.39 (m, 1H), 3.31 (s, 3H), 0.90 - 0.83 (m, 4H).

Scheme 39.



To a solution of Compound **1** (29.2 g, 156.12 mmol, 1 eq) in CHCl₃ (300 mL) was added Ac₂O (79.69 g, 780.59 mmol, 73.11 mL, 5 eq) dropwise at 0 °C, the reaction mixture was

stirred at 0 °C for 2 hr under N₂. Then AcOK (4.60 g, 46.84 mmol, 0.3 eq) and isopentyl nitrite (45.72 g, 390.30 mmol, 52.55 mL, 2.5 eq) was added dropwise at 0 °C under N₂, the reaction mixture was stirred at 60 °C for 12 hr. The mixture was concentrated to give a crude product. A lot of solid was formed and the mixture was filtered and the cake was collected, the cake was washed with MTBE (500 mL), and dried to give a crude product, the crude product used for next step without further purification. Compound **2** (25 g, crude) was obtained as brown solid.

To a solution of Compound **2** (15 g, 75.75 mmol, 1 eq) in 2-MeTHF (150 mL) was added NaH (4.54 g, 113.62 mmol, 60% purity, 1.5 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 h, then SEM-Cl (18.94 g, 113.62 mmol, 20.11 mL, 1.5 eq) was added dropwise at 0 °C, the mixture was stirred at 20 °C for 2 h. The mixture was poured into saturated NH₄Cl (500 mL) solution, and extracted with EtOAc (500 mL X3), the combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1, desired product R_f= 0.7). Compound **3** (3.5 g, 10.66 mmol, 14.07% yield) was obtained as brown oil.

To a solution of Compound **3** (3.4 g, 10.36 mmol, 1 eq) in dioxane (20 mL) and H₂O (2 mL) was added Compound **4** (4.49 g, 12.43 mmol, 4.19 mL, 1.2 eq), K₂CO₃ (4.29 g, 31.07 mmol, 3 eq) and Pd (PPh₃)₂Cl₂ (1.09 g, 1.55 mmol, 0.15 eq), the mixture was stirred at 100 °C for 12 h under N₂. The mixture was diluted with saturated potassium fluoride solution (100 mL), and stirred at 20 °C for 2 h, then the extracted with EtOAc (100 mL X3), the combined organic phase was washed with brine (100 mL X 3), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1/1, desired product R_f= 0.4). Compound **5** (2.6 g, 8.14 mmol, 78.58% yield) was obtained as yellow oil.

To a solution of Compound **5** (2.6 g, 8.14 mmol, 1 eq) in MeOH (30 mL) was added HCl (1 M, 30 mL, 3.69 eq) The reaction mixture was stirred at 20 °C for 1h . The mixture was poured into water (500mL), and extracted with EtOAc (500mL X3), the combined organic phase was washed with brine (500mL X 3), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. No purification. Compound **6** (2.12 g, 7.27 mmol, 89.39% yield) was obtained as yellow oil, which was used directly in the next step.

To a solution of Compound **6** (700 mg, 2.40 mmol, 1 eq) in DCM (7 mL) was added TFA (10.78 g, 94.54 mmol, 7 mL, 39.36 eq), the reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with dichloromethane: methanol=1:0 to 10:1(desired compound R_f= 0.5). Compound **7** (370 mg, crude) was obtained as yellow solid.

To a solution of Compound **7** (274 mg, 1.70 mmol, 1 eq) in MeOH (10 mL) was added MeNH₂ in THF (2 M, 2.55 mL, 3 eq) and AcOH (10.21 mg, 170.02 μ mol, 9.72 μ L, 0.1 eq), the reaction mixture was stirred at 50 °C for 2 hr. Then NaBH₄ (192.96 mg, 5.10 mmol, 3 eq) was added to the reaction mixture slowly at 0 °C, the reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was quenched by saturated NH₄Cl aqueous (20 mL), the resulting mixture was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5 μ m; mobile phase: [water (NH₃H₂O)-ACN]; B%: 1%-25%, 8min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give white solid. Compound **8** (128 mg, 646.47 μ mol, 38.02% yield, 89% purity) was obtained as white solid.

To a solution of Compound **8** (126.39 mg, 645.51 μ mol, 90% purity, 1.2 eq) in DCM (5 mL) was added Compound **9** (140 mg, 537.92 μ mol, 1 eq), EDCI (154.68 mg, 806.89 μ mol, 1.5 eq) and DMAP (6.57 mg, 53.79 μ mol, 0.1 eq), the reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μ m; mobile phase: [water (FA)-ACN]; B%: 19%-49%, 9min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give white solid. Compound **10** (150 mg, 354.87 μ mol, 65.97% yield, 99% purity) was obtained as white solid.

Compound **10** (80 mg, 191.18 μ mol, 1 eq) was purified by SFC to give **209** (21.0 mg, 50.18 μ mol, 26.25% yield, 100% purity) and **210** (23.8 mg, 54.60 μ mol, 28.56% yield, 96% purity). The product was purified by SFC (column: DAICEL CHIRALCEL OJ (250mm*30mm, 10 μ m); mobile phase: [0.1%NH₃H₂O MEOH]; B%: 15%-15%, 7.7; 162min). After SFC, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give white solid. **209** (21.0 mg, 50.18 μ mol, 26.25% yield, and 100% purity) was obtained as white solid. **210** (23.8 mg, 54.60 μ mol, 28.56% yield, and 96% purity) was obtained as white solid. ¹H NMR of **209**: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.11 (br s, 1H), 9.26 - 8.88 (m, 1H), 8.53 - 8.26 (m, 1H), 8.20 (s, 1H), 7.33 - 7.21 (m, 4H), 7.01 - 6.93 (m, 3H), 6.45 - 6.36 (m, 1H), 4.00 (br dd, J = 7.0, 16.9 Hz, 2H), 2.75 (s, 3H), 1.82 (d, J = 7.3 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H). ¹H NMR of **210**: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.20 (br d, J = 1.4 Hz, 1H), 9.42 - 8.89 (m, 1H), 8.67 - 8.35 (m, 1H), 8.29 (s, 1H), 7.42 - 7.29 (m, 4H), 7.12 - 7.04 (m, 3H), 6.51 (br d, J = 7.5 Hz, 1H), 4.17 - 4.01 (m, 2H), 2.84 (s, 3H), 1.91 (d, J = 7.1 Hz, 3H), 1.39 (t, J = 6.9 Hz, 3H).

Compound 186 was prepared in a similar manner to **209** and **210** and isolated as a white solid (19.2 mg, 55.27 μ mol, 37.62% yield, 100% purity). LCMS: m/z = 348.2 (M+H+). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 8.11 (s, 1H), 7.79 - 7.72 (m, 1H), 7.39 - 7.34 (m,

1H), 7.25 (s, 1H), 7.15 - 7.09 (m, 1H), 6.97 - 6.89 (m, 2H), 4.96 - 4.90 (m, 2H), 4.10 (q, J = 7.0 Hz, 2H), 2.93 (s, 3H), 2.11 (s, 3H), 1.46 (t, J = 6.9 Hz, 3H).

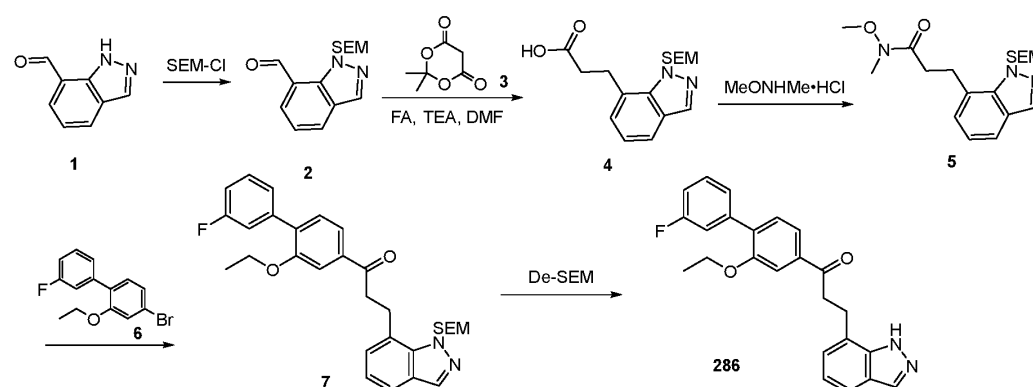
Compound 389 was prepared in a similar manner to **209** and **210** and isolated as a white solid (4.04 mg, 9.44 μ mol, 5.88% yield, 99% purity). LCMS: m/z = 424.1 (M+H+) ¹H

NMR (400 MHz, CHLOROFORM-d) δ = 8.14 (br s, 1H), 7.78 (br d, J = 8.0 Hz, 1H), 7.50 - 7.40 (m, 4H), 7.35 - 7.29 (m, 2H), 7.14 (br t, J = 7.5 Hz, 1H), 7.09 - 7.04 (m, 2H), 4.97 (s, 2H), 4.04 (q, J = 6.8 Hz, 2H), 3.01 (s, 3H), 2.08 (s, 3H), 1.35 (br t, J = 6.9 Hz, 3H)

Compounds 258 and 390 were prepared in a similar manner to **209** and **210**. **258** (18.5 mg, 45.74 μ mol, 46.25% yield, and 100% purity) was obtained as white solid. **390**

(17.6 mg, 43.52 μ mol, 44.00% yield, and 100% purity) was obtained as white solid. ¹H **NMR of 258**: (400 MHz, CHLOROFORM-d) δ = 12.88 - 12.58 (m, 1H), 9.00 - 8.88 (m, 1H), 8.52 - 8.36 (m, 1H), 8.28 (s, 1H), 8.01 - 7.73 (m, 1H), 7.57 (s, 1H), 7.46 (br d, J = 7.4 Hz, 1H), 7.35 - 7.24 (m, 3H), 7.22 (br d, J = 0.6 Hz, 1H), 7.02 - 6.88 (m, 1H), 5.89 (br s, 1H), 4.16 - 4.00 (m, 2H), 1.99 - 1.93 (m, 3H), 1.32 - 1.26 (m, 3H) ¹H **NMR of 390**: (400 MHz, CHLOROFORM-d) δ = 12.85 - 12.42 (m, 1H), 8.93 (s, 1H), 8.42 (br s, 1H), 8.24 (s, 1H), 7.76 - 7.56 (m, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.22 (br d, J = 6.6 Hz, 2H), 7.01 - 6.90 (m, 1H), 5.93 - 5.84 (m, 1H), 4.09 (br dd, J = 4.0, 7.0 Hz, 2H), 1.95 (br d, J = 7.1 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H).

Scheme 40



20

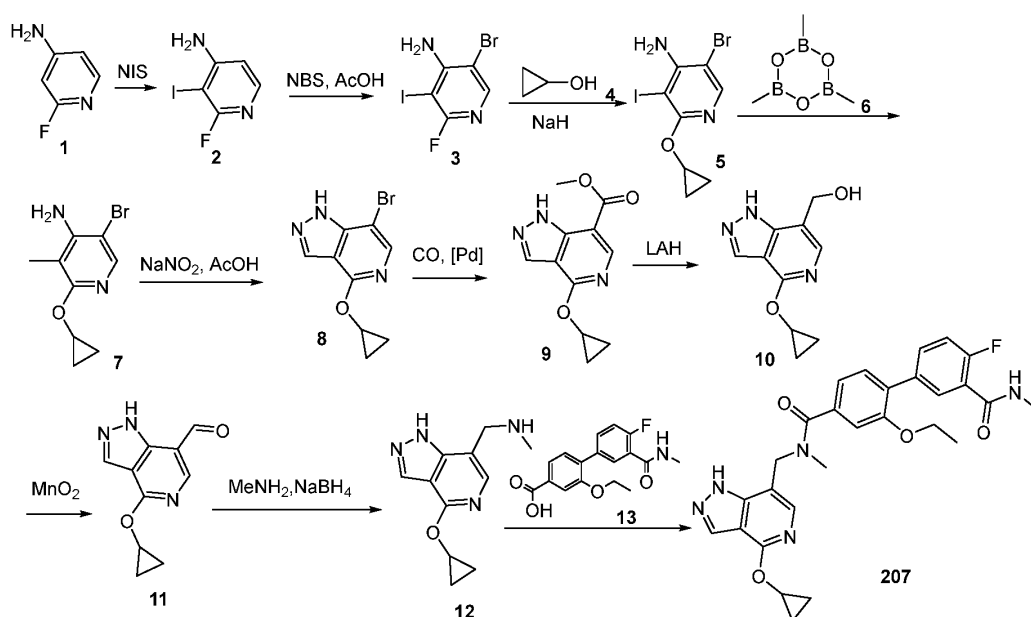
25

To a solution of compound **1** (950 mg, 6.50 mmol, 1 eq) in THF (30 mL) was added NaH (389.98 mg, 9.75 mmol, 60% purity, 1.5 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 h, then SEM-Cl (1.30 g, 7.80 mmol, 1.38 mL, 1.2 eq) was added dropwise, the mixture was stirred at 0 °C for 3 h. TLC (Petroleum ether : Ethyl acetate=5:1) showed the reaction was completed. The mixture was poured into saturated NH₄Cl (100 mL) solution, and extracted with EtOAc (80mL X2), the combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The residue was

- purified by silica gel column chromatography (Petroleum ether : Ethyl acetate=10 : 1) to give compound **2** (1.37 g, 4.96 mmol, 76.25% yield, N/A purity) as colorless oil.
- HCOOH (157.10 mg, 3.27 mmol, 3 eq) and Et₃N (132.36 mg, 1.31 mmol, 182.06 uL, 1.2 eq) was combined in a flask and stirred at 20 °C for 15 minutes. Then DMF (1 mL) was added.
- 5 To this mixture compound **2** (300 mg, 1.09 mmol, 1 eq) and compound **3** (157.10 mg, 1.09 mmol, 1 eq) was added. The reaction was stirred at 100 °C 16 h. The mixture was poured into H₂O (100 mL). The aqueous phase was extracted with EtOAc (60 mL). The combined organic phase was washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography
- 10 (Petroleum ether/Ethyl acetate=3:1) to give (177 mg, 552.33 umol, 50.67% yield, N/A purity) was obtained as colourless oil. **LCMS**: m/z = 321.2 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.13 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.16 - 7.12 (m, 1H), 7.06 (dd, J = 6.7, 8.3 Hz, 1H), 5.80 (s, 2H), 3.67 (dd, J = 7.7, 8.9 Hz, 2H), 3.37 (t, J = 7.8 Hz, 2H), 2.95 - 2.87 (m, 2H), 1.02 - 0.90 (m, 2H), -0.01 (s, 9H).
- 15 A solution of compound **4** (157 mg, 489.92 umol, 1 eq), N-methoxymethanamine;hydrochloride (57.35 mg, 587.91 umol, 1.2 eq) and Et₃N (74.36 mg, 734.89 umol, 102.29 uL, 1.5 eq) in DCM (3 mL) was added EDCI (140.88 mg, 734.89 umol, 1.5 eq), DMAP (5.99 mg, 48.99 umol, 0.1 eq) at 20 °C. The mixture which resulted was allowed to stir at 20 °C for 12 hrs. The reaction mixture was concentrated under vacuum.
- 20 The residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate=2/1) to give compound **5** (150 mg, 412.63 umol, 84.22% yield) was obtained as colourless oil. **LCMS**: m/z = 364.1 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.09 (s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 6.4 Hz, 1H), 7.03 (dd, J = 6.8, 8.4 Hz, 1H), 5.73 (s, 2H), 3.67 - 3.62 (m, 2H), 3.60 (s, 3H), 3.36 (t, J = 7.9 Hz, 2H), 3.19 (s, 3H), 3.11 - 2.90
- 25 (m, 2H), 0.99 - 0.90 (m, 2H), -0.02 (s, 9H)
- To a solution of compound **6** (253.31 mg, 858.26 umol, 2 eq) in 2-MeTHF (3 mL) was added n-BuLi (2.5 M, 514.96 uL, 3 eq) at -65 °C under N₂ atmosphere, the mixture was stirred at -65 °C for 1.5 hr. Compound **5** (156 mg, 429.13 umol, 1 eq) in 2-MeTHF (0.5 mL) was added to the mixture, the mixture was stirred at -65 °C for another 3 hrs under N₂ atmosphere. The
- 30 mixture was poured into ice-NH₄Cl (sat. 50 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (40 mL x 2). The combined organic phase was washed with brine (60 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; B%: 70%-100%,8min), lyophilized, to give compound **7**
- 35 (20 mg, 38.29 umol, 8.92% yield, 99.3% purity) was obtained as white solid. **LCMS**: m/z = 519.2 (M+H)⁺

To a mixture of compound **7** (20. mg, 38.29 μ mol, 99.3% purity, 1 eq) in DCM (1 mL) was added TFA (770.00 mg, 6.75 mmol, 0.5 mL, 176.37 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hrs. The mixture was concentrated under vacuum. The residue was dissolved with MeCN (1 mL) and basified with Et₃N to pH about 8. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10 μ m; mobile phase: [water(NH₄HCO₃)-ACN];B%: 50%-80%,11min), lyophilized to give **286** (12.2 mg, 30.47 μ mol, 79.57% yield, 97% purity) as off-white solid. **LCMS**: m/z = 389.1 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.09 - 7.94 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.52 - 7.45 (m, 2H), 7.32 - 7.28 (m, 1H), 7.27 - 7.11 (m, 4H), 7.10 - 6.92 (m, 2H), 4.02 (q, J = 6.9 Hz, 2H), 3.44 - 3.38 (m, 2H), 3.38 - 3.31 (m, 2H), 1.30 (t, J = 6.9 Hz, 3H).

Scheme 41



To a solution of Compound **1** (5 g, 44.60 mmol, 1 eq) in DMF (50 mL) was added NIS (10.03 g, 44.60 mmol, 1 eq) at 0 °C, the reaction mixture was stirred at 70 °C for 12hr. The reaction mixture was extracted with EtOAc (150mL X3), the combined organic phase was washed with brine (150 mLX3), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether: ethyl acetate=1/0 to 0/1 (desired compound R_f= 0.9). Compound **2** (9 g, 36.64 mmol, 82.16% yield, 96.9% purity) was obtained as brown solid, **LCMS**: Rt = 0.328 min, m/z = 238.9 (M+H)⁺

To a solution of Compound **2** (9 g, 37.81 mmol, 1 eq) in AcOH (90 mL) was added NBS (6.73 g, 37.81 mmol, 1 eq), the reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was extracted with EtOAc (100 mLX3), the combined organic phase was washed

with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether: ethyl acetate=1/0 to 2/1 (desired compound R_f=0.7). Compound **3** (7.8 g, 23.14 mmol, 61.18% yield, 94% purity) was obtained as white solid. **LCMS**: R_t = 0.443 min, m/z = 318.7 (M+H⁺)

To a solution of Compound **4** (3.13 g, 53.96 mmol, 1.5 eq) in 2-MeTHF (120 mL) was added NaH (4.32 g, 107.92 mmol, 60% purity, 3 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 hr. Then Compound **3** (11.4 g, 35.97 mmol, 1 eq) was added at °C, the reaction mixture was stirred at 20 °C for 12 hr. The mixture was poured into saturated NH₄Cl (500 mL) solution, and extracted with EtOAc (200mL X3), the combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether: ethyl acetate=1:0 to 1:1(desired compound R_f=0.9). Compound **4** (1.3 g, 2.31 mmol, 6.41% yield, 63% purity) was obtained as brown oil **LCMS**: R_t = 0.520 min, m/z = 354.8 (M+H⁺)

To a solution of Compound **5** (2 g, 2.82 mmol, 50% purity, 1 eq) in dioxane (20 mL) was added Cs₂CO₃ (1.84 g, 5.63 mmol, 2 eq), Compound **6** (848.76 mg, 3.38 mmol, 945.16 uL, 50% purity, 1.2 eq) and Pddppf) Cl₂·CH₂Cl₂ (230.06 mg, 281.71 umol, 0.1 eq), the reaction mixture was stirred at 80 °C for 12 hr. under N₂. The reaction mixture was filtered, the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether: ethyl acetate=1:0 to 5:1 (desired compound R_f=0.6). Compound **7** (522 mg, 1.95 mmol, 69.22% yield, 91% purity) was obtained as brown oil **LCMS**: R_t = 0.298 min, m/z = 244.9 (M+H⁺)

To a solution of Compound **7** (500 mg, 1.85 mmol, 90% purity, 1 eq) in AcOH (10 mL) and H₂O (1 mL) was added NaNO₂ (255.43 mg, 3.70 mmol, 2 eq), the reaction mixture was stirred at 80 °C for 12 hr. The reaction mixture was extracted with EtOAc (100mLX3), the combined organic phase was washed with brine (100mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether: ethyl acetate=1:0 to 5:1(desired compound R_f= 0.3). Compound **8** (158 mg, 572.10 umol, 30.91% yield, 92% purity) was obtained as yellow solid. **LCMS**: R_t = 0.410 min, m/z = 253.9 (M+H⁺)

To a solution of Compound **8** (150 mg, 590.36 umol, 1 eq) in MeOH (20 mL) was added DPPF (65.46 mg, 118.07 umol, 0.2 eq), Pd(OAc)₂ (26.51 mg, 118.07 umol, 0.2 eq) and TEA (298.69 mg, 2.95 mmol, 410.85 uL, 5 eq), the reaction mixture was stirred at 80 °C for 12 hr under CO (590.36 umol, 1 eq) (50 Psi). TLC (petroleum ether: ethyl acetate=1:1) showed the reaction was completed. After the reaction was completed, the mixture was filtered under N₂ and the filtrate was concentrated to give a crude product. The crude product was purified

by prep-TLC (petroleum ether: ethyl acetate=1:1, desired compound Rf= 0.5). Compound **9** (113 mg, 477.68 μ mol, 80.91% yield, 98.59% purity) was obtained as white solid. **LCMS**: Rt = 0.403 min, m/z = 234.0 (M+H⁺)

To a solution of Compound **9** (110 mg, 471.65 μ mol, 1 eq) in 2-MeTHF (5 mL) was added
5 LAH (26.85 mg, 707.48 μ mol, 1.5 eq) at 0 °C, the reaction mixture was stirred at 0 °C for 1hr. TLC (petroleum ether: ethyl acetate=1:1) showed the starting material was consumed completely. The reaction mixture was quenched by Na₂SO₄•10H₂O (1 g), then the mixture was filtered, the filtrate was concentrated under vacuum to give a residue. The residue was used to the next step without purification. Compound **10** (110 mg, crude) was obtained as
10 yellow solid.

To a solution of Compound **10** (90 mg, 438.57 μ mol, 1 eq) in DCM (5 mL) was added MnO₂ (762.56 mg, 8.77 mmol, 20 eq), the reaction mixture was stirred at 30 °C for 12 hr. The reaction mixture was concentrated to give a crude product. The crude product was purified by prep-TLC (petroleum ether: ethyl acetate=1:1, desired compound Rf= 0.6). Compound **11**
15 (54 mg, crude) was obtained as white solid. **LCMS**: m/z = 204.0 (M+H⁺)

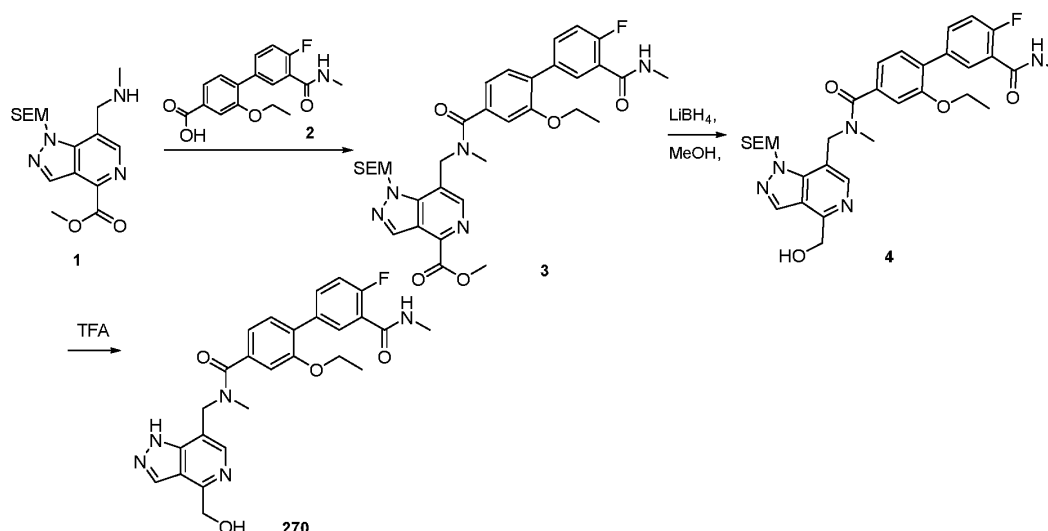
To a solution of Compound **11** (54 mg, 265.75 μ mol, 1 eq) in MeOH (2 mL) was added MeNH₂ in THF (2 M, 797.26 μ L, 6 eq) and AcOH (1.60 mg, 26.58 μ mol, 1.52 μ L, 0.1 eq), the reaction mixture was stirred at 50 °C for 3 hr. Then NaBH₄ (30.16 mg, 797.26 μ mol, 3 eq) was added slowly at 0 °C, the reaction mixture was stirred at 20 °C for 2 hr. The reaction
20 mixture was quenched by saturated NH₄Cl aqueous (10mL), the resulting mixture was concentrated under vacuum to give a residue. The crude product was used to the next step without purification. Compound **12** (65 mg, crude) was obtained as white solid. **LCMS**: Rt = 0.532 min, m/z = 219.2 (M+H⁺)

To a solution of Compound **12** (65.00 mg, 297.82 μ mol, 1.5 eq) in DCM (4 mL) was added
25 Compound **13** (63 mg, 198.54 μ mol, 1 eq), EDCI (38.06 mg, 198.54 μ mol, 1 eq) and DMAP (2.43 mg, 19.85 μ mol, 0.1 eq), the reaction mixture was stirred at 20 °C for 12 hr. **LCMS** (EC2950-181-P1A) showed the reaction was completed and desired mass was detected.

The reaction mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μ m; mobile phase: [water (FA)-ACN]; B%: 34%-64%, 9min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give white solid. **207** (10.97 mg, 21.20 μ mol, 10.68% yield, and 100% purity) was obtained as white solid. **LCMS**: Rt = 0.492 min, m/z = 518.2 (M+H⁺) **¹H NMR**: ¹H NMR (400 MHz, CHLOROFORM-d) δ = 12.04 (br s, 1H), 8.22 - 8.16 (m, 1H), 8.09 - 8.05 (m, 1H), 7.84 - 7.79
30 (m, 1H), 7.63 - 7.57 (m, 1H), 7.31 - 7.26 (m, 1H), 7.11 - 7.04 (m, 1H), 7.02 - 6.99 (m, 1H), 6.99 - 6.97 (m, 1H), 6.76 - 6.63 (m, 1H), 4.79 - 4.74 (m, 2H), 4.48 - 4.39 (m, 1H), 4.02 - 3.95 (m, 2H), 3.00 - 2.97 (m, 3H), 2.97 - 2.93 (m, 3H), 1.31 - 1.26 (m, 3H), 0.86 - 0.81 (m, 4H).

Compound 171 was prepared in a similar manner to **207** and isolated as a white solid (13.42 mg, 31.38 μmol , 12.48% yield, 99.7% purity). LCMS: $m/z = 427.2$ ($M+H$)⁺ ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 12.57 - 11.40 (m, 1H), 8.15 (s, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.71 - 7.65 (m, 1H), 7.65 - 7.58 (m, 1H), 7.54 - 7.45 (m, 1H), 7.39 - 7.33 (m, 1H), 7.33 - 7.28 (m, 1H), 7.22 - 7.16 (m, 1H), 6.92 - 6.82 (m, 1H), 6.77 - 6.68 (m, 1H), 4.95 - 4.87 (m, 2H), 3.89 - 3.82 (m, 1H), 0.94 - 0.85 (m, 2H), 0.78 - 0.70 (m, 2H)

Scheme 42



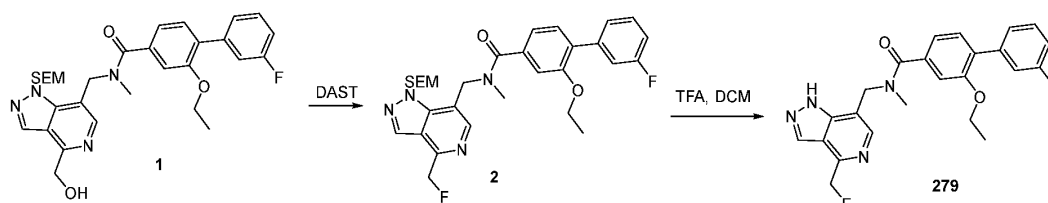
To a solution of **Compound 1** (100 mg, 285.32 μmol , 1 eq) and **Compound 2** (90.53 mg, 285.32 μmol , 1 eq) in DCM (2 mL) was added EDCI (82.04 mg, 427.98 μmol , 1.5 eq) and DMAP (3.49 mg, 28.53 μmol , 0.1 eq). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was poured into water (10 mL) and extracted by ethyl acetate (10 mL x3), the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate=1:2, R_F =0.2), the purified solution was concentrated under vacuum to give a residue. **Compound 3** (100 mg, 153.90 μmol , 53.94% yield) was obtained as a colorless oil. LCMS: $m/z = 650.5$ ($M+H$)⁺

To a solution of **Compound 3** (100 mg, 153.90 μmol , 1 eq) in MeOH (2 mL) was added LiBH₄ (2 M, 115.42 μL , 1.5 eq) under 0 °C. The mixture was stirred at 0~20 °C for 12 hr. The reaction mixture was quenched by saturated NH₄Cl aqueous (10 mL), the resulting mixture was concentrated under vacuum to give a residue. **Compound 4** (70 mg, 112.58 μmol , 73.15% yield) was obtained as a yellow oil. LCMS: $m/z = 622.2$ ($M+H$)⁺

To a solution of **Compound 6** (70 mg, 112.58 μmol , 1 eq) in TFA (1 mL). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was poured into water (10 mL) and extracted by ethyl acetate (10 mL x3), the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by prep-HPLC

(column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 13%-43%, 15min), the purified solution was lyophilized to give a white solid. **Compound 270** (6.5 mg, 12.70 umol, 11.28% yield, 96% purity) was obtained as a white solid. **LCMS**: m/z = 492.3 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ ppm 12.56 - 12.97 (m, 1 H) 8.44 - 8.52 (m, 1 H) 8.33 - 8.41 (m, 1 H) 8.25 - 8.31 (m, 1 H) 7.64 - 7.71 (m, 1 H) 7.36 - 7.41 (m, 1 H) 7.16 (dd, J=11.51, 8.63 Hz, 1 H) 7.04 - 7.11 (m, 2 H) 6.73 - 6.83 (m, 1 H) 5.23 - 5.35 (m, 2 H) 4.94 - 5.06 (m, 2 H) 4.07 (q, J=6.84 Hz, 2 H) 3.05 - 3.10 (m, 6 H) 1.37 (br t, J=6.88 Hz, 3 H).

Scheme 43



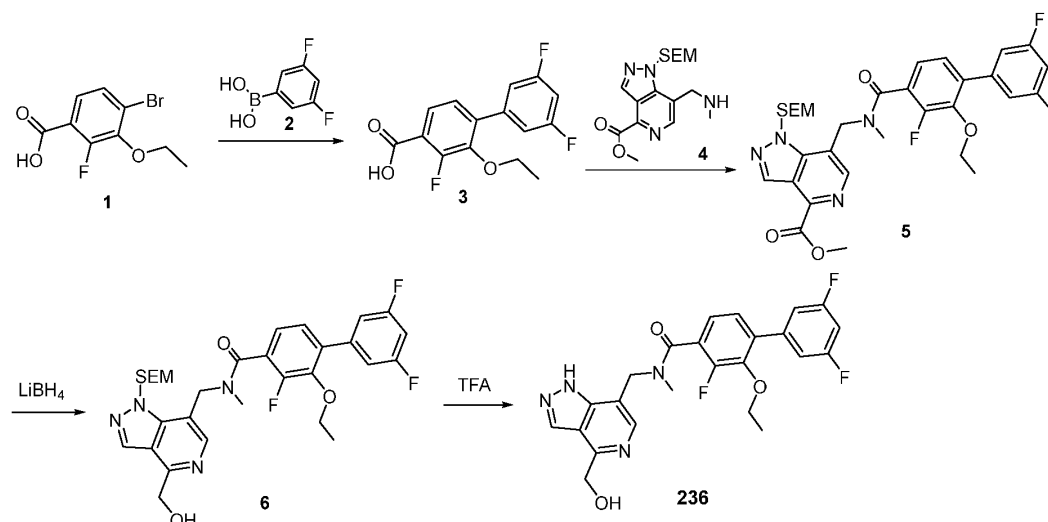
To a solution of **Compound 1** (100 mg, 177.08 umol, 1 eq) in DCM (2 mL) was added DAST (57.09 mg, 354.16 umol, 46.79 uL, 2 eq) slowly, then the mixture was stirred at 0 °C for 1 hr. The reaction mixture was poured into saturated NaHCO₃ aqueous (5 mL) and extracted by ethyl acetate (10 mLx3), the combined organic phase was dried and concentrated under vacuum to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate=0:1) to give **Compound 2** (30 mg, 52.94 umol, 29.89% yield) as a yellow oil. **LCMS**: m/z = 567.2 (M+H)⁺

A mixture of **Compound 2** (30 mg, 52.94 umol, 1 eq) in DCM (0.5 mL) and TFA (1 mL) was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 32%-62%, 8min), the purified solution was concentrated under vacuum to give **Compound 279** (5.1 mg, 11.64 umol, 21.99% yield, 99.6% purity) as a white solid. **LCMS**: m/z = 437.1 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.40 - 12.17 (m, 1H), 8.43 (d, J = 2.5 Hz, 1H), 8.27 (s, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.33 - 7.28 (m, 2H), 7.10 - 7.03 (m, 3H), 5.94 - 5.75 (m, 2H), 4.96 (s, 2H), 4.07 (q, J = 6.9 Hz, 2H), 3.05 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H).

Compound 248 was prepared in the same manner as compound **279** and was obtained as a red solid (35.2 mg, 80.47 umol, 53.74% yield, 100% purity). **LCMS**: m/z = 438.3 (M+H)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.90 - 11.57 (m, 1H), 8.44 (br s, 1H), 8.35 - 8.17 (m, 1H), 7.75 (br d, J = 7.5 Hz, 1H), 7.54 - 7.46 (m, 1H), 7.42 - 7.33 (m, 3H), 7.09 (br t, J = 8.4 Hz, 1H), 5.96 - 5.76 (m, 2H), 5.05 - 4.88 (m, 2H), 4.42 (q, J = 7.0 Hz, 2H), 3.29 - 3.16 (m, 3H), 1.39 (br t, J = 7.0 Hz, 3H).

Compound 257 was prepared in the same manner as compound **279** and was obtained as a red solid (16.6 mg, 37.35 μmol , 53.66% yield, 100% purity). **LCMS**: m/z = 445.1 (M+H) + **1H NMR** (400 MHz, CHLOROFORM- d) δ = 8.60 (br s, 1H), 8.38 (s, 1H), 7.91 (s, 1H), 7.81 (br d, J = 8.0 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.60 - 7.51 (m, 2H), 6.27 - 6.00 (m, 2H), 5.02 (s, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.27 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H).

Scheme 44



A mixture in 40 mL bottle of **Compound 1** (1.1 g, 4.18 mmol, 1 eq), **Compound 2** (990.47 mg, 6.27 mmol, 1.5 eq), Pd(dppf)Cl₂·CH₂Cl₂ (341.48 mg, 418.16 μmol , 0.1 eq), K₂CO₃ (1.16 g, 8.36 mmol, 2 eq) in dioxane (12 mL), and then the mixture was stirred at 100 °C for 12 hr under N₂ atmosphere. After the reaction was completed and cooled, the reaction mixture was filtered by ethyl acetate (50 mL) in 100 mL stand-up bottle, the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by RP-HPLC (column: 150 mm*H400 mm Welch Ultimate XB_C18 20-40 μm , 120 Å; mobile phase: [water (H₂O)-ACN]; B%: 40% 10min), the purified solution was concentrated under vacuum to give residue. **Compound 3** (1 g, 3.38 mmol, 80.73% yield) was obtained as a yellow solid. **LCMS**: m/z = 295.0 (M-H)⁺

To a 40 mL bottle solution of **Compound 4** (200 mg, 570.63 μmol , 1 eq), **Compound 3** (169.05 mg, 570.63 μmol , 1 eq) in DCM (6 mL) was added EDCI (164.09 mg, 855.95 μmol , 1.5 eq) and DMAP (6.97 mg, 57.06 μmol , 0.1 eq). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was poured into water (15 mL) and extracted by ethyl acetate (15 mL x3), the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1/3). The purified solution was concentrated under vacuum to give a

residue. **Compound 5** (230 mg, 365.83 μmol , 64.11% yield) was obtained as a green oil.

LCMS: $m/z = 629.3$ ($M+H$)⁺

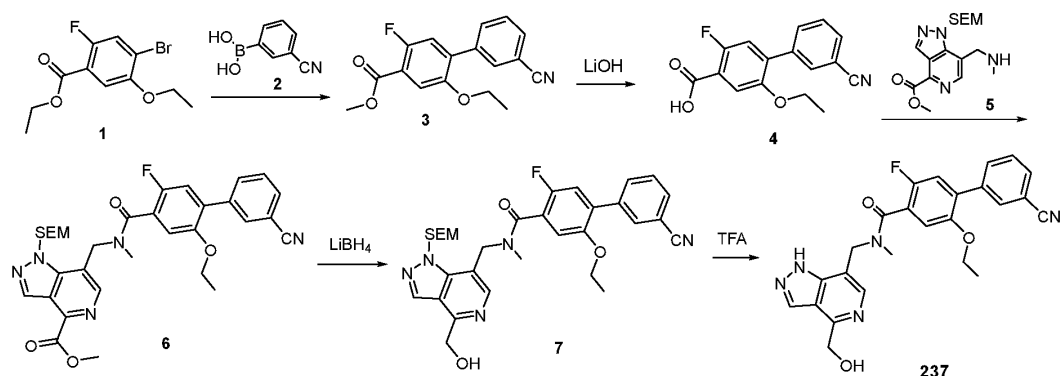
To a 100 mL round-bottomed flask solution of **Compound 5** (225 mg, 357.87 μmol , 1 eq) in THF (5 mL) was added LiBH_4 in THF (2 M, 536.81 μL , 3 eq). The mixture was stirred at 20 °C for 2 hr. The reaction mixture was poured into saturated NH_4Cl aqueous (15 mL) and extracted by extracted by ethyl acetate (10 mL x3), the combined organic phase was dried and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 0/1). The purified solution was concentrated under vacuum to give a residue. **Compound 6** (65 mg, 108.21 μmol , 30.24% yield) was obtained as a green oil. **LCMS:** $m/z = 601.3$ ($M+H$)⁺

To a 100 mL round-bottomed flask solution of **Compound 6** (65 mg, 108.21 μmol , 1 eq) in TFA (1 mL) was DCM (0.5 mL). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under vacuum to give residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (FA)-ACN]; B%: 20%-50%, 10min), the purified solution was lyophilized to give a white solid. **Compound 236** (17.1 mg, 36.35 μmol , 33.59% yield, 100% purity) was obtained as a white solid. **LCMS:** $m/z = 471.1$ ($M+H$)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ ppm 11.88 - 12.18 (m, 1 H) 8.24 - 8.32 (m, 2 H) 7.14 - 7.19 (m, 2 H) 7.11 - 7.14 (m, 1 H) 7.09 (dd, $J=8.25, 2.25$ Hz, 2 H) 6.81 - 6.88 (m, 1 H) 5.15 (s, 2 H) 4.96 - 5.00 (m, 2 H) 3.89 - 3.97 (m, 2 H) 2.99 (s, 3 H) 1.21 (t, $J=7.07$ Hz, 3 H).

Compound 240 was prepared in the same manner as compound **236** using (3-cyanophenyl)boronic acid in the first step. **Compound 240** (10.1 mg, 21.08 μmol , 63.42% yield, 98.4% purity) was obtained as white solid. **LCMS:** $m/z = 472.2$ ($M+H$)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.49 - 12.07 (m, 1H), 8.33 (s, 2H), 7.68 - 7.63 (m, 2H), 7.61 - 7.57 (m, 1H), 7.55 - 7.50 (m, 1H), 7.25 (s, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 5.19 (s, 2H), 4.97 (s, 2H), 3.76 (td, $J = 2.9, 5.8$ Hz, 1H), 3.10 (s, 3H), 0.85 - 0.78 (m, 2H), 0.74 - 0.67 (m, 2H).

Compound 241 was prepared in the same manner as compound **236** and was obtained as yellow solid (26.3 mg, 59.57 μmol , 37.84% yield, 100% purity). **LCMS:** $m/z = 442.1$ ($M+H$)⁺ **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 8.32 - 8.35 (m, 1 H) 8.29 (s, 1 H) 7.84 - 7.87 (m, 1 H) 7.75 - 7.79 (m, 1 H) 7.63 (dt, $J=7.72, 1.33$ Hz, 1 H) 7.49 - 7.55 (m, 1 H) 7.33 (d, $J=7.75$ Hz, 1 H) 7.10 (dd, $J=7.75, 1.50$ Hz, 1 H) 7.07 - 7.08 (m, 1 H) 5.16 (s, 2 H) 4.96 (s, 2 H) 4.08 (q, $J=6.92$ Hz, 2 H) 3.06 (s, 3 H) 1.34 - 1.39 (m, 3 H).

Scheme 45



- A mixture in 40 mL bottle of **Compound 1** (500 mg, 1.72 mmol, 1 eq), **Compound 2** (504.75 mg, 3.44 mmol, 2 eq), K₂CO₃ (474.75 mg, 3.44 mmol, 2 eq), Pd(dppf)Cl₂•CH₂Cl₂ (140.26 mg, 171.75 μmol, 0.1 eq) in dioxane (10 mL) at 20 °C, and then the mixture was stirred at 100 °C for 12 hr under N₂ atmosphere. After the reaction was completed and cooled, the reaction mixture was filtered by ethyl acetate (50 mL) in 100 mL stand-up bottle, the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1). The purified solution was concentrated under vacuum to give a residue.
- Compound 3** (425 mg, 1.36 mmol, 78.97% yield) was obtained as a white solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.87 - 7.91 (m, 1 H) 7.75 - 7.81 (m, 1 H) 7.63 - 7.68 (m, 1 H) 7.52 - 7.57 (m, 1 H) 7.48 - 7.51 (m, 1 H) 7.09 - 7.14 (m, 1 H) 4.40 - 4.47 (m, 2 H) 4.07 - 4.12 (m, 2 H) 1.40 - 1.46 (m, 3 H) 1.35 - 1.40 (m, 3 H)

- To a 100 mL round-bottomed flask solution of **Compound 3** (420 mg, 1.34 mmol, 1 eq) in MeOH (6 mL) and H₂O (2 mL) was added LiOH•H₂O (168.75 mg, 4.02 mmol, 3 eq). The mixture was stirred at 20 °C for 3 hr. The solvents was removed by evaporated under reduced pressure, then the mixture was acidified by 1N HCl to pH 4, The mixture was filtered and the filter cake was washed with 10 mL of MeOH, dried and in vacuum to give a residue. **Compound 4** (290 mg, 1.02 mmol, 75.84% yield) was obtained as a white solid which was used in the next step. LCMS: m/z =284.0 (M-H)⁺

- To a 100 mL round-bottomed flask solution of **Compound 4** (290 mg, 1.02 mmol, 1 eq), **Compound 5** (356.30 mg, 1.02 mmol, 1 eq) in DCM (8 mL) was added EDCI (292.32 mg, 1.52 mmol, 1.5 eq) and DMAP (12.42 mg, 101.66 μmol, 0.1 eq). The mixture was stirred at 20 °C for 3 hr. The reaction mixture was poured into water (15 mL) and extracted by ethyl acetate (15 mL x3), the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0/1). The purified solution was concentrated under vacuum to give a residue. **Compound 6** (440 mg, 712.27 μmol, 70.07% yield) was obtained as a green oil. LCMS: m/z =618.3 (M+H)⁺

To a 100 mL round-bottomed flask solution of **Compound 6** (440 mg, 712.27 μmol , 1 eq) in MeOH (6 mL) was added LiBH_4 in THF (2 M, 1.07 mL, 3 eq) at 0 °C. The mixture was stirred at 20 °C for 3 hr. The reaction mixture was poured into saturated NH_4Cl aqueous (15 mL) and extracted by extracted by ethyl acetate (10 mLx3), the combined organic phase was
5 dried and concentrated under vacuum to give a residue. **Compound 7** (390 mg, 661.32 μmol , 92.85% yield) was obtained as a green oil which was used in the next step. **LCMS**: $m/z = 590.3$ ($\text{M}+\text{H}$)⁺

To a 100 mL round-bottomed flask solution of **Compound 7** (90 mg, 152.61 μmol , 1 eq) in TFA (1 mL) and DCM (0.5 mL). The mixture was stirred at 20 °C for 2 hr. **LCMS** (5-95
10 AB/0.8 min) showed desired mass was detected. The reaction mixture was concentrated under vacuum to give residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (FA)-ACN]; B%: 15%-45%, 10min), the purified solution was lyophilized to give a white solid. **Compound 237** (32.1 mg, 69.86 μmol , 45.78% yield, 100% purity) was obtained as a white solid. **LCMS**: $m/z = 460.2$
15 ($\text{M}+\text{H}$)⁺ **¹H NMR** (400 MHz, CHLOROFORM- d) δ ppm 12.10 - 12.29 (m, 1 H) 8.32 (br d, $J=9.38$ Hz, 2 H) 7.84 - 7.86 (m, 1 H) 7.73 - 7.77 (m, 1 H) 7.64 - 7.68 (m, 1 H) 7.51 - 7.57 (m, 1 H) 7.06 - 7.10 (m, 1 H) 6.94 - 6.98 (m, 1 H) 5.16 - 5.21 (m, 2 H) 4.98 (br s, 2 H) 4.00 - 4.06 (m, 2 H) 3.00 - 3.04 (m, 3 H) 1.33 - 1.37 (m, 3 H).

Compound 239 was prepared in the same manner as compound **237** using (3,5-
20 difluorophenyl)boronic acid in the first step. **Compound 239** (24.5 mg, 54.15 μmol , 52.59% yield, 100% purity) was obtained as off-white solid. **LCMS**: $m/z = 453.1$ ($\text{M}+\text{H}$)⁺ **¹H NMR**: (400 MHz, CHLOROFORM- d) $\delta = 8.69 - 8.29$ (m, 2H), 7.35 (br d, $J = 7.1$ Hz, 1H), 7.08 (br d, $J = 7.1$ Hz, 4H), 6.89 - 6.73 (m, 1H), 5.31 (br s, 2H), 5.00 (br s, 2H), 4.08 (br d, $J = 6.5$ Hz, 2H), 3.09 (br s, 3H), 1.39 (br t, $J = 5.9$ Hz, 3H).

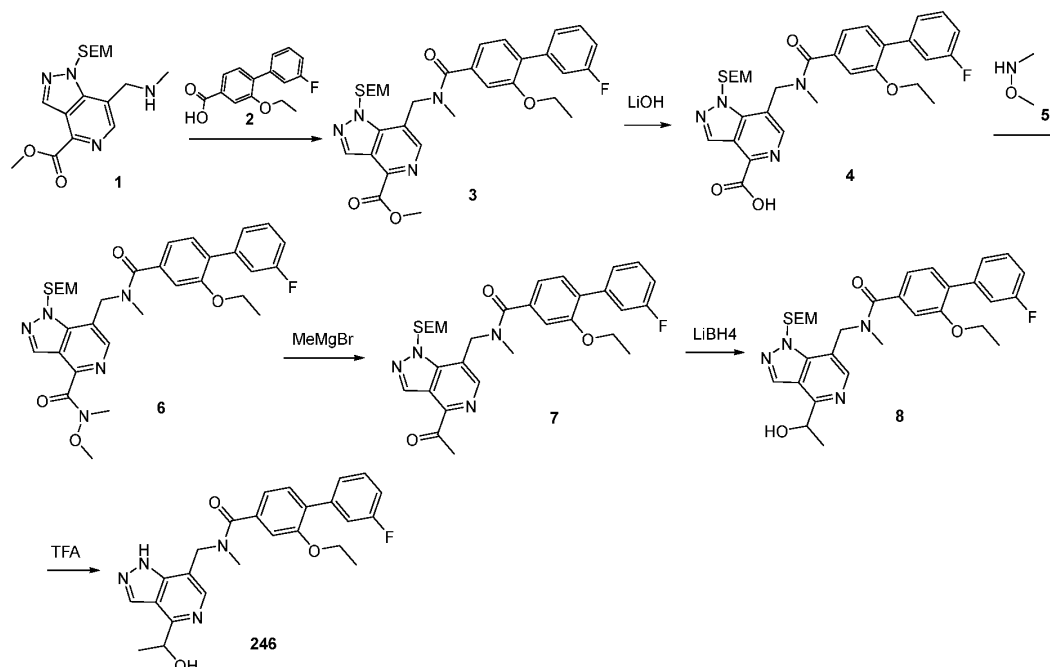
Compound 243 was prepared in the same manner as compound **237** and was
25 obtained as a white solid (15.7 mg, 33.30 μmol , 66.79% yield, 100% purity). **LCMS**: $m/z = 472.2$ ($\text{M}+\text{H}$)⁺ **¹H NMR**: (400 MHz, CHLOROFORM- d) $\delta = 12.58 - 12.07$ (m, 1H), 8.43 - 8.38 (m, 1H), 8.38 - 8.32 (m, 1H), 7.81 - 7.76 (m, 1H), 7.75 - 7.66 (m, 2H), 7.59 - 7.52 (m, 1H), 7.21 - 7.15 (m, 2H), 5.24 (s, 2H), 5.05 - 4.97 (m, 2H), 3.91 (qt, $J = 2.9, 6.0$ Hz, 1H), 3.03 (d, $J = 1.5$ Hz, 3H), 0.52 - 0.43 (m, 4H).
30

Compound 244 was prepared in the same manner as compound **237** and was
obtained as a light red solid (10.5 mg, 23.01 μmol , 14.93% yield, 99.4% purity). **LCMS**: $m/z = 454.2$ ($\text{M}+\text{H}$)⁺ **¹H NMR**: (400 MHz, CHLOROFORM- d) $\delta = 12.42 - 12.09$ (m, 1H), 8.30 - 8.25 (m, 2H), 7.79 - 7.76 (m, 1H), 7.71 - 7.67 (m, 1H), 7.65 - 7.61 (m, 1H), 7.54 - 7.48 (m,
35 1H), 7.48 - 7.45 (m, 1H), 7.33 - 7.30 (m, 1H), 7.16 - 7.11 (m, 1H), 5.16 - 5.13 (m, 2H), 4.99 - 4.95 (m, 2H), 3.82 - 3.75 (m, 1H), 3.10 - 3.05 (m, 3H), 0.87 - 0.81 (m, 2H), 0.78 - 0.71 (m, 2H).

Compound 245 was prepared in the same manner as compound **237** and was obtained as a white solid (40.7 mg, 91.16 μmol , 65.72% yield, 100% purity). **LCMS**: m/z = 447.3 ($M+H^+$) **1H NMR**: (400 MHz, CHLOROFORM- d) δ = 8.52 - 8.47 (m, 1H), 8.43 - 8.36 (m, 1H), 7.47 - 7.43 (m, 1H), 7.40 - 7.32 (m, 2H), 7.26 - 7.16 (m, 2H), 7.15 - 7.09 (m, 1H), 7.07 - 7.00 (m, 1H), 5.34 - 5.23 (m, 2H), 5.01 (s, 2H), 3.81 - 3.74 (m, 1H), 3.11 (s, 3H), 2.03 - 2.00 (m, 1H), 0.85 - 0.79 (m, 2H), 0.79 - 0.73 (m, 2H).

Compound 247 was prepared in the same manner as compound **237** and was obtained as a white solid (8 mg, 17.50 μmol , 34% yield, 99% purity). **LCMS**: m/z = 453.1 ($M+H^+$) **1H NMR**: (400 MHz, CHLOROFORM- d) δ = 8.55 (s, 1H), 8.42 (s, 1H), 7.38 (dd, J = 6.0, 8.0 Hz, 1H), 7.30 (s, 2H), 7.13 - 7.05 (m, 2H), 6.93 (d, J = 5.6 Hz, 1H), 5.33 (s, 2H), 5.02 (br s, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.06 (d, J = 1.4 Hz, 3H), 1.36 (t, J = 7.0 Hz, 3H).

Scheme 46



To a solution of Compound **1** (202.00 mg, 576.35 μmol , 1.5 eq) and Compound **2** (100 mg, 384.23 μmol , 1 eq) in DCM (5 mL) was added EDCI (110.49 mg, 576.35 μmol , 1.5 eq) and DMAP (4.69 mg, 38.42 μmol , 0.1 eq), the reaction mixture was stirred at 20 $^{\circ}\text{C}$ for 12 hr. The reaction mixture was concentrated to give a crude product. The crude product was purified by prep-TLC (petroleum ether: ethyl acetate=0:1, desired compound R_f = 0.6). Compound **3** (200 mg, 337.42 μmol , 87.82% yield) was obtained as yellow solid. **LCMS**: m/z = 593.2 ($M+H^+$)

To a solution of methyl Compound **3** (200 mg, 337.42 μmol , 1 eq) in H_2O (2 mL), MeOH (2 mL) and THF (2 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (70.80 mg, 1.69 mmol, 5 eq), the

reaction mixture was stirred at 20 °C for 12 hr. After the reaction was completed, the mixture was extracted with EtOAc (25 mL X3), the combined organic phase was washed with brine (50 ml), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was used to the next step without purification. Compound **4** (160 mg, 276.48 umol, 81.94% yield) was obtained as brown solid. **LCMS**: m/z = 579.2 (M+H⁺)

To a solution of Compound **4** (160 mg, 276.48 umol, 1 eq) in DMF (5 mL) was added Compound **5** (40.45 mg, 414.72 umol, 1.5 eq), DIPEA (71.47 mg, 552.96 umol, 96.32 uL, 2 eq) and HATU (157.69 mg, 414.72 umol, 1.5 eq), the mixture was stirred at 20 °C for 12 hr. After the reaction was completed, the mixture was extracted with EtOAc (25 mL X3), the combined organic phase was washed with brine (50 ml), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by prep-TLC (petroleum ether: ethyl acetate=0:1, desired compound R_f= 0.6. Compound **6** (200 mg, crude) was obtained as brown oil. **LCMS**: m/z = 622.2 (M+H⁺)

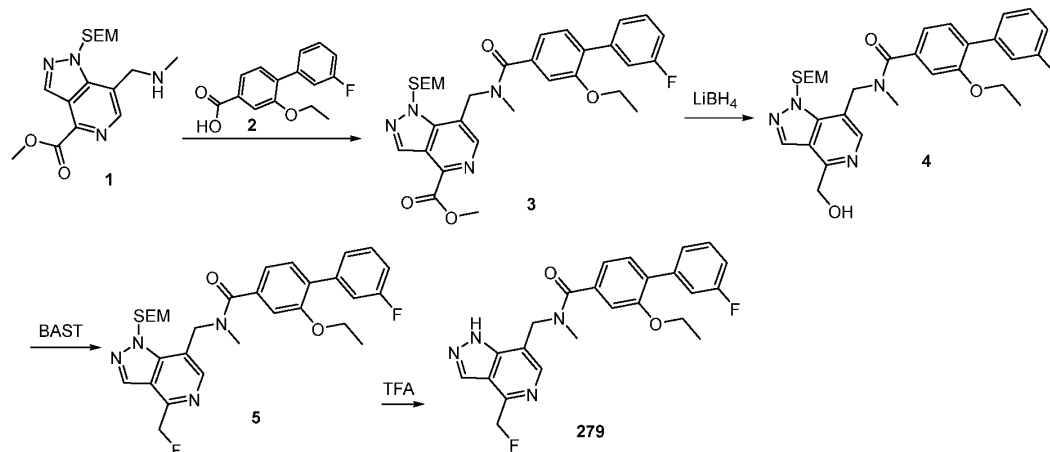
To a solution of Compound **6** (200 mg, 321.66 umol, 1 eq) in 2-MeTHF (4 mL) was added MeMgBr in THF (3 M, 214.44 uL, 2 eq) slowly at 0 °C under N₂, the reaction mixture was stirred at 20 °C for 12 hr under N₂. The mixture was poured into saturated NH₄Cl (25 mL) solution, and extracted with EtOAc (25mL X3), the combined organic phase was washed with brine (25mL), dried over anhydrous Na₂SO₄, and concentrated to give a crude product. The crude product was purified by rep-TLC (petroleum ether: ethyl acetate=0:1, desired compound R_f=0.8). Compound **7** (146 mg, 253.15 umol, 78.70% yield) was obtained as brown oil. **LCMS**: m/z = 577.2 (M+H⁺)

To a solution of Compound **7** (140 mg, 242.75 umol, 1 eq) in MeOH (5 mL) was added LiBH₄ in THF (2 M, 364.12 uL, 3 eq) slowly at 0°C, the reaction mixture was stirred at 20 °C for 12 hr. The reaction mixture was poured into saturated NH₄Cl (10 mL) and extracted by ethyl acetate (10 mLx3), the combined organic phase was dried and concentrated under vacuum to give a crude product. The crude product was purified by prep-TLC (dichloromethane: methanol=10:1, desired compound R_f= 0.6). Compound **8** (110 mg, 190.07 umol, 78.30% yield) was obtained as off-white oil. **LCMS**: m/z = 579.2 (M+H⁺)

To a solution of Compound **8** (110 mg, 190.07 umol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 71.06 eq), the reaction mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 18%-48%, 9min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give white solid. Compound **246** (51.2 mg, 114.16 umol, 60.06% yield, and 100% purity) was obtained as white solid. **LCMS**: m/z = 449.1 (M+H⁺) ¹H NMR: (400 MHz, CHLOROFORM-d) δ = 13.01 - 12.49 (m, 1H), 8.47 (s, 1H), 8.35 (s, 1H), 7.45 - 7.36 (m, 2H), 7.35 - 7.29 (m, 2H),

7.15 - 7.03 (m, 3H), 5.55 - 5.42 (m, 1H), 4.99 (br d, $J = 3.8$ Hz, 2H), 4.09 (q, $J = 7.0$ Hz, 2H), 3.11 (s, 3H), 1.78 (d, $J = 6.8$ Hz, 3H), 1.40 (t, $J = 6.9$ Hz, 3H).

Scheme 47



5 To a solution of **Compound 2** (371.28 mg, 1.43 mmol, 1 eq) in DCM (10 mL) was added **Compound 1** (500 mg, 1.43 mmol, 1 eq), EDCI (410.22 mg, 2.14 mmol, 1.5 eq), DMAP (17.43 mg, 142.66 μ mol, 0.1 eq), then the mixture was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 0/1), the purified solution was concentrated under vacuum to give **Compound 3** (600 mg, 1.01 mmol, 70.96% yield) as a yellow oil. **LCMS**: $m/z = 593.9$ ($M+H$)⁺ **¹H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.78 (s, 1H), 8.64 - 8.55 (m, 1H), 7.37 (br s, 4H), 7.23 - 7.05 (m, 3H), 6.09 - 5.74 (m, 2H), 5.57 - 5.29 (m, 2H), 4.25 - 4.15 (m, 5H), 3.74 - 3.48 (m, 2H), 3.30 - 3.13 (m, 3H), 1.51 - 1.36 (m, 3H), 1.08 - 0.78 (m, 2H), 0.10 - -0.09 (m, 9H)

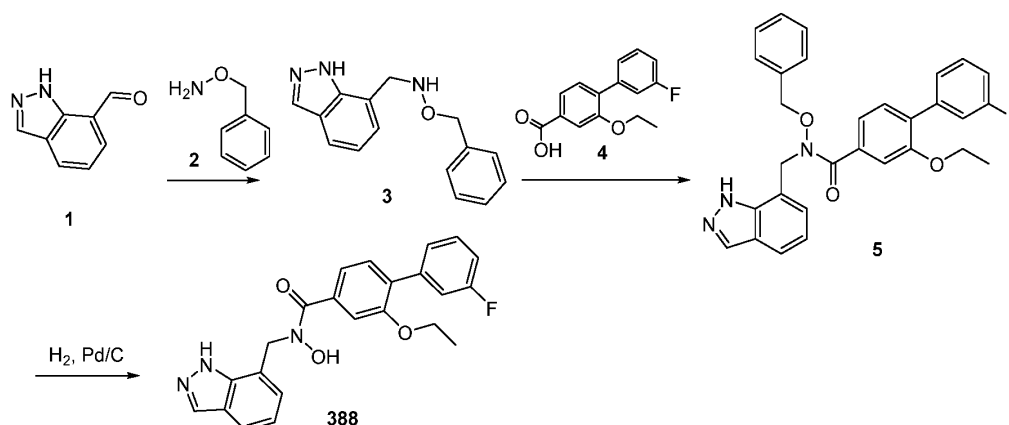
15 The mixture of **Compound 3** (400 mg, 674.84 μ mol, 1 eq) in MeOH (10 mL) was added LiBH₄ in THF (2 M, 674.84 μ L, 2 eq), then the reaction was stirred at 20 °C for 1hr. The mixture was added LiBH₄ in THF (2 M, 674.84 μ L, 2 eq), then the mixture was stirred at 20 °C for 1 hr. The reaction mixture was poured into saturated NH₄Cl (50 mL) and extracted by ethyl acetate (50 mLx3), the combined organic phase was dried and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/4), the purified solution was concentrated under vacuum to give **Compound 4** (250 mg, 442.70 μ mol, 65.60% yield) as a yellow oil. **LCMS**: $m/z = 565.5$ ($M+H$)⁺

25 To a solution of **Compound 4** (230 mg, 407.28 μ mol, 1 eq) in DCM (3 mL) was added BAST (180.21 mg, 814.56 μ mol, 178.43 μ L, 2 eq), the mixture was stirred at 0~20 °C for 1 hr. The reaction mixture was poured into saturated NaHCO₃ aqueous (10 mL) and extracted by ethyl acetate (10 mLx3), the combined organic phase was dried and

concentrated under vacuum to give a residue. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate=0/1), the purified solution was concentrated under vacuum to give **Compound 5** (70 mg, 123.52 μ mol, 30.33% yield) as a yellow oil. **LCMS**: m/z = 567.2 (M+H)⁺

- 5 To a solution of **Compound 5** (70 mg, 123.52 μ mol, 1 eq) in TFA (1 mL) was stirred at 20 °C for 1hr. The reaction mixture was basified by saturated NaHCO₃ aqueous (10 mL), then the reaction mixture was diluted with H₂O (10mL) and extracted with EA (10 mL x3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-
- 10 HPLC (column: Phenomenex luna C18 150*25mm* 10 μ m; mobile phase: [water(FA)-ACN]; B%: 38%-68%, 9min), the purified solution was lyophilized to give **Compound 279** (17 mg, 37.63 μ mol, 30.46% yield, 96.6% purity) as an orange solid. **LCMS**: m/z = 437.1 (M+H)⁺
- 15 **¹H NMR** (400 MHz, CHLOROFORM-d) δ = 12.47 - 12.07 (m, 1H), 8.46 - 8.41 (m, 1H), 8.31 - 8.23 (m, 1H), 7.41 - 7.34 (m, 2H), 7.31 (br d, J = 7.5 Hz, 2H), 7.12 - 7.01 (m, 3H), 5.95 - 5.73 (m, 2H), 5.01 - 4.89 (m, 2H), 4.11 - 4.04 (m, 2H), 3.05 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H).

Scheme 48



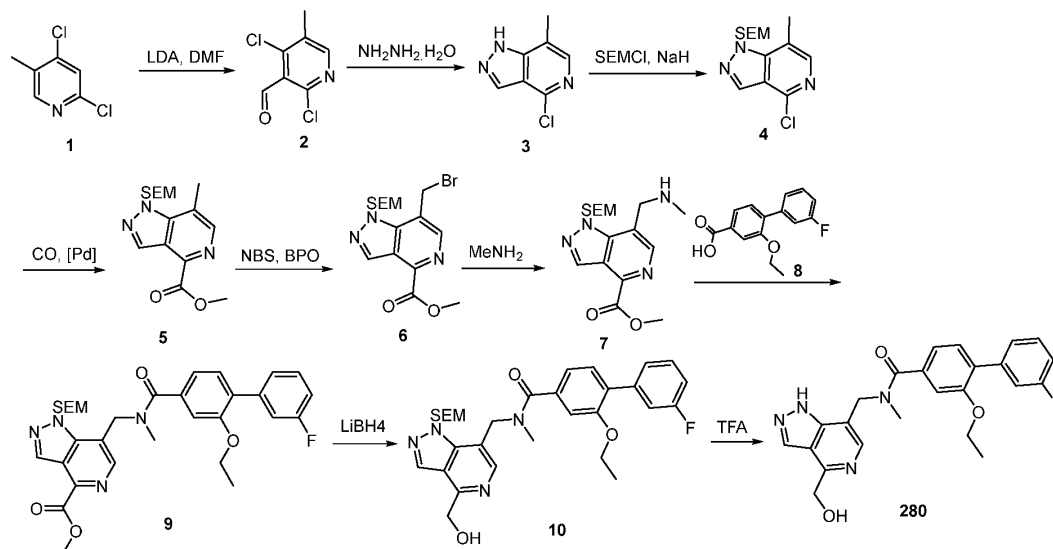
- To the solution of compound 1 (500 mg, 3.42 mmol, 1 eq) and 2 (505.60 mg, 4.11 mmol, 1.2 eq) in MeOH (10 mL) was added in AcOH (20.55 mg, 342.12 μ mol, 19.57 μ L, 0.1 eq). The mixture was stirred at 20°C for 2h. The mixture was added in borane;2-
- 20 methylpyridine (1.10 g, 10.26 mmol, 3 eq) at 0°C and stirred for 5min. The mixture was added in HCl (3 M, 11.40 mL, 10 eq) at 0°C. The mixture was stirred at 20°C for 12h. After cooling to 0°C, the mixture was added Na₂CO₃ (1 g), the solution was filtered, the mixture was extracted by ethyl acetate (500 mL x 3), the combined organic phase was dried and
- 25 concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 5/1. The compound of 3 (200 mg, 789.58 μ mol, 23.08% yield) was obtained as yellow solid. **LCMS**: m/z = 254.1 (M+H)⁺

To a solution of **3** (180 mg, 710.62 μmol , 1 eq) and **4** (221.94 mg, 852.75 μmol , 1.2 eq) in DCM (5 mL) was added EDCI (204.34 mg, 1.07 mmol, 1.5 eq) and DMAP (8.68 mg, 71.06 μmol , 0.1 eq) in stand-up flask at 20°C. The mixture was stirred at 20°C for 12h.

Evaporate the solution on a water bath under reduced pressure using a rotary evaporator. Then the crude product was purified by prep-HPLC. Column: Waters xbridge 150*25mm 10 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 55%-85%, 8min. LCMS: m/z = 496.3 ($\text{M}+\text{H}^+$)

To a solution of 35 mL hydrogenated bottle of **5** (130 mg, 262.34 μmol , 1 eq) in MeOH (5 mL) was added Pd/C (130 mg, 262.34 μmol , 10% purity, 1 eq) at 20°C. The mixture was stirred at 30°C for 1h under H_2 (528.82 ug, 262.34 μmol , 1 eq) (15 PSI). After the reaction was completed, the mixture was filtered under N_2 atmosphere, the filtrate was concentrated. The crude product was purified by prep-HPLC. column: Welch Xtimate C18 150*25mm*5 μm ; mobile phase: [water($\text{NH}_3\text{H}_2\text{O}$)-ACN]; B%: 35%-65%, 8min. lyophilized. The compound **388** (9.71 mg, 23.70 μmol , 9.03% yield, 98.945% purity) was obtained as white solid. LCMS: m/z = 406.3 ($\text{M}+\text{H}^+$). ^1H NMR: (400 MHz, $\text{DMSO}-d_6$) δ = 12.95 (br s, 1H), 10.96 - 9.47 (m, 1H), 8.13 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.51 - 7.31 (m, 7H), 7.21 - 7.12 (m, 2H), 5.17 (s, 2H), 4.05 (br d, J = 6.5 Hz, 2H), 1.26 (br t, J = 6.8 Hz, 3H).

Scheme 49



To a solution of **Compound 1** (25 g, 154.31 mmol, 1 eq) in 2-MeTHF (200 mL) was added LDA (2 M, 115.73 mL, 1.5 eq) under -70 °C, then the mixture was stirred at -70 °C for 1 h. DMF (22.56 g, 308.61 mmol, 23.74 mL, 2 eq) was added into the reaction mixture, the resulting mixture was stirred at -70 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched by NH_4Cl (500 mL) and extracted by ethyl acetate (500 mLx3), the combined

organic phase was dried and concentrated under vacuum to give **Compound 2** (58 g, 305.22 mmol, 98.90% yield) as a brown oil which was used directly in the next step.

To a solution of **Compound 2** (58 g, 305.22 mmol, 1 eq) in DME (600 mL) was added $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (61.12 g, 1.22 mol, 59.34 mL, 100% purity, 4 eq), then the mixture was stirred at 80 °C for 2 hr. The reaction mixture was poured into water (1 L) and extracted by ethyl acetate (1 Lx3), the combined organic phase was dried and concentrated under vacuum to give a residue. The crude product was purified by silica gel column chromatography eluted with PE:EtOAc= 5:1-1:1 to give **Compound 3** (40 g, 238.67 mmol, 78.20% yield) as a yellow solid. LCMS: $m/z = 168.0$ (M+H)⁺

To a solution of **Compound 3** (40 g, 238.67 mmol, 1 eq) in 2-MeTHF (400 mL) was added NaH (14.32 g, 358.01 mmol, 60% purity, 1.5 eq) slowly under 0 °C, then the mixture was stirred at 0 °C for 1 h, SEM-Cl (59.69 g, 358.01 mmol, 63.36 mL, 1.5 eq) was added into the reaction mixture slowly, the resulting mixture was stirred at 20 °C for 2 h. LCMS (5-95AB/0.8 min) showed desired mass was detected. The reaction mixture was poured into saturated aqueous NH_4Cl (1 L) and extracted by ethyl acetate (1 Lx3), the combined organic phase was dried and concentrated under vacuum to give a residue. The residue was purified by silica on column chromatography eluted by petroleum ether/ethyl acetate=5:1, the purified solution was concentrated under vacuum to give **Compound 4** (10 g, 33.57 mmol, 14.07% yield) as a yellow oil. LCMS: $m/z = 298.1$ (M+H)⁺

A solution of **Compound 4** (5 g, 16.79 mmol, 1 eq), TEA (3.40 g, 33.57 mmol, 4.67 mL, 2 eq) and $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ (685.43 mg, 839.33 μmol , 0.05 eq) in MeOH (50 mL) was stirred at 80 °C for 12 hr under CO(50 psi) atmosphere. The reaction was filtered and concentrated under vacuum to give a residue. The residue was purified by silica on column chromatography eluted by petroleum ether/ethyl acetate=5:1 to give a green solid. **Compound 5** (4.4 g, 13.69 mmol, 81.54% yield) was obtained as a green solid. LCMS: $m/z = 322.2$ (M+H)⁺

A mixture of **Compound 5** (4.2 g, 13.07 mmol, 1 eq), NBS (3.49 g, 19.60 mmol, 1.5 eq) and BPO (316.49 mg, 1.31 mmol, 0.1 eq) in trifluoromethylbenzene (50 mL) was stirred at 80 °C for 12 hr. The reaction mixture was poured into water (20 mL) and extracted by ethyl acetate (20 mLx3), the combined organic phase was dried and concentrated under vacuum to give a residue. The residue was purified by silica on column chromatography eluted by petroleum ether/ethyl acetate=5:1, the purified solution was concentrated to give **Compound 6** (1 g, 2.50 mmol, 19.13% yield) a brown oil. LCMS: $m/z = 401.9$ (M+H)⁺

To a solution of methanamine (2 M, 3.75 mL, 3 eq) in 2-MeTHF (10 mL) was added **Compound 6** (1 g, 2.50 mmol, 1 eq) slowly, then the mixture was stirred at 20 °C for 1 hr. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give **Compound 7** (1g, crude) as a brown oil. LCMS: $m/z = 351.1$ (M+H)⁺

To a solution of **Compound 7** (300 mg, 855.95 μmol , 1 eq) and **Compound 8** (222.77 mg, 855.95 μmol , 1 eq) in DCM (4 mL) was added EDCI (246.13 mg, 1.28 mmol, 1.5 eq) and DMAP (10.46 mg, 85.60 μmol , 0.1 eq). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was poured into water (20 mL) and extracted by ethyl acetate (20 mL x3), the combined organic phase was dried and concentrated under vacuum to give residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/1 to 1/1). The purified solution was concentrated under vacuum to give **Compound 9** (308 mg, 519.63 μmol , 60.71% yield) as a yellow oil. LCMS: m/z = 593.5 (M+H)⁺

To a solution of **Compound 9** (250 mg, 421.78 μmol , 1 eq) in MeOH (10 mL) was added LiBH_4 (2 M, 316.33 μL , 1.5 eq) under 0 °C, the resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was quenched by saturated NH_4Cl aqueous (10 mL), the resulting mixture was concentrated under vacuum to give **Compound 10** (130 mg, 230.20 μmol , 54.58% yield) as a yellow oil which was used directly in the next step. LCMS: m/z = 593.4 (M+H)⁺

A mixture of **Compound 10** (30 mg, 53.12 μmol , 1 eq) in TFA (1 mL) was stirred at 20 °C for 1 hr. The reaction mixture was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water(FA)-ACN]; B%: 16%-46%, 9min), the purified solution was concentrated under vacuum to give **Compound 280** (6.9 mg, 15.41 μmol , 29.00% yield, 97% purity) as a white solid. LCMS: m/z = 435.1 (M+H)⁺ ¹H NMR (400 MHz, CHCl_3 -d) δ = 12.77 - 12.17 (m, 1H), 8.44 - 8.19 (m, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.31 (br d, J = 7.8 Hz, 2H), 7.11 - 7.01 (m, 3H), 5.20 (s, 2H), 4.96 (s, 2H), 4.07 (q, J = 6.9 Hz, 2H), 3.07 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H).

Example 2: THP-1 Cell-based NLRP3 Activation Assay

THP-1 cells are cultured in complete media (CM) until they reach logarithmic growth and achieve a viability > 90%. CM is composed of RPMI-1640(+Glutamax)/ 10% fetal bovine serum / 55 μM β -mercaptoethanol/ pen/strep. Cells are spun down and resuspended to 1,000,000 cells/mL in CM containing either 20 nM or 500 nM PMA. 150,000 cells (150 μL) are then added to each well of a 96-well TC plate and incubated for either 24hr or 3hr, respectively, in a standard cell culture incubator (37°C; 5% CO_2). After this incubation, the plate is tilted and media carefully removed. 200 μL of CM containing 100 ng/mL LPS is then added to the wells and the cells incubated an additional 3 hrs. The media is again removed and replaced with Opti-Mem medium containing pre-determined dilutions of test compounds in replicate wells. After a 30 min pre-incubation with test compound, 10 μM nigericin (final concentration) in Opti-Mem medium with the corresponding concentration of compound is

added to the wells for an additional 1 hr. Positive control wells contain 10 μ M nigericin in Opti-Mem in the absence of test compound, while negative control wells contain Opti-Mem only. Supernatants are then transferred to a fresh 96-well plate for storage and assayed for IL-1 β (human; DuoSet; R&D) and for TNF α (human; DuoSet; R&D) levels and relative pyroptosis using a CytoTox 96 Kit (do not freeze prior to testing; Promega). Once supernatants are removed, the relative viability of adherent cells in the 96-well TC plate are determined using a CellTiter-Glo[®] luminescent cell viability assay (Promega).

Table 1 below provides IC₅₀ data for the compounds disclosed herein where “+” is indicative of an IC₅₀ value of <50uM, “++” is indicative of an IC₅₀ value of <10uM, and “+++” is indicative of an IC₅₀ value of <1uM.

Compound No.	IC ₅₀	Compound No.	IC ₅₀
001	+	200	+
002	++	201	+
003	++	202	++
004	++	203	+
005	++	204	+
006	+	205	++
007	++	206	++
008	+	207	+
009	++	208	+
010	++	209	+++
011	++	210	+++
012	++	211	+++
013	++	212	++
014	++	213	+
015	+	214	+
016	+	215	++
017	+	216	+
018	+	217	++
019	+	218	+
020	++	219	++
021	++	220	+
022	++	221	++
028	+	222	+
029	+++	223	+
030	++	224	++
031	++	225	+++
032	+	226	+++
033	+++	227	+++
034	++	228	++
035	++	229	++

036	+++	230	+
037	+	231	++
038	+++	232	++
039	+	233	+++
040	+	234	+++
041	+	235	++
042	+	236	++
043	+++	237	++
044	+++	238	++
045	+	239	+++
046	+++	240	+++
047	+++	241	+++
048	++	242	+++
049	+++	243	+++
050	++	244	+++
051	+	245	+++
052	++	246	+++
053	++	247	+++
054	+	248	+++
055	+	249	+++
056	+	250	++
057	+	251	++
058	++	252	+++
059	++	253	++
060	+	254	++
061	++	255	++
062	++	256	+++
063	+++	257	+++
064	+++	258	++
065	+	259	+
066	+	260	++
067	+	261	+
068	+	262	++
069	+	263	+
070	+	264	+++
071	++	265	+++
072	+++	266	+++
073	+	267	+++
074	+	268	+++
075	+++	269	+++
076	+++	270	+
077	+	271	+

078	+	272	++
079	+	273	+++
080	+++	274	+
081	+	275	++
082	+++	276	+++
083	++	277	+++
084	+	278	+++
085	+++	279	+++
086	+	280	+++
087	+	281	+++
088	+	282	+++
089	+	283	+++
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113	+	306	+++
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115	+	308	+++
116	++	309	++
117	+++	310	+
118	++	311	+
119	++	312	+++
120	++	313	+++
121	+	314	+++

122	+	315	+
123	+	316	+
124	++	317	+++
125	+	318	++
126	++	319	++
127	++	320	+++
128	+++	321	+++
129	+	322	+++
130	++	323	+
131	++	324	++
132	+++	325	++
133	+++	326	+++
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136	++	329	+++
137	++	330	+++
138	+++	331	+++
139	+	332	+
140	+	333	+++
141	+	334	+++
142	+	335	+
143	+	336	+
144	+++	337	+
145	++	338	++
146	+	339	+++
147	+++	340	+++
148	+	341	+
149	+	342	++
150	+	343	+
151	+++	344	+
152	+	345	+
153	+	346	+
154	+++	347	+
155	+++	348	+
156	+	349	+
157	+	350	+
158	+	351	+++
151	+++	352	+++
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153	+	354	+++
154	+++	355	+++
155	+++	356	+++
156	+	357	+++

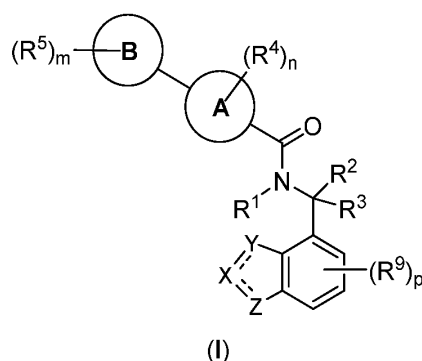
157	+	358	+
158	+	359	+
159	+	360	+++
160	+	361	+++
161	+	362	+++
162	+	363	++
163	+	364	+
164	+++	365	+
165	+	366	++
166	+++	367	+
167	++	368	+
168	+	369	+
169	++	370	+
170	+	371	+
171	++	372	+
172	+	373	+
173	+	374	+
174	+	375	+
175	+	376	+
176	++	377	+
177	++	378	+++
178	++	379	+++
179	++	380	+
180	++	381	+
181	+	382	+
182	+	383	+
183	+	384	+
184	+	385	+++
185	+	386	+++
186	+	387	+++
187	++	388	+++
188	++	389	+
189	++		
190	++		
191	++		
192	+		
193	+		
194	++		
195	++		
196	++		
197	++		
198	+		
199	+		

The disclosed subject matter is not to be limited in scope by the specific
embodiments and examples described herein. Indeed, various modifications of the
5 disclosure in addition to those described will become apparent to those skilled in the art from
the foregoing description and accompanying figures. Such modifications are intended to fall
within the scope of the appended claims.

All references (e.g., publications or patents or patent applications) cited herein are
incorporated herein by reference in their entirety and for all purposes to the same extent as if
10 each individual reference (e.g., publication or patent or patent application) was specifically
and individually indicated to be incorporated by reference in its entirety for all purposes.
Other embodiments are within the following claims.

CLAIMS

1. A compound of Formula I:



5 or a pharmaceutically acceptable salt thereof;

wherein

== is an optional double bond;

X is CH or N;

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S,
10 N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl,
C₄₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆
16 cycloalkyl, and 3-6 membered heterocycloalkyl;

15 alternatively, Ring B is absent and m is 0;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein
alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl,
C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

20 alternatively, R² and R³, together with the atom to which they are attached, form a
ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered
heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH,
OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7
25 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring
selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and
4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three
R⁷;

each R^5 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6 , and SO_2R^6 ;

alternatively, two R^5 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-6} alkyl- C_{6-10} aryl, C_{0-6} alkyl-5-10 membered heteroaryl, OC_{1-6} alkyl, C_{3-6} cycloalkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

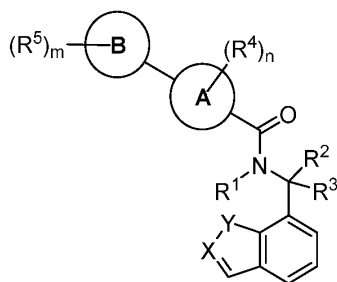
each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

2. The compound of claim 1, wherein the compound of Formula I is a compound of Formula Ia:



(Ia)

or a pharmaceutically acceptable salt thereof;

wherein

X is CH or N;

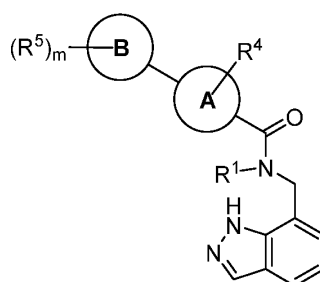
Y is NH, O, or S;

Ring A is phenyl or 5-6 membered heteroaryl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

- R¹ is H or C₁₋₆ alkyl;
 R² and R³ are each independently H or C₁₋₆ alkyl;
 each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, C₁₋₆ haloalkyl, and COR⁶;
 5 each R⁵ is independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁶, and SO₂R⁶;
 each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;
 m is 1, 2, or 3; and
 10 n is 0, 1, 2, or 3.

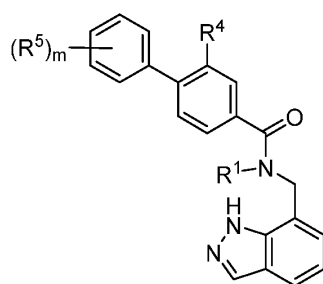
3. The compound of claim 1 or 2, wherein Ring A is selected from the group consisting of phenyl, pyridine, pyrimidine, and pyrazine.
- 15 4. The compound of any one of claims 1-3, wherein Ring A is selected from the group consisting of phenyl, pyridine, pyridazine, pyrimidine, imidazole, pyrazole, and C₃₋₆ cycloalkyl.
5. The compound of any one of claims 1-4, wherein R¹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl,
 20 optionally substituted with C₁₋₆ alkyl.
6. The compound of any one of claims 1-5, wherein Y is NH, X is N, and Z is CH.
7. The compound of any one of claims 1-6, wherein the compound of Formula I is a
 25 compound of Formula Ib:



(Ib)

or a pharmaceutically acceptable salt thereof.

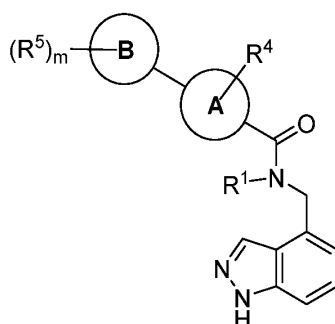
- 30 8. The compound of any one of claims 1-7, wherein the compound of Formula I is a compound of Formula Ic:



(Ic)

or a pharmaceutically acceptable salt thereof.

- 5 9. The compound of claim 1, wherein the compound of Formula I is a compound of Formula Id:



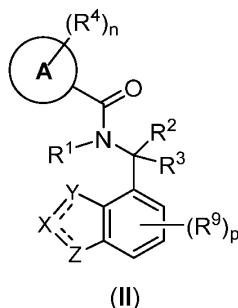
(Id)

or a pharmaceutically acceptable salt thereof.

10

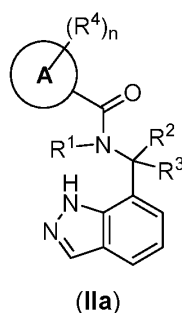
10. The compound of any one of claims 1-9, wherein R⁴ is OC₁₋₆ alkyl.
11. The compound of any one of claims 1-10, wherein R⁵ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, NH₂, CN, CONH₂, CONH(C₁₋₆ alkyl), and
- 15 SO₂NH₂.
12. The compound of any one of claims 1-11, wherein the compound of Formula I is selected from the group consisting of a compound from Table 1, or a pharmaceutically acceptable salt thereof.
- 20
13. The compound of any one of claims 1-11, wherein the compound of Formula I is selected from the group consisting of a compound from Table 2, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, wherein the compound of Formula I is a compound of Formula II:



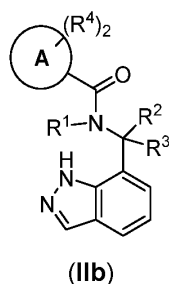
or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, wherein the compound of Formula II is a compound of Formula IIa:



or a pharmaceutically acceptable salt thereof.

16. The compound of claim 14, wherein the compound of Formula II is a compound of Formula IIb:



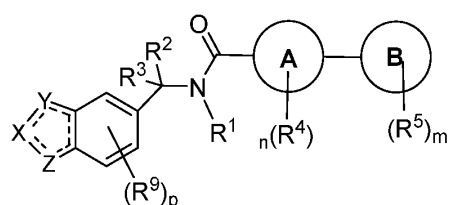
or a pharmaceutically acceptable salt thereof;

20 wherein two R^4 , together with Ring A, form a ring selected from the group consisting of dihydrobenzooxazine, dihydrobenzodioxine, indazole, and indole, all of which are optionally substituted with one, two, or three R^7 .

17. The compound of any one of claims 14-16, wherein the compound of Formula II is selected from the group consisting of a compound from Table 3 and Table 4, or a pharmaceutically acceptable salt thereof.

5

18. A compound of Formula III:



(III)

or a pharmaceutically acceptable salt thereof;

10 wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;

15 Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B is absent and m is 0;

20 R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

25 alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

30 alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6 , and SO_2R^6 ;

alternatively, two R^5 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-6} alkyl- C_{6-10} aryl, C_{0-6} alkyl-5-10 membered heteroaryl, OC_{1-6} alkyl, C_{3-6} cycloalkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

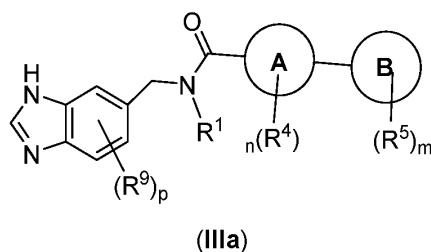
each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

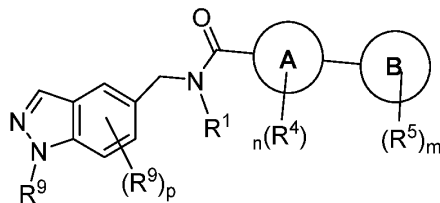
p is 0, 1, 2, or 3.

19. The compound of claim 18, wherein the compound of Formula III is a compound of Formula IIIa:



or a pharmaceutically acceptable salt thereof.

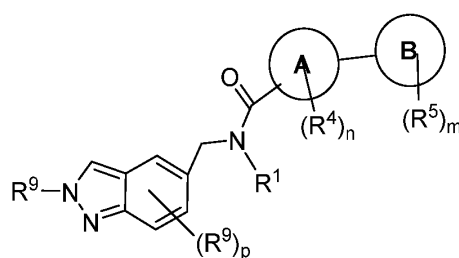
20. The compound of claim 18, wherein the compound of Formula III is a compound of Formula IIIb:



(IIIb)

wherein p is 0, 1, or 2;
or a pharmaceutically acceptable salt thereof.

- 5 21. The compound of claim 18, wherein the compound of Formula III is a compound of Formula IIIc:



(IIIc)

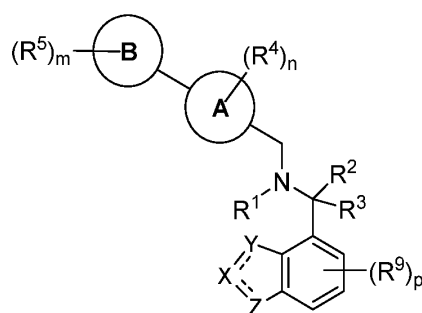
wherein p is 0, 1, or 2;
or a pharmaceutically acceptable salt thereof.

10

22. The compound of any one of claims 18-21, wherein the compound of Formula III is selected from the group consisting of a compound from Table 5, or a pharmaceutically acceptable salt thereof.

15

23. A compound of Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof;

20 wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

5 alternatively, Ring B is absent and m is 0;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

10 alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

15 alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

20 each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

25

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

30 each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁹ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, CN, OH, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

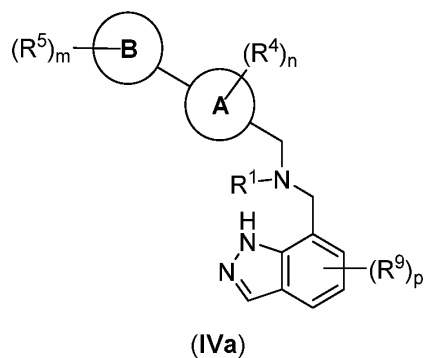
35

m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

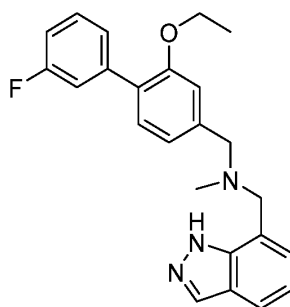
p is 0, 1, 2, or 3.

24. The compound of claim 23, wherein the compound of Formula IV is a compound of Formula IVa:



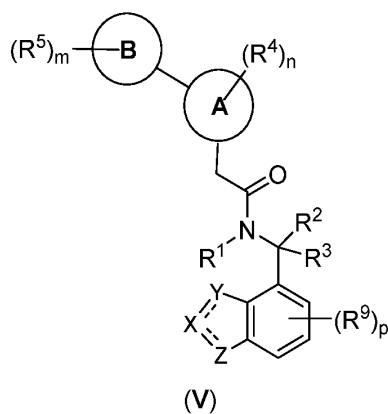
or a pharmaceutically acceptable salt thereof.

25. The compound of claim 23 or 24, wherein the compound of Formula IV is



or a pharmaceutically acceptable salt thereof.

26. A compound of Formula V:



or a pharmaceutically acceptable salt thereof;

wherein

== is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;

5 Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B is absent and m is 0;

10 R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, R² and R³, together with the atom to which they are attached, form a
15 ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

20 alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

alternatively, two R⁵, together with the atoms to which they are attached, form a ring
selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three
30 R⁷;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl) $_2$;

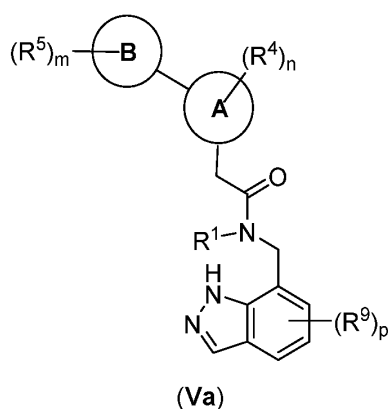
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

5

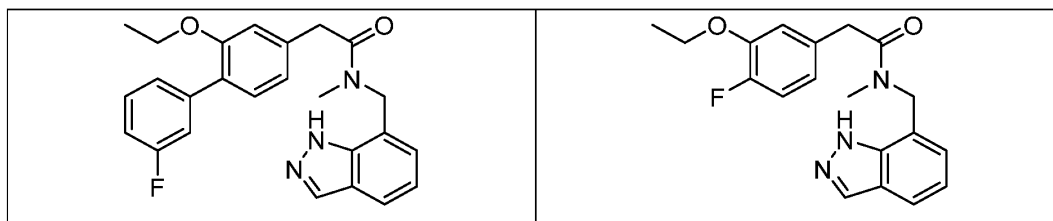
27. The compound of claim 26, wherein the compound of Formula V is a compound of Formula Va:



10

or a pharmaceutically acceptable salt thereof.

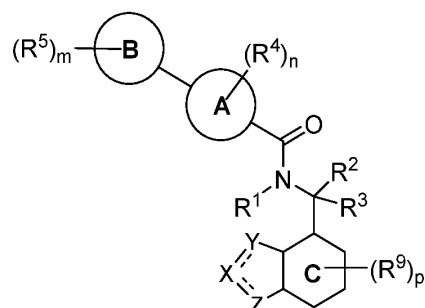
28. The compound of claim 26 or 27, wherein the compound of Formula V is selected from the group consisting of



15

or a pharmaceutically acceptable salt thereof.

29. A compound of Formula VI:



(VI)

or a pharmaceutically acceptable salt thereof;

wherein

$\equiv$ is an optional double bond;

5 X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

10 Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B is absent and m is 0;

Ring C is pyridine;

15 R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered

20 heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

25 alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

30 each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

35 each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl) $_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl) $_2$;

5 each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl) $_2$;

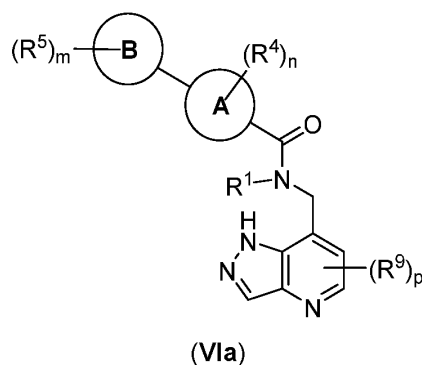
m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3.

10

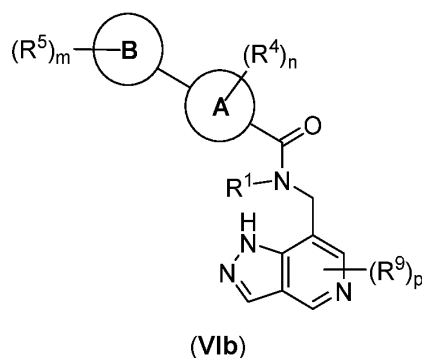
30. The compound of claim 29, wherein the compound of Formula VI is a compound of Formula VIa:



15

or a pharmaceutically acceptable salt thereof.

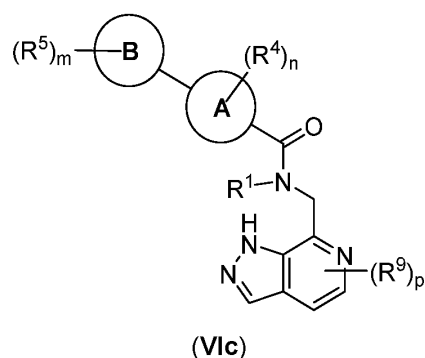
31. The compound of claim 29, wherein the compound of Formula VI is a compound of Formula VIb:



20

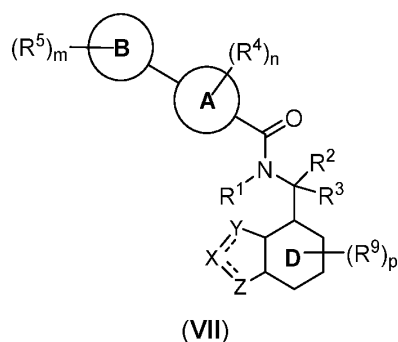
or a pharmaceutically acceptable salt thereof.

32. The compound of claim 29, wherein the compound of Formula VI is a compound of Formula VIc:



or a pharmaceutically acceptable salt thereof.

- 5 33. A compound of Formula VII:



or a pharmaceutically acceptable salt thereof, wherein

== is an optional double bond;

- 10 X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-10 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

- 15 Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B is absent and m is 0;

Ring D is phenyl or pyridine;

- 20 R¹ is selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, OC₁₋₆ alkyl, OC₃₋₆ cycloalkyl, O(C₀₋₆ alkyl-C₆₋₁₀ aryl), C₀₋₆ alkyl-C₆₋₁₀ aryl, and OH, wherein alkyl, aryl, and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, C₁₋₆ alkyl-NHCOR⁶, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁵ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, COR⁶, and SO₂R⁶;

alternatively, two R⁵, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R⁶ is independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₀₋₆ alkyl-C₆₋₁₀ aryl, C₀₋₆ alkyl-5-10 membered heteroaryl, OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁷ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, OH, OC₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, CN, COR⁸, and SO₂R⁸;

each R⁸ is independently selected from the group consisting of C₁₋₆ alkyl, OC₁₋₆ alkyl, halo, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

each R⁹ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OH, OC₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, O(C₃₋₆ cycloalkyl), halo, CN, OH, NH₂, NH(C₁₋₆ alkyl), and N(C₁₋₆ alkyl)₂;

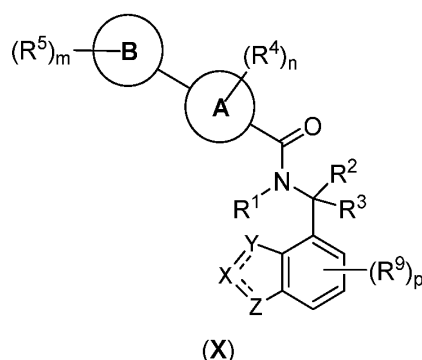
m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

34. The compound of any one of claims 39-33, wherein the compound of Formula VI is selected from the group consisting of a compound from Table 6 or Table 8, or a pharmaceutically acceptable salt thereof.

35. A compound of Formula X:



or a pharmaceutically acceptable salt thereof;

wherein

5 $\equiv$ is an optional double bond;

X is CH, N, NH, or N(C₁₋₆ alkyl);

Y and Z are each independently selected from the group consisting of NH, NR⁹, O, S, N, CH, and CR⁹;

Ring A is selected from the group consisting of C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₃₋₁₀ cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₃₋₆ cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B is absent and m is 0;

R¹ is selected from the group consisting of H, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl are each optionally substituted with R⁶;

R² and R³ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and 4-10 membered heterocycloalkyl, wherein alkyl, cycloalkyl, and heterocycloalkyl are each optionally substituted with R⁶;

alternatively, R² and R³, together with the atom to which they are attached, form a ring selected from the group consisting of C₃₋₇ cycloalkyl and 3-7 membered heterocycloalkyl;

each R⁴ is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, halo, OH, OR⁶, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, NHCOR⁶, CN, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, and COR⁶ wherein alkyl, cycloalkyl, and heterocycloalkyl are each optionally substituted with R⁶;

alternatively, two R⁴, together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C₄₋₆ cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R⁷;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6 , NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6 , and SO_2R^6 ;

alternatively, two R^5 , together with the atoms to which they are attached, form a ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{4-6} cycloalkyl, and 4-6 membered heterocycloalkyl all of which are optionally substituted with one, two, or three R^7 ;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{0-6} alkyl- C_{6-10} aryl, C_{0-6} alkyl-5-10 membered heteroaryl, OC_{1-6} alkyl, C_{3-6} cycloalkyl, halo, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OC_{1-6} alkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, CN, COR^8 , and SO_2R^8 ;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, NH_2 , $NH(C_{1-6} \text{ alkyl})$, and $N(C_{1-6} \text{ alkyl})_2$;

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, OC_{1-6} alkyl, halo, CN, OH, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $C(O)NHR^8$, $C(O)N(R^8)_2$, and $NHC(O)R^8$;

m is 0, 1, 2, or 3;

n is 1, 2, or 3; and

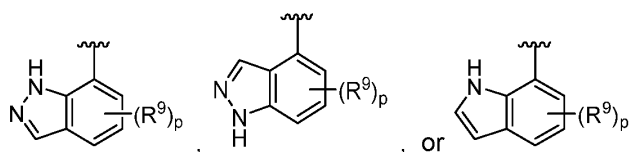
p is 0, 1, 2, or 3.

20

36. The compound of claim 35, wherein the compound of Formula X is selected from the group consisting of a compound from Table 7, or a pharmaceutically acceptable salt thereof.

37. The compound of any one of claims 1, 14, 23, 26, 33, and 35 wherein the compound of Formulae I, II, IV, VII, and X has one of the following core structures:

25



38. A pharmaceutical composition comprising a compound of any one of claims 1-37, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30

39. A method of inhibiting NLRP3 inflammasome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-37, or the pharmaceutical composition of claim 38.

40. A method of treating inflammation in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-37, or the pharmaceutical composition of claim 38.
- 5 41. A method of treating inflammaging in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-37, or the pharmaceutical composition of claim 38.
42. A method of treating cryopyrin-associated periodic syndrome (CAPS) in a subject in
10 need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-37, or the pharmaceutical composition of claim 38.
43. A method of treating a disease or disorder of the inner ear in a subject in need
15 thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-37, or the pharmaceutical composition of claim 38.
44. The method of claim 43, wherein the disease or disorder of the inner ear is selected
20 from the group consisting of hearing loss, hearing impairment, vertigo, Meniere's disease, and tinnitus.