INHIBITORS OF NLRP3 INFLAMMASOME

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

The content of the electronically submitted sequence listing in XML file (Name: 762525_BIOT-007PC_ST26.xml; Size: 2,722 bytes; Date of Creation: March 24, 2025) is incorporated herein by reference in its entirety.

RELATED APPLICATIONS

This application is related to U.S. Provisional Application No. 63/570,087 filed March 26, 2024, U.S. Provisional Application No. 63/656,967, filed June 6, 2024, U.S. Provisional Application No. 63/669,006, filed July 9, 2024, and U.S. Provisional Application No. 63/708,034, filed October 16, 2024, the entire contents of each are incorporated herein.

BACKGROUND

Aging frailty poses a very concerning problem for the overall health and well-being of 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., Biogerontology 11(5):635-641 (2010)). Immunosenescence is characterized by a low grade, chronic systemic inflammatory state known as inflammaging (Franceshi, 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.

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 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 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. 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).

Inactivation of NLRP3 inflammasome significantly alleviates obesity-mediated metabolic disorders, such as non-alcoholic fatty liver disease (NAFLD) (Wani, K., et. al., Int. J. Environ. Res. Public Health, **2021**, *18*, 511) and has been shown to reverse obesity in the diet-induced obesity mice model (Thornton, P., *J. Pharmacol. Exp. Ther.*, **2024**, *388*, 813-826). Other metabolic disorders linked to NLRP3 include insulin resistance (Vandanmagsar, B., et. al., *Nature Medicine*, **2011** *17*, 179–188), obesity-induced inflammation (Sokolova, M., *Scientific Reports*, **2020**, *10*, 21006), diabetes-associated atherosclerosis (Sharma, A., et al., *Diabetes* 2021;70(3):772–787), and ischemic stroke concomitant with diabetes (Hong, P., et al., *J. Neuroinflammation,* 2019; 16:121). Inhibiting the NLRP3 inflammasome has also been shown to ameliorate kidney injury in diabetic nephropathy (Yang, M., et al., *Curr. Med. Chem.*, 2022, *30*, 3261-3270) and play a role in obesity-related low-grade inflammation and insulin resistance in skeletal muscle (Jorquera, G., et al., *Int. J. Mol. Sci.*, 2021, *21*, 3254).

NLRPs, including NLRP3, have been implicated in various eye diseases with not all being related to aging (Niu, L., et al., PLoS ONE 10(5): e0126277; and Mugisho, O., et al., Experimental Eye Research 215 (2022) 108911). For example, the NLRP3 inflammasome has been shown to play a role in both glaucoma, an ocular disease most commonly occuring in older adults, and dry eye, which can occur in people of any age.

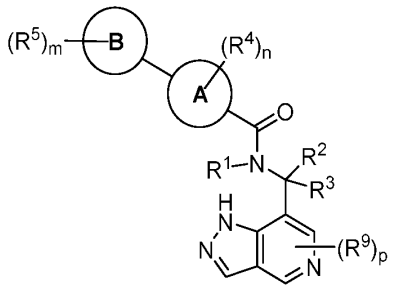
The NLRP3 inflammasome is therefore a promising drug target. The breadth of the indications it is implicated in speak to the need for therapeutics that target the NLRP3 inflammasome.

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 particular, provided herein is a compound that binds to amino acids of Y143, R147, F257, Y258, H260, E263, V264, L272, L275, I276, C279, F299, G328, L331, L332, L335, and C514 of a NLRP3 amino acid sequence of SEQ ID NO: 1. Such a compound is useful for the treatment of a variety of conditions in a subject, such as cancer, inflammaging, inflammation, and age-related diseases.

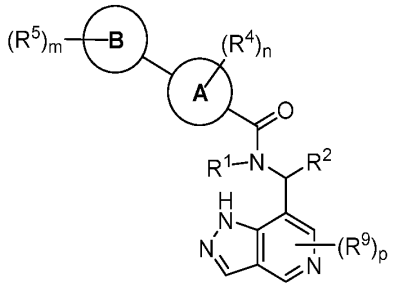
In an aspect, provided herein is a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof.

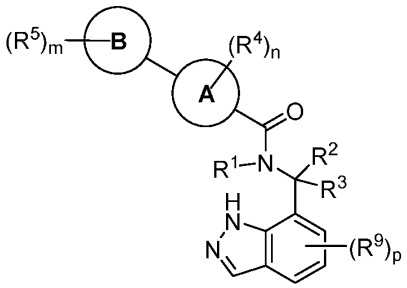
In another aspect, provided herein is a compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof.

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



(III)

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.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts a cryo-EM image of Compound 007 binding into a characteristic pocket on the NACHT domain of NLRP3.

Fig. 2 depicts ribbon-structure images of Compound 007 and ADP binding on two different sites of the NLRP3 NBD.

Fig. 3 depicts a ribbon-structure image of a hydrogen-bond network of Compound 007 to the β2 main chain of NLRP3.

Fig. 4 depicts a ribbon-structure image of the biphenyl moiety of Compound 007 binding into a hydrophobic pocket on NLRP3.

Fig. 5 depicts a ribbon-structure image of Compound 007 in proximity to Cys279 and Cys514 of NLRP3.

Fig. 6 depicts ATP hydrolysis over time by Compound 007 and an additional 5-azaindazole-containing compound incubated with NLRP3.

Fig. 7 depicts randomization of mice for treatment.

Fig. 8 depicts the body weight and body weight percent changes in a diet-induced obesity (DIO) mouse model using Compound 040 or semaglutide.

Fig. 9 depicts the food consumption in the DIO mouse model using Compound 040 or semaglutide.

Fig. 10 depicts the change in fat mass and lean mass percentages in the DIO mouse model using Compound 040 or semaglutide.

Fig. 11 depicts glucose metabolism in the DIO mouse model using Compound 040 or semaglutide.

Fig. 12 depicts the body weight changes in the DIO mouse model to compare NT-0796, calorie restriction, VTX3232, Compound 040 and semaglutide.

Fig. 13 depicts the terminal tissue weights or tissue to body weight percent of DIO mice after Compound 040 or semaglutide treatment for 4 weeks.

Fig. 14 depicts the body weight (A), body weight percent change (B), and cumulative food consumption (C) in the DIO mouse model using Compound 096, Compound 211, or semaglutide.

Fig. 15 depicts the fat mass in the DIO mouse model using Compound 096, Compound 211, or semaglutide.

Fig. 16 depicts the swelling reduction effect of Compound 096 and MCC950 in a foot gout model.

Fig. 17 depicts the reduction in paw swelling in a mouse gout model using Compound 040 or MCC950.

DETAILED DESCRIPTION

Provided here are compounds that inhibit the NLRP3 inflammasome. In a non-limiting embodiment, the compounds bind to amino acids of Y143, R147, F257, Y258, H260, E263, V264, L272, L275, I276, C279, F299, G328, L331, L332, L335, and C514 of a NLRP3 amino acid sequence of SEQ ID NO: 1. Such compounds are useful for the treatment of a variety of conditions in a subject, such as cancer, inflammaging, inflammation, and age-related diseases. As such, these compounds, as well as pharmaceutical compositions that comprise these compounds, are useful in the treatment of a variety of indications, including cancer, inflammaging, inflammation, and age-related diseases. These compounds are also useful for treating obesity and obesity-related disorders.

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. 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 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 term “about” is meant to encompass variations of ±10%, including ±5%, ±1%, and ±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 in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

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 compound into a sample containing a purified preparation containing the cell.

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 the symptoms of inflammaging and age-related disorders.

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 “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 mammal.

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.

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, 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 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 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.

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 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, an “epitope” refers to a surface or region on one or more entities (e.g., an NLRP3 polypeptide) that is capable of interacting with a binding molecule (e.g., the compounds of the disclosure). For example, a protein epitope may contain one or more amino acids and/or post-translational modifications (e.g., phosphorylated residues) which interact with the binding molecule. In some embodiments, an epitope may be a “conformational epitope,” which refers to an epitope involving a specific three-dimensional arrangement of the entity(ies) having or forming the epitope. For example, conformational epitopes of proteins may include combinations of amino acids and/or post-translational modifications from folded, non-linear stretches of amino acid chains.

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

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

As used herein, “GLP-1” refers to glucagon-like peptide-1, which is a 30- or 31-amino-acid-long peptide hormone deriving from the tissue-specific posttranslational processing of the proglucagon peptide. It is produced and secreted by intestinal enteroendocrine L-cells and certain neurons within the nucleus of the solitary tract in the brainstem upon food consumption. Beside the insulinotropic effects, GLP-1 has been associated with numerous regulatory and protective effects. Glucagon-like peptide-1 receptor agonists have gained approval as drugs to treat diabetes and obesity.

As used herein, “comorbidity” refers to a disease or medical condition that is simultaneously present with another disease or medical condition in a patient.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl and C_6 alkyl.

The term "n-membered," where n is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted," unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. It is to be understood that substitution at a given atom results in a chemically stable molecule. The phrase "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms.

In some embodiments, the compounds herein are substantially isolated. As used herein, "substantially isolated" means that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in a compound of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound.

The term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-4}, C_{1-6} and the like.

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., C_1-C_6 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 C_1-C_6 alkyl include ethyl, methyl, isopropyl, isobutyl, n-pentyl, and n-hexyl.

The term "alkenyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or

more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term "C_{n-m} alkenyl" refers to an alkenyl group having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.

The term "alkynyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term "C_{n-m} alkynyl" refers to an alkynyl group having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

The term "alkylene," employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term "C_{n-m} alkylene" refers to an alkylene group having n to m carbon atoms. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, ethan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, propan-1,1-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

The term "alkoxy," employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group is as defined above. The term "C_{n-m} alkoxy" refers to an alkoxy group, the alkyl group of which has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

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.

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" 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 an embodiment, "cycloalkyl" is C_{3-10} cycloalkyl. In another embodiment, "cycloalkyl" is C_{3-6} 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 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, azetidinyl, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, oxazolidinyl, thiazolidinyl, piperidinyl, 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 yet another embodiment, "heterocycloalkyl" refers to 3-, 4-, 5-, or 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.

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 an embodiment, “heteroaryl” refers to 5-10 membered heteroaryl. In another embodiment, “heteroaryl” refers to 5-6 membered heterocycloalkyl. In yet another embodiment, “heteroaryl” refers to 5-, 6-, 7-, 8-, 9-, or 10-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.

NLRP3

As used herein, the term “Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing 3” or “NOD-, LRR-, and pyrin domain-containing protein 3” or “NLRP3” refers to UNIPROT reference number Q96P20 and the amino acid sequence of SEQ ID NO: 1, shown below.

MKMASTRCKLARYLEDLEDVDLKKFKMHLEDYPPQKGCIPLPRGQTEKADHVDLATLMIDF
NGEEKAWAMAVWIFAAINRRDLYEKAKRDEPKWGSDNARVSNPTVICQEDSIEEEWMGLL
EYLSRISICKMKKDYRKKYRKYVRSRFQCIEDRNARLGESVSLNKRYTRLRLIKEHRSQQER
EQELLAIGKTKTCESPVSPIKMELLFDPDDEHSEPVHTVVFQGAAGIGKTILARKMMLDWAS
GTLYQDRFDYLFYIHCREVSLVTQRSLGDLIMSCCPDPNPPIHKIVRKPSRILFLMDGFDELQ
GAFDEHIGPLCTDWQKAERGDILLSSLIRKKLLPEASLLITTRPVALEKLQHLLDHPRHVEILG
FSEAKRKEYFFKYFSDEAQARAAFSLIQENEVLFTMCFIPLVCWIVCTGLKQQMESGKSLAQ
TSKTTTAVYVFFLSSLLQPRGGSQEHGLCAHLWGLCSLAADGIWNQKILFEESDLRNHGLQ

KADVSAFLRMNLFQKEVDCEKFYSFIHMTFQEFFAAMYYLLEEEKEGRTNVPGSRLKLPSR
DVTVLLENYGKFEKGYLIFVVRFLFGLVNQERTSYLEKKLSCKISQQIRLELLKWIEVKAKAKK
LQIQPSQLELFYCLYEMQEEDFVQRAMDYFPKIEINLSTRMDHMVSSFCIENCHRVESLSLG
FLHNMPKEEEEEEKEGRHLDMVQCVLPSSSHAACSHGLVNSHLTSSFCRGLFSVLSTSQS
LTELDLSDNSLGDPGMRVLCETLQHPGCNIRRLWLGRCGLSHECCFDISLVLSSNQKLVEL
DLSDNALGDFGIRLLCVGLKHLLCNLKKLWLVSCCLTSACCQDLASVLSTSHSLTRLYVGEN
ALGDSGVAILCEKAKNPQCNLQKLGLVNSGLTSVCCSALSSVLSTNQNLTHLYLRGNTLGD
KGIKLLCEGLLHPDCKLQVLELDNCNLTSHCCWDLSTLLTSSQSLRKLSLGNNDLGDLGVM
MFCEVLKQQSCLLQNLGLSEMYFNYETKSALETLQEEKPELTVVFEPSW (SEQ ID NO: 1)

NLRP3 is a member of the Nod-like receptor (NLR) family of proteins. NLRP3 is an intracellular sensor that detects a broad range of danger signals and environmental insults resulting in a protective pro-inflammatory response designed to impair pathogens and repair tissue damage via the formation and activation of the NLRP3 inflammasome (Coll, R.C., et al., *Trends Pharmacol. Sci.*, 2022, *43(8)*, 653-668). NLRP3 is highly expressed in subsets of peripheral leukocytes and microglia of the central nervous system.

NLRP3 displays a tripartite structure consisting of a Pyrin Domain (PYD), a central nucleotide binding and oligomerization domain of the NACHT subfamily of NTPases, and a Leucine Rich Repeat domain (LRR). The NACHT domain has ATPase activity that is required to induce an inactive ADP-bound decameric assembly in cells (Hochheiser, I., et al., *Nature*, 2022, *604*, 184-189), (Brinkschulte, R., et al., *Commun. Biol.*, 2022, *5*, 1176).

Assembly of the NLRP3 inflammasome leads to caspase 1-dependent secretory release of the pro-inflammatory cytokines IL-1β and IL-18 as well as to gasdermin D-mediated pyroptotic cell death.

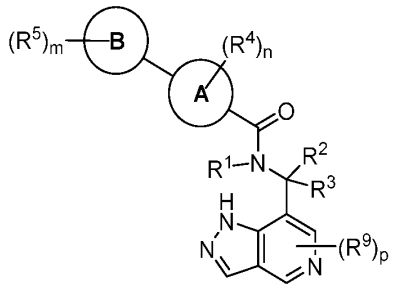
In an aspect, provided herein is a compound that binds to one or more amino acids of Y143, R147, F257, Y258, H260, E263, V264, L272, L275, I276, C279, F299, G328, L331, L332, L335, and C514 of a NLRP3 amino acid sequence of SEQ ID NO: 1.

In an embodiment, the compound binds to at least amino acids of L275 and C279 of a NLRP3 amino acid sequence of SEQ ID NO: 1. In another embodiment, the compound binds to amino acids of Y143, R147, F257, Y258, H260, E263, V264, L272, L275, I276, C279, F299, G328, L331, L332, L335, and C514 of a NLRP3 amino acid sequence of SEQ ID NO: 1.

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:



(I)

or a pharmaceutically acceptable salt thereof;

wherein

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is independently optionally oxidized and independently optionally substituted by C_{1-6} alkyl; the nitrogen atom of NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized; and one or more carbon atoms of the alkyl groups on the nitrogen atom are optionally substituted with 1-6 deuterium atoms or C_{1-6} alkoxy;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In an embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)(C_{1-6}$ haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl$)_2$, $N(C_{1-6}$ haloalkyl$)_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl;

and the nitrogen atom of NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized.

In another embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl; and the nitrogen atom of NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized. In another embodiment, R^3 is C_{1-6} alkyl substituted by OH, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, or C_{1-3} alkoxy. In another embodiment, R^3 is C_{1-6} alkyl substituted by $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, or C_{1-3} alkoxy. In yet another embodiment, R^3 is C_{1-6} alkyl substituted by $NH(C_{1-6}$ alkyl) or $N(C_{1-6}$ alkyl)$_2$.

In yet another embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is independently optionally oxidized and independently optionally substituted by C_{1-6} alkyl; and the nitrogen atom of $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized and the carbon atom of the alkyl groups on the nitrogen atom are optionally substituted with 1-6 deuterium atoms or C_{1-6} alkoxy.

In an embodiment,

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo; and

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo, or C_{0-3} alkyene-5-10 membered heteroaryl, and wherein 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl.

In an embodiment,

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, halo, SO_2R^6, or C_{0-3} alkyene-5-10 membered heteroaryl;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In another embodiment,

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is C_{1-6} alkyl;

R^2 is H;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH or C_{1-6} alkoxy;

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, both of which is substituted by OH;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $NHC(O)C_{1-6}$ alkyl, CN, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $CONH_2$, $CONH(C_{1-6}$ alkyl), CN, and C_{1-6} haloalkyl;

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

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

In yet another embodiment,

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is C_{1-6} alkyl;

R^2 is H;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, or C_{1-6} alkoxy;

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, both of which is substituted by OH;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $NHC(O)C_{1-6}$ alkyl, CN, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $CONH_2$, $CONH(C_{1-6}$ alkyl), CN, and C_{1-6} haloalkyl;

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

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

In another embodiment,

Ring A is phenyl;

Ring B is phenyl;

R^1 is C_{1-6} alkyl;

R^2 is H;

R^3 is C_{1-6} alkyl substituted by $N(R^a)_2$;

each R^a is independently H or C_{1-6} alkyl;

R^4 is C_{1-6} alkoxy;

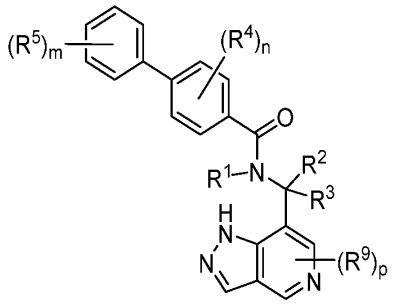
R^5 is selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, CN, and C_{1-6} haloalkyl;

m is 1;

n is 1; and

p is 0.

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



(**Ia**)

or a pharmaceutically acceptable salt thereof.

In still another embodiment, Ring A is phenyl.

In an embodiment, Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl. In another embodiment, Ring B is phenyl. In yet another embodiment, Ring B and R^5 are absent.

In still another embodiment, R^1 is C_{1-6} alkyl. In an embodiment, R^1 is methyl. In another embodiment, R^1 is ethyl. In an embodiment, R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl. In yet another embodiment, R^1 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo. In still another embodiment, R^1 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-3}$ alkyl, $C(O)C_{1-3}$ alkyl, NH_2, NHC_{1-3} alkyl, $N(C_{1-3}$ alkyl$)_2$, and halo.

In another embodiment, R^2 is H.

In an embodiment, R^3 is C_{1-6} alkyl substituted by OH or C_{1-3} alkoxy. In still another embodiment, R^3 is C_{1-6} alkyl substituted by OH. In an embodiment, R^3 is C_{1-6} alkyl substituted by C_{1-3} alkoxy. In an embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, halo, SO_2R^6, or C_{0-3} alkyene-5-10 membered heteroaryl. In another embodiment, R^3 is C_{1-6} alkyl substituted by 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH. In yet another embodiment, R^3 is 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl. In an embodiment, R^3 is C_{1-6} alkyl substituted by $N(R^a)_2$. In another embodiment, each R^a is independently H or C_{1-6} alkyl.

In yet another embodiment, R^3 is C_{1-6} alkyl substituted by OH or C_{1-3} alkoxy. In still another embodiment, R^3 is C_{1-6} alkyl substituted by OH. In an embodiment, R^3 is C_{1-6} alkyl substituted by C_{1-3} alkoxy. In an embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, halo, SO_2R^6, or C_{0-3} alkyene-5-10 membered heteroaryl. In another embodiment, R^3 is C_{1-6} alkyl substituted by 3-6 membered heterocycloalkyl optionally substituted with one or two halo. In yet another embodiment, R^3 is 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl. In an embodiment, R^3 is C_{1-6} alkyl substituted by $N(R^a)_2$. In another embodiment, each R^a is independently H or C_{1-6} alkyl.

In an embodiment, R^3 is C_{1-6} alkyl substituted by OH, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, or C_{1-3} alkoxy. In another embodiment, R^3 is C_{1-6} alkyl substituted by $NH(C_{1-6}$ alkyl), $N(C_{1-6}$

alkyl)$_2$, or C_{1-3} alkoxy. In yet another embodiment, R^3 is C_{1-6} alkyl substituted by NH(C_{1-6} alkyl) or N(C_{1-6} alkyl)$_2$.

In another embodiment, R^2 and R^3, together with the atom to which they are attached, form a ring selected from the group consisting of C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, both of which is substituted by OH. In yet another embodiment, R^2 and R^3, together with the atom to which they are attached, form C_{3-6} cycloalkyl substituted by OH. In still another embodiment, R^2 and R^3, together with the atom to which they are attached, form 3-6 membered heterocycloalkyl substituted by OH.

In an embodiment, each R^4 is independently selected from the group consisting of halo, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, and C_{1-6} haloalkyl. In another embodiment, each R^4 is independently selected from the group consisting of halo, C_{1-3} alkoxy, O-cyclopropyl, and C_{1-3} haloalkyl. In an embodiment, R^4 is C_{1-6} alkoxy.

In yet another embodiment, each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, CN, and C(O)NH(C_{1-6} alkyl). In still another embodiment, each R^5 is independently selected from the group consisting of C_{1-3} alkyl, halo, CN, and C(O)NH(C_{1-3} alkyl). In another embodiment, R^5 is selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, CN, and C_{1-6} haloalkyl.

In an embodiment, each R^9 is independently selected from the group consisting of C_{1-3} alkyl, C_{1-6} alkoxy, C_{1-3} alkyl-OH, and halo.

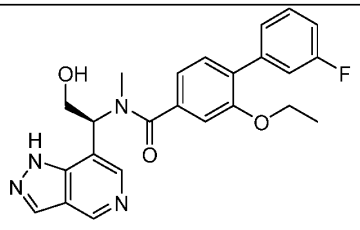
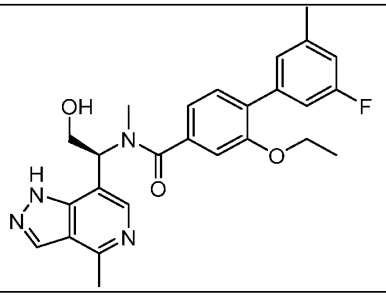
In another embodiment, m is 0, 1, or 2. In yet another embodiment, m is 0. In still another embodiment, m is 1. In an embodiment, m is 2.

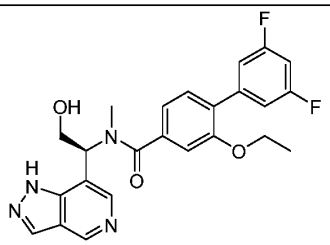
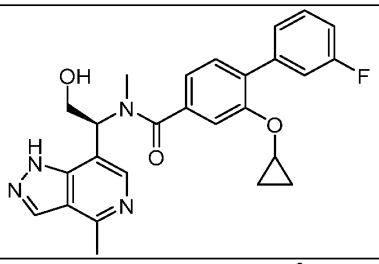
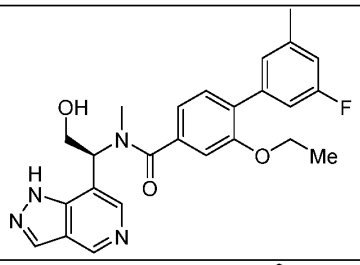
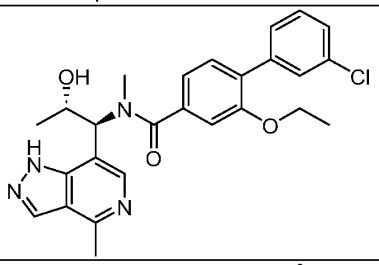
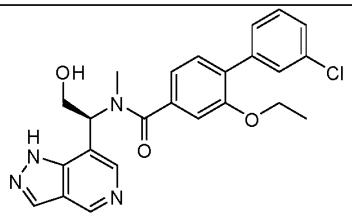
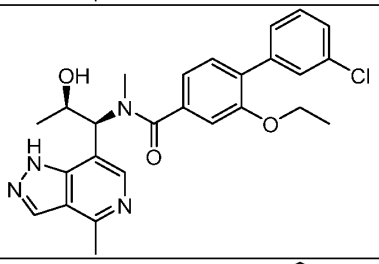
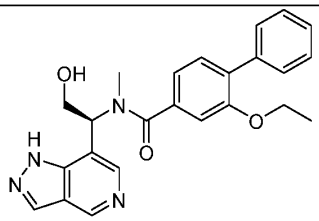
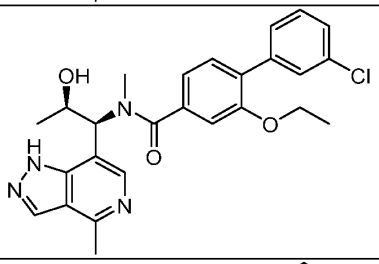
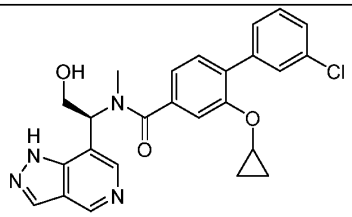
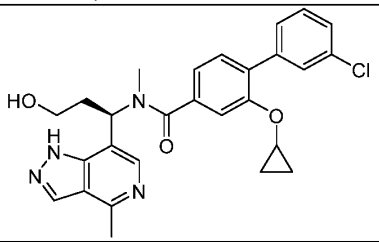
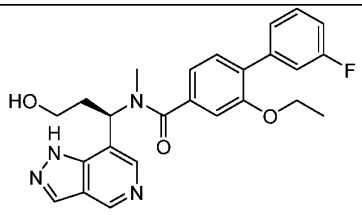
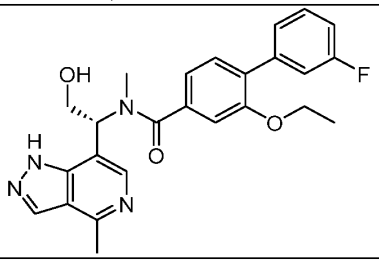
In another embodiment, n is 1. In yet another embodiment, n is 0. In still another embodiment, n is 2.

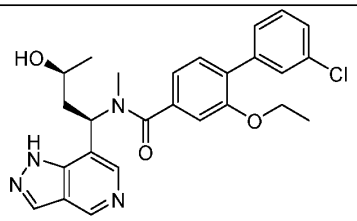
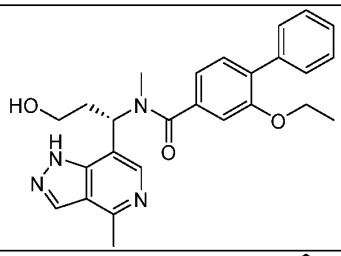
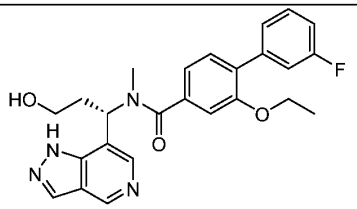
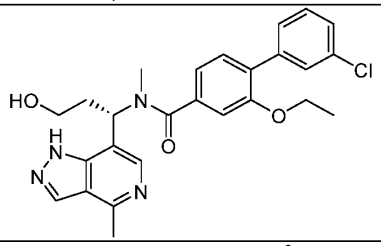
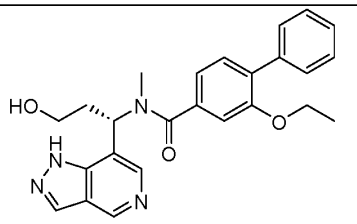
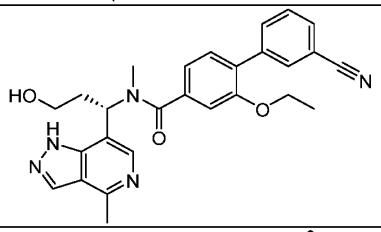
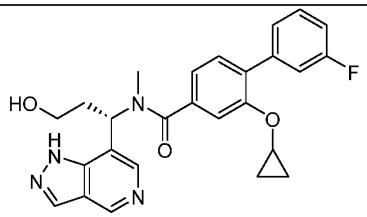
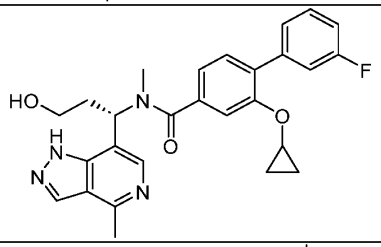
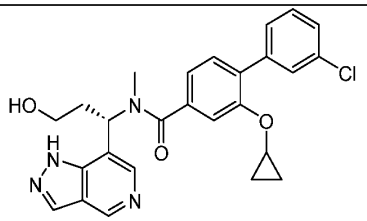
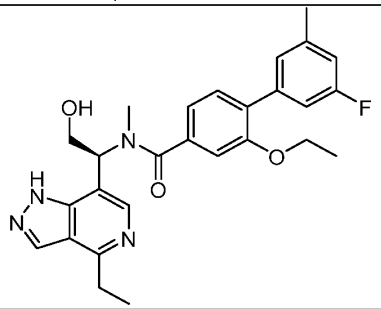
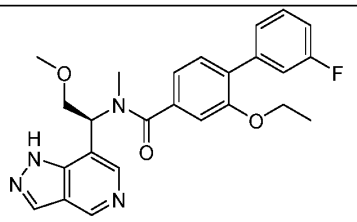
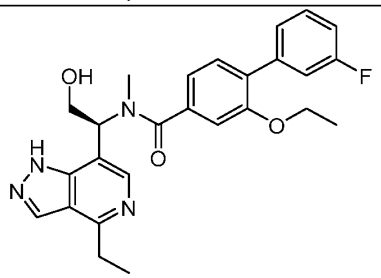
In another embodiment, p is 0, 1, or 2. In yet another embodiment, p is 0. In still another embodiment, p is 1. In an embodiment, p is 2.

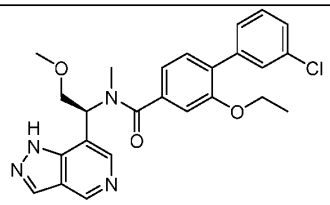
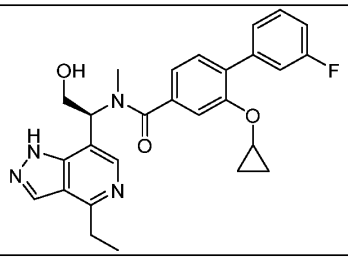
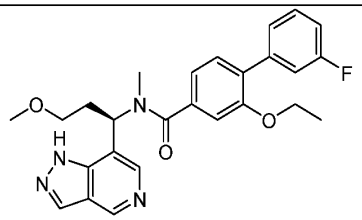
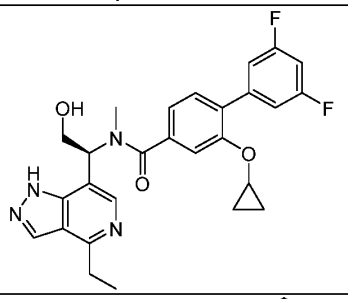
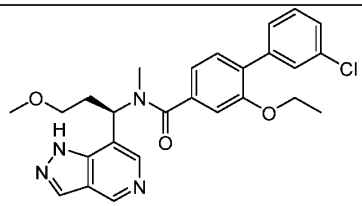
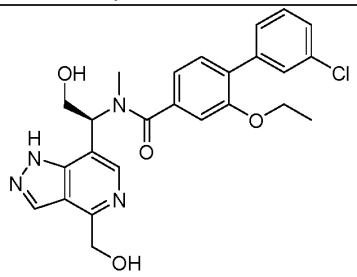
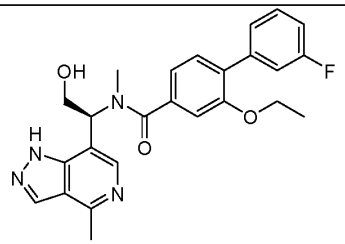
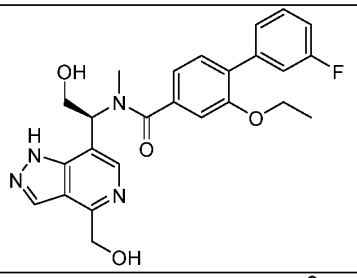
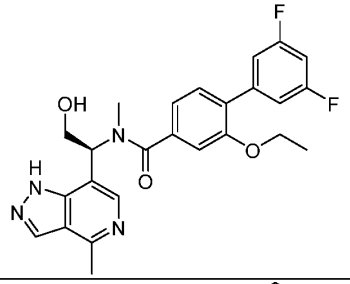
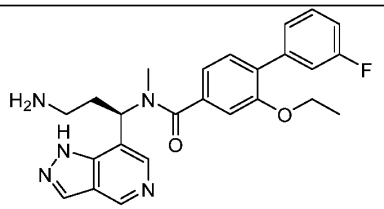
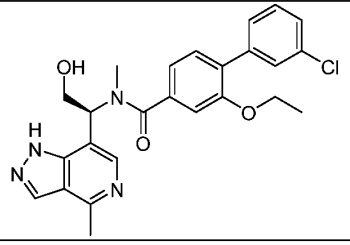
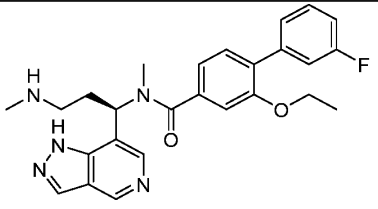
In another embodiment, the compound of Formula I is selected from the group consisting of a compound in Table 1.

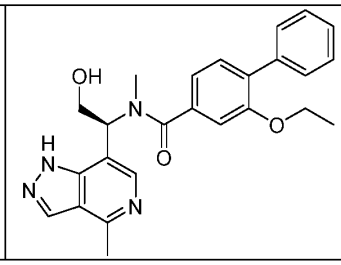
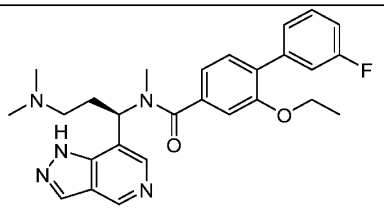
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013		033	

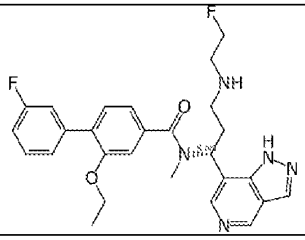
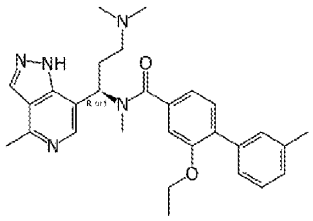
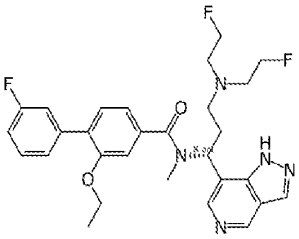
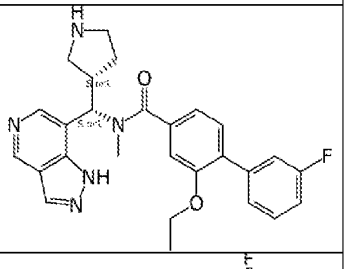
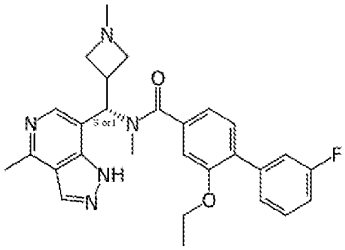
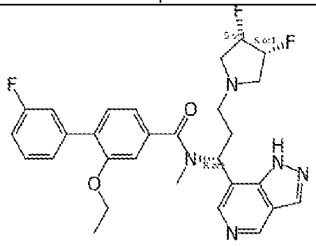
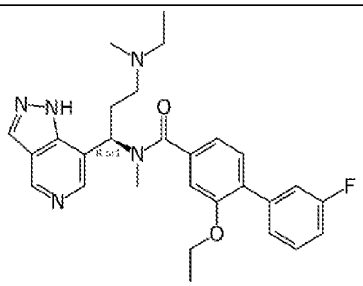
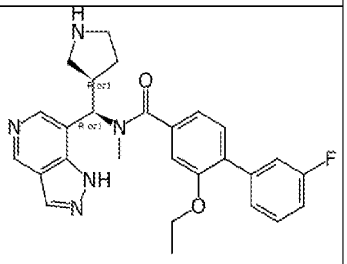
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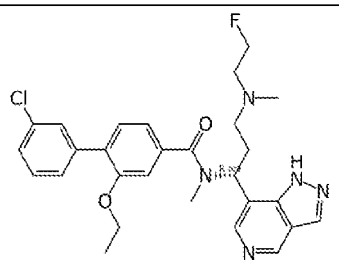
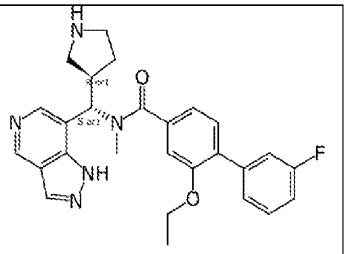
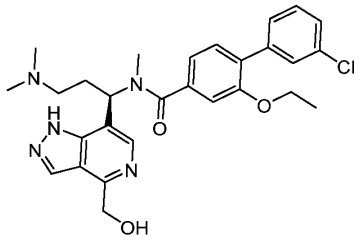
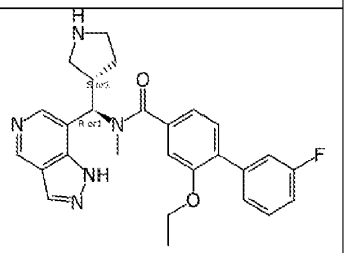
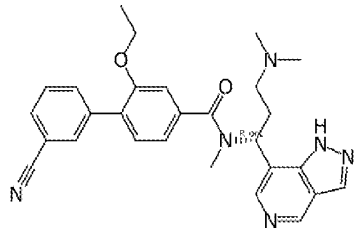
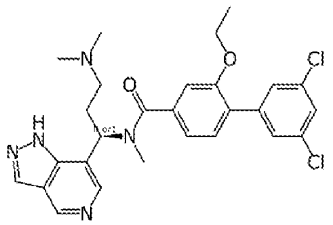
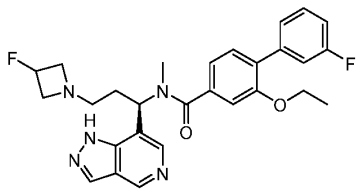
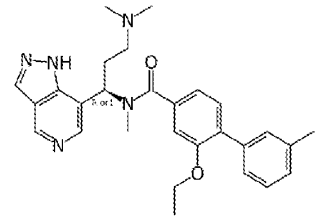
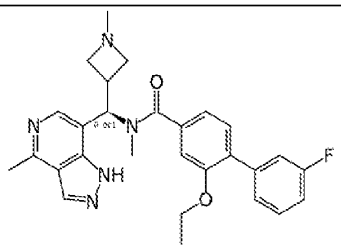
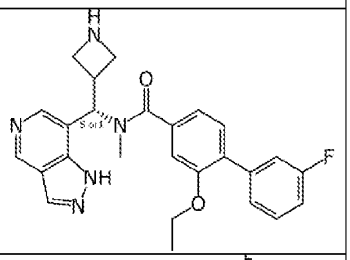
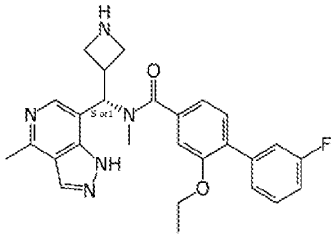
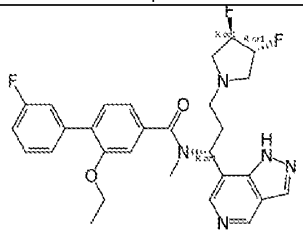
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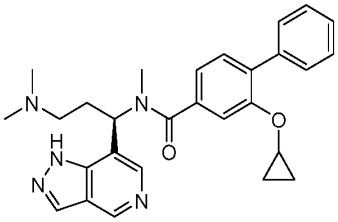
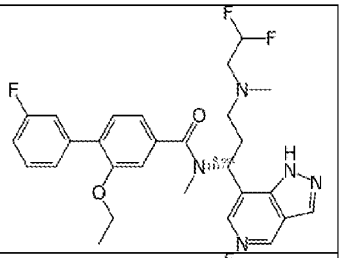
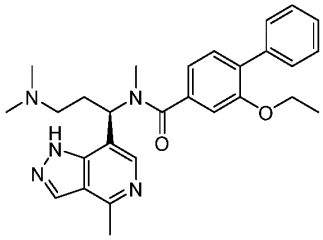
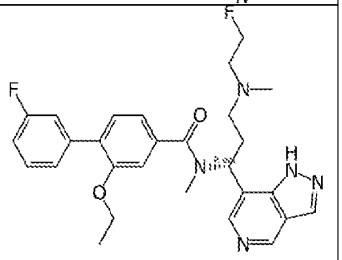
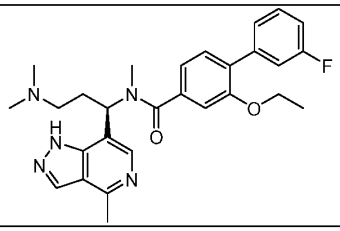
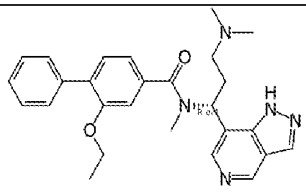
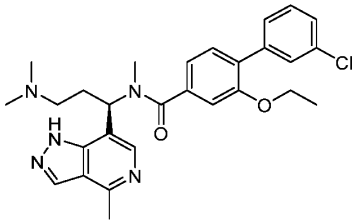
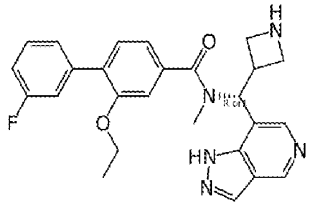
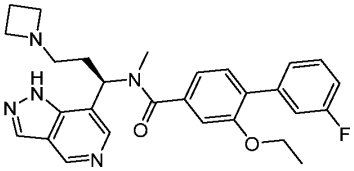
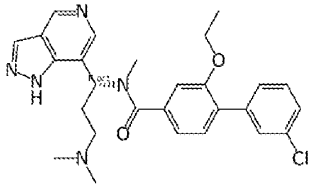
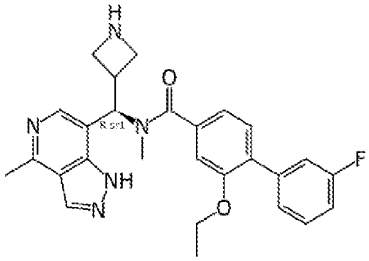
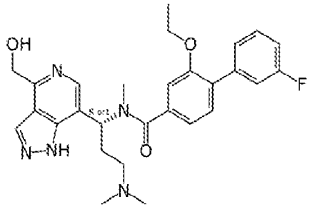
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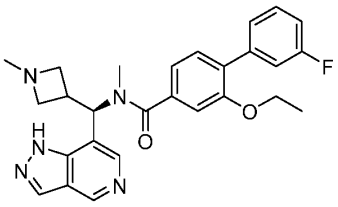
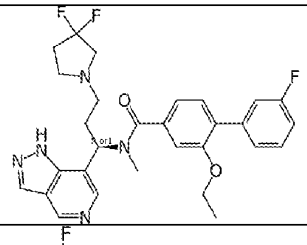
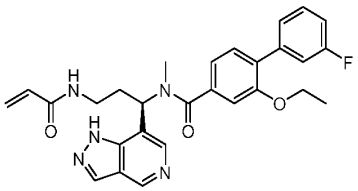
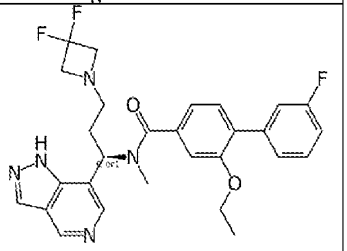
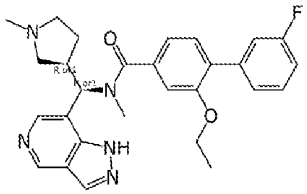
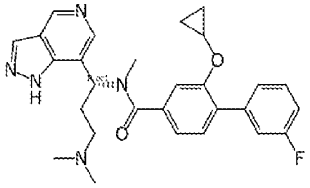
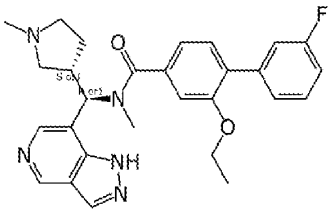
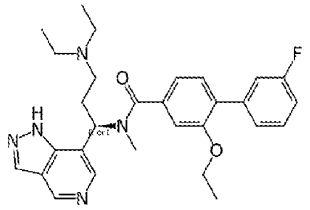
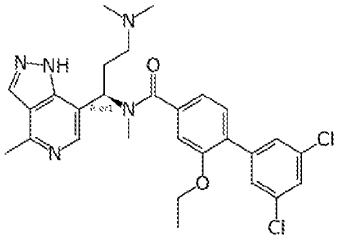
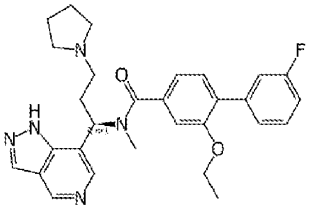
In another embodiment, the compound of Formula I is selected from the group consisting of a compound in Table 1A.

Table 1A

Ex. No.	Structure	Ex. No.	Structure
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064		085	
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066		087	

067		088	
068		089	
069		090	
070		091	
071		092	
072		093	

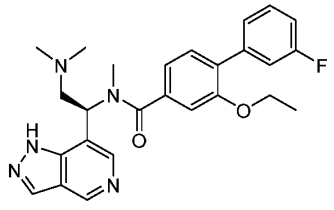
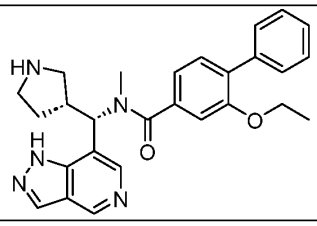
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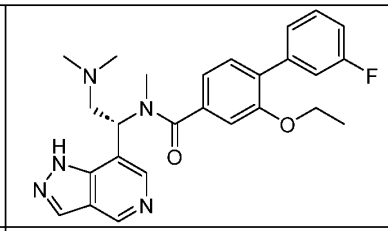
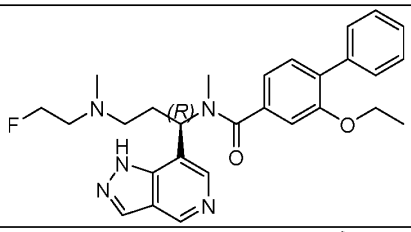
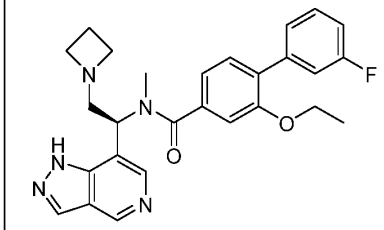
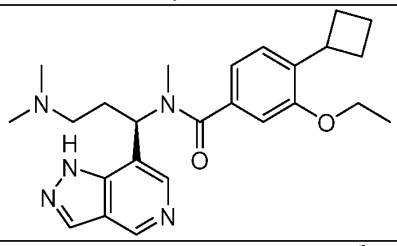
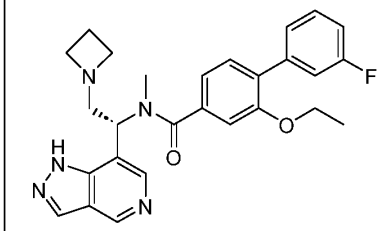
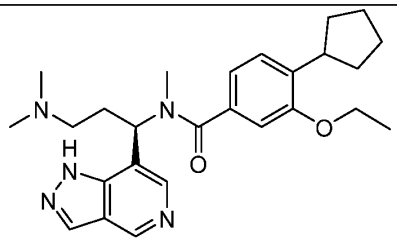
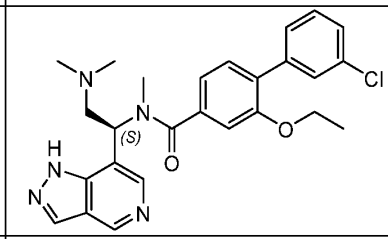
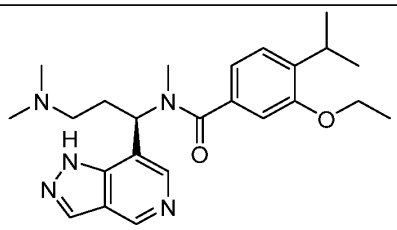
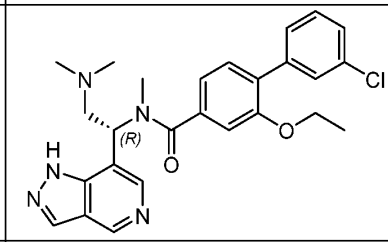
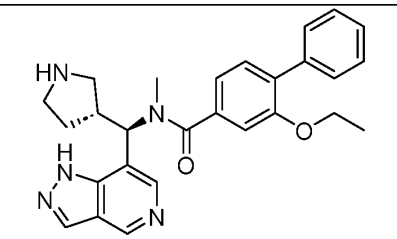
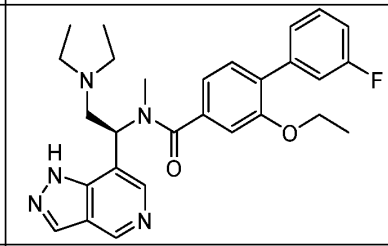
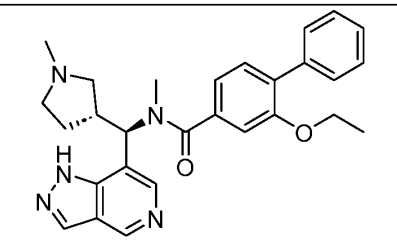
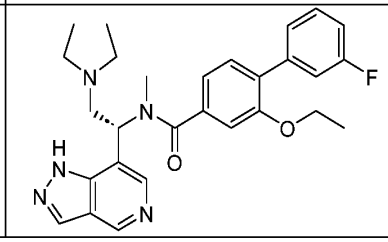
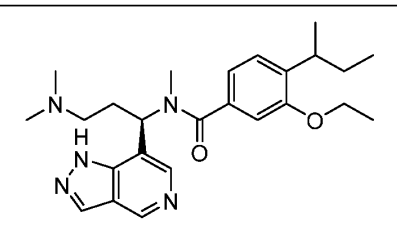
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083		104	

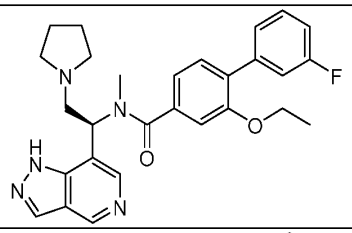
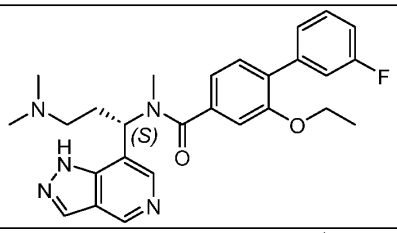
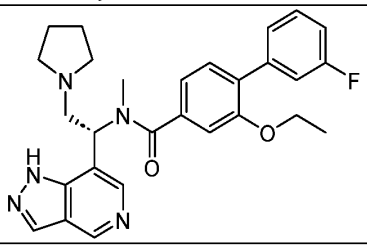
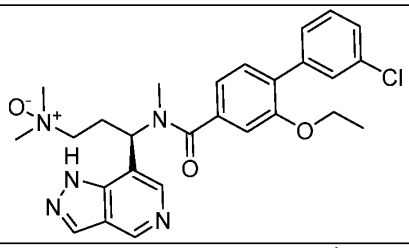
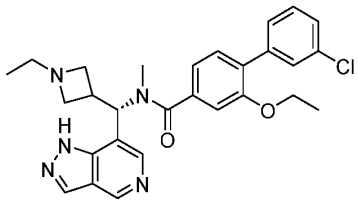
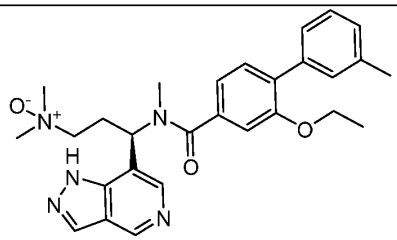
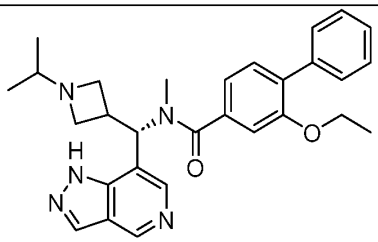
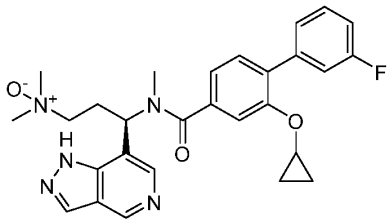
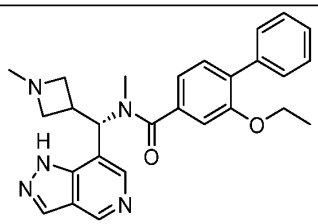
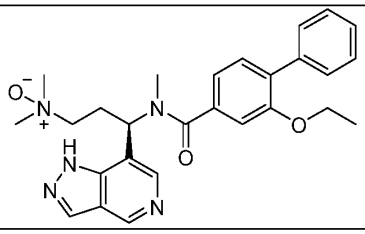
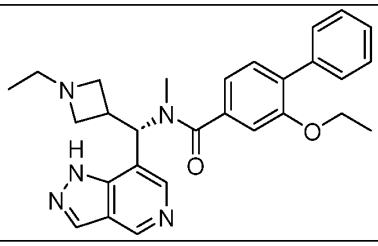
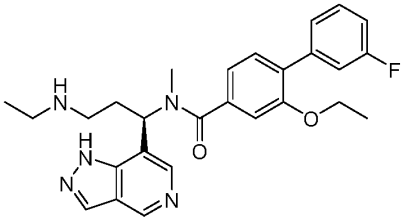
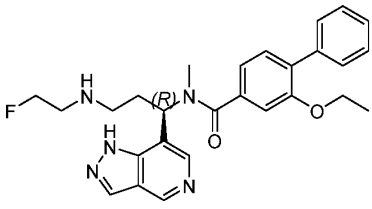
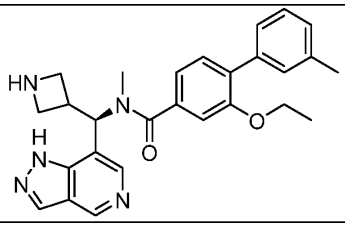
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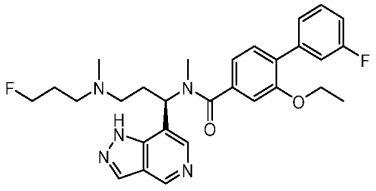
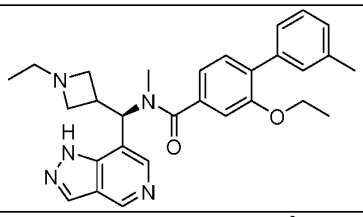
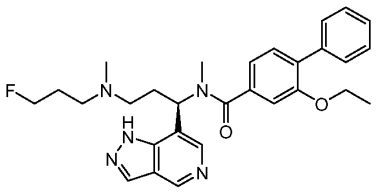
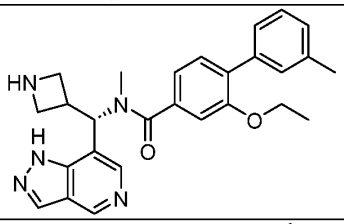
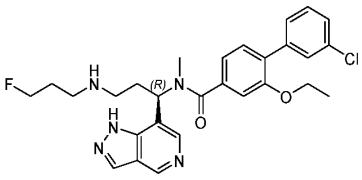
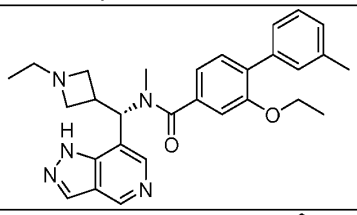
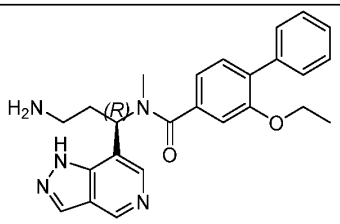
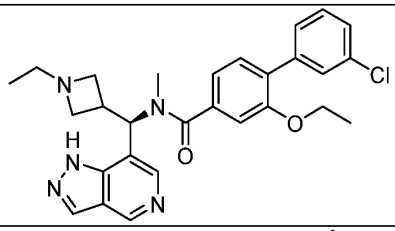
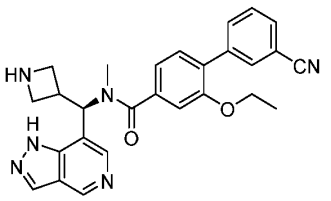
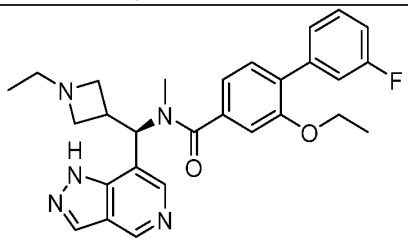
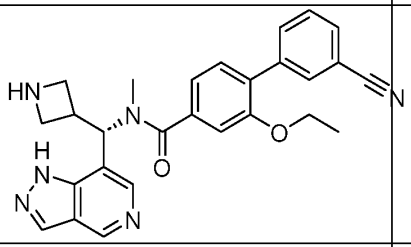
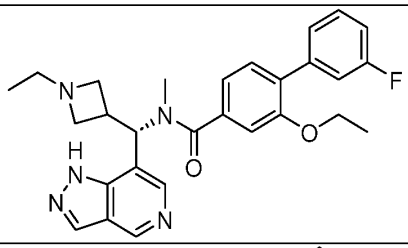
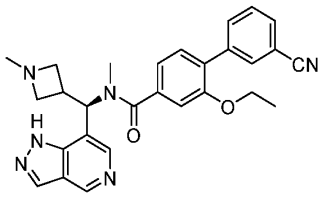
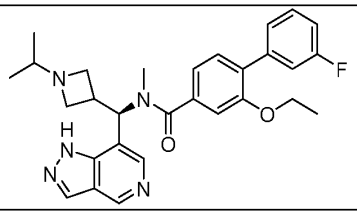
In another embodiment, the compound of Formula I is selected from the group consisting of a compound in Table 1B.

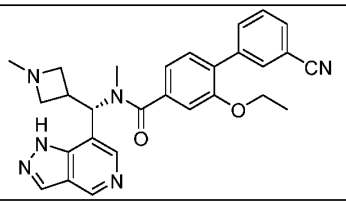
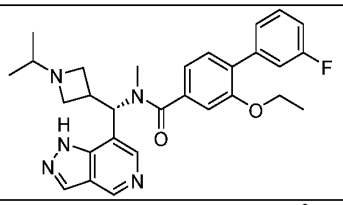
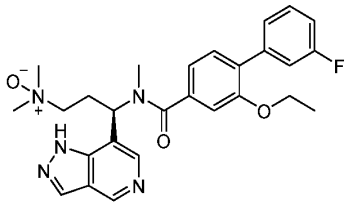
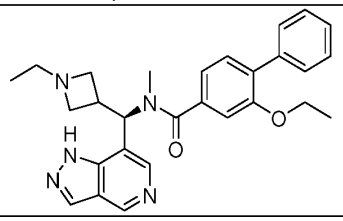
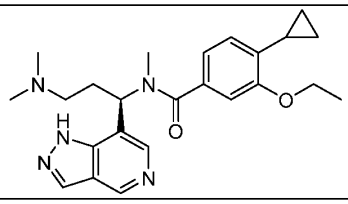
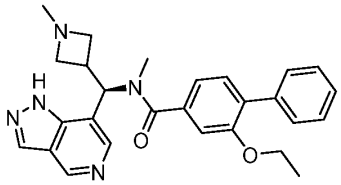
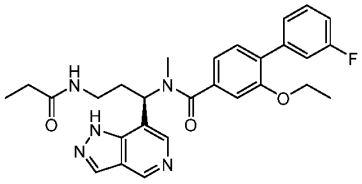
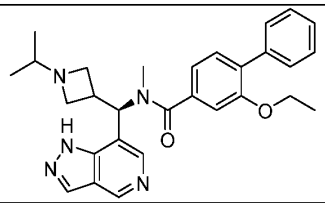
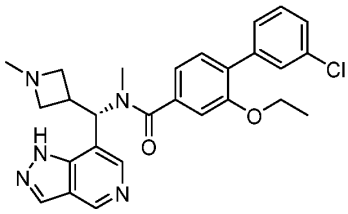
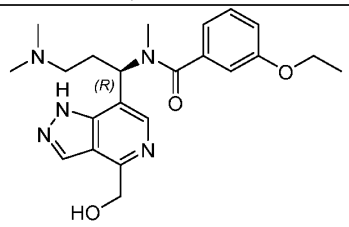
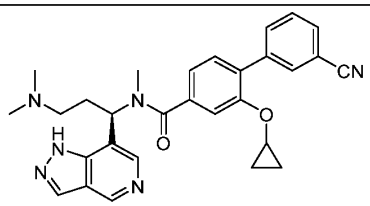
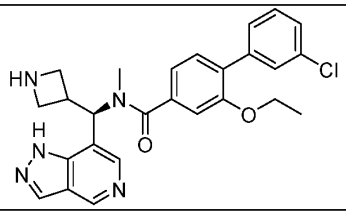
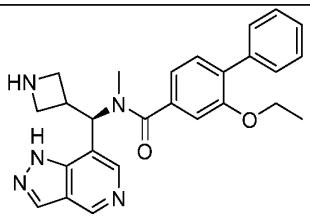
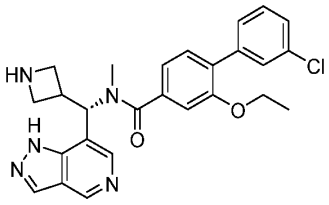
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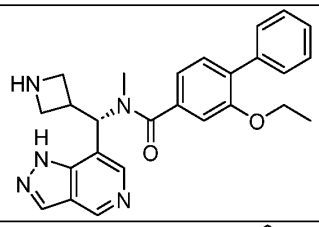
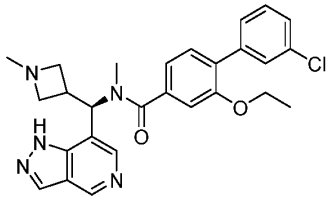
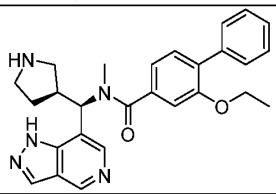
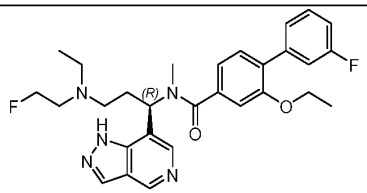
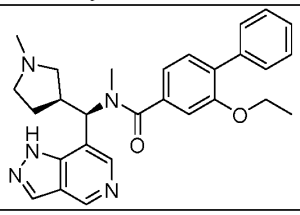
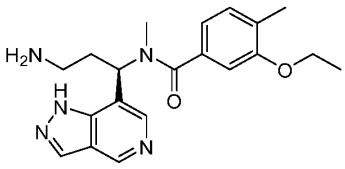
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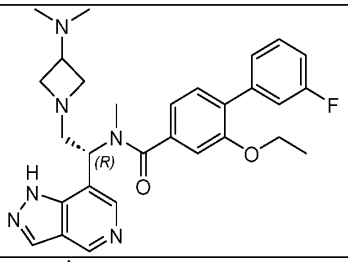
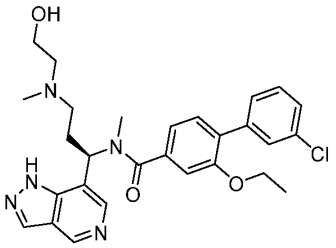
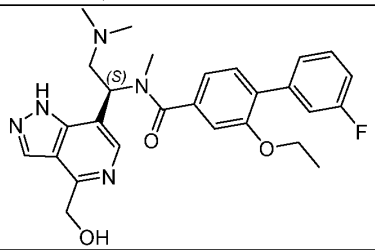
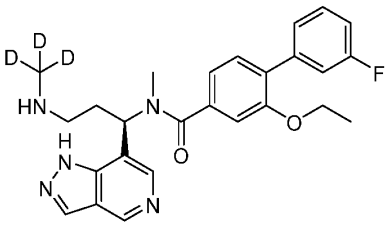
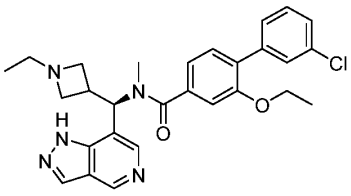
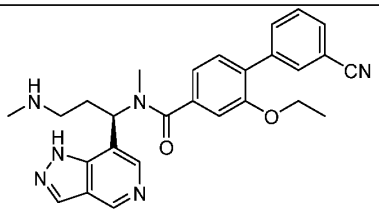
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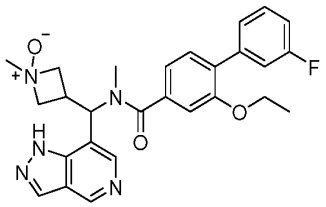
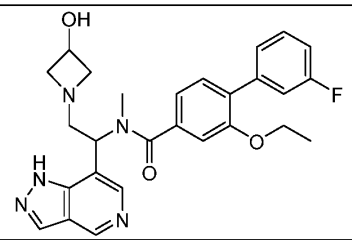
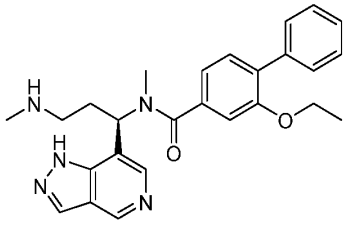
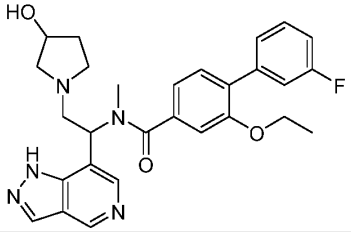
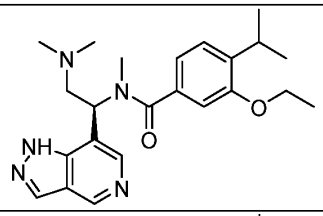
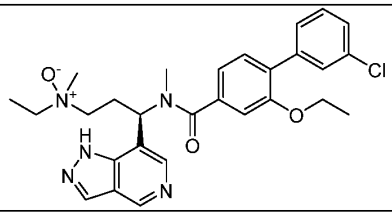
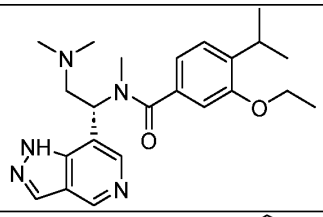
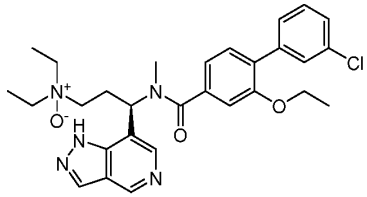
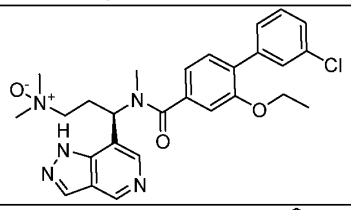
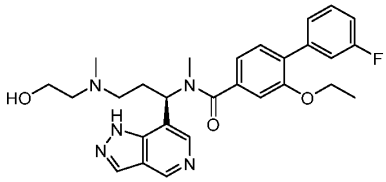
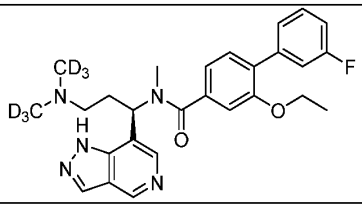
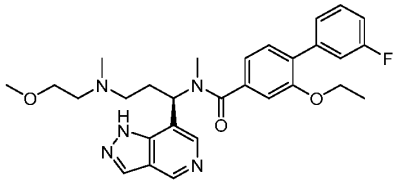
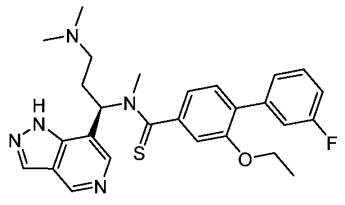
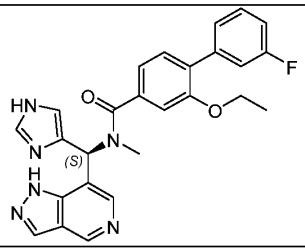
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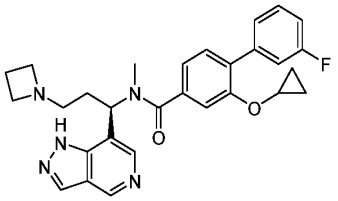
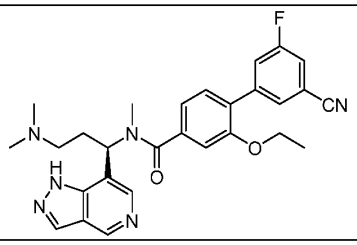
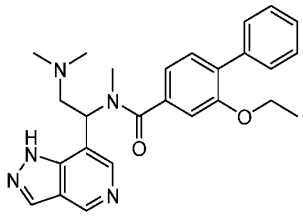
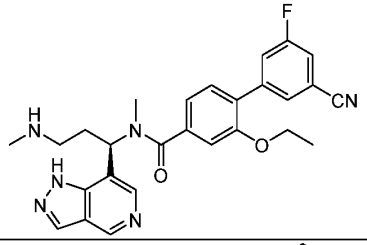
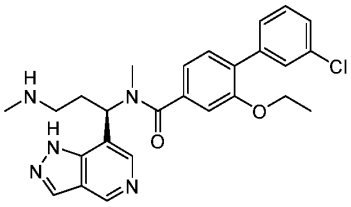
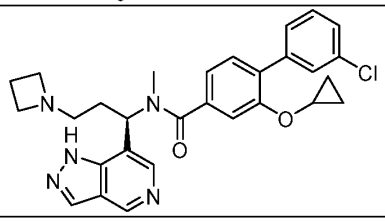
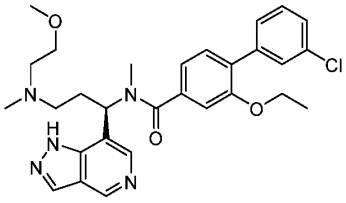
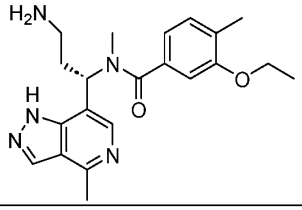
151		183	
152		184	
153		185	

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

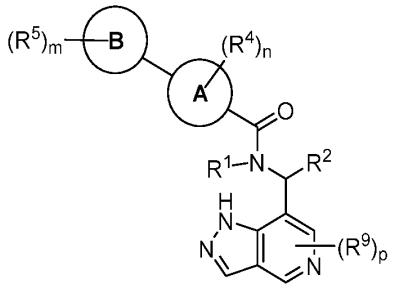
Table 1C

Ex. No.	Structure	Ex. No.	Structure
187		230	
188		231	
190		232	

192		246	
193		247	
208		254	
209		255	
210		262	
211		263	
224		267	

225		279	
226		280	
228		281	
229		299	

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



(II)

or a pharmaceutically acceptable salt thereof;

wherein

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} 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 and R^5 are absent;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{0-6} alkylene-C_{6-10} aryl, and 3-7 membered heterocycloalkyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{0-6} alkylene-C_{6-10} aryl are substituted with OH, halo, SO_2R^6, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, 3-6 membered heterocycloalkyl, and $N(R^a)_2$, wherein 3-6 membered heterocycloalkyl is optionally substituted by one or two halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, C_{1-6} alkyl-$NH(C_{1-3}$ alkyl), halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In an embodiment,

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, all of which are substituted with OH, halo, SO_2R^6, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, and $N(R^a)_2$,;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

each R^4 is independently selected from the group consisting of halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, CN, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $CONH_2$, and $CONH(C_{1-6}$ alkyl);

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In another embodiment,

Ring A is phenyl;

Ring B is phenyl;

R^1 is selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl, both of which are substituted with OH;

R^2 is H or C_{1-6} alkyl;

each R^4 is independently selected from the group consisting of halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $CONH_2$, and $CONH(C_{1-6}$ alkyl);

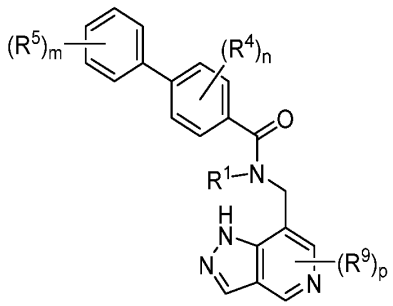
each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

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



(**IIa**)

or a pharmaceutically acceptable salt thereof.

In still another embodiment, Ring A is phenyl.

In an embodiment, Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl. In another embodiment, Ring B is phenyl. In yet another embodiment, Ring B and R^5 are absent.

In still another embodiment, R^1 is C_{1-6} alkyl substituted by OH. In another embodiment R^1 is C_{1-6} alkyl substituted by OH, halo, SO_2R^6, $OC(O)C_{1-3}$ alkyl, $C(O)C_{1-3}$ alkyl, NH_2, NHC_{1-3} alkyl, or $N(C_{1-3}$ alkyl$)_2$. In an embodiment, R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{0-6} alkylene-C_{6-10} aryl, and 3-7 membered heterocycloalkyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{0-6} alkylene-C_{6-10} aryl are substituted with OH, halo, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), or $N(C_{1-6}$ alkyl$)_2$.

In an embodiment, R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{0-6} alkylene-C_{6-10} aryl, and 3-7 membered heterocycloalkyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{0-6} alkylene-C_{6-10} aryl are substituted with OH, halo, SO_2R^6, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, and $N(R^a)_2$.

In an embodiment, each R^4 is independently selected from the group consisting of C_{1-6} alkoxy and OC_{3-6} cycloalkyl. In another embodiment, each R^4 is independently selected from the group consisting of C_{1-3} alkoxy and O-cyclopropyl. In yet another embodiment, R^4 is C_{1-3} alkoxy. In still another embodiment, R^4 is O-cyclopropyl. In an embodiment, R^4 is O-cyclobutyl.

In another embodiment, each R^5 is independently selected from the group consisting of halo, CN, $CONH_2$, and $CONH(C_{1-6}$ alkyl). In yet another embodiment, R^5 is halo. In still another embodiment, R^5 is is CN. In an embodiment, R^5 is $CONH_2$. In another embodiment, $CONH(C_{1-3}$ alkyl).

In yet another embodiment, each R^9 is independently selected from the group consisting of C_{1-6} alkyl-OH, halo, OH, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$. In still another embodiment, R^9 is C_{1-6} alkyl-OH. In an embodiment, R^9 is OH. In another embodiment, R^9 is

is halo. In yet another embodiment, R^9 is NH_2. In still another embodiment, R^9 is $NH(C_{1-3}$ alkyl). In an embodiment, R^9 is $N(C_{1-3}$ alkyl$)_2$.

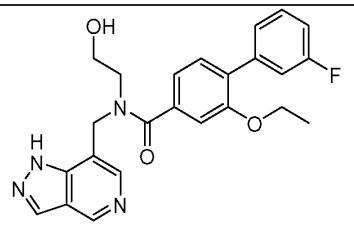
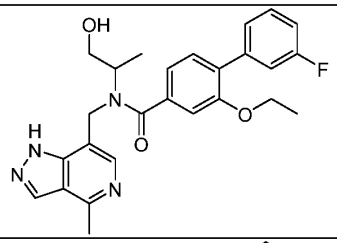
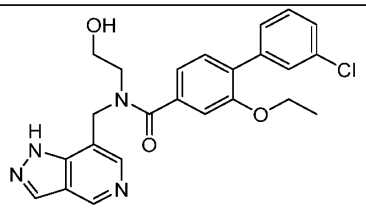
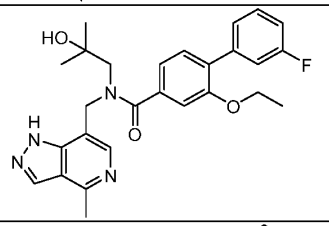
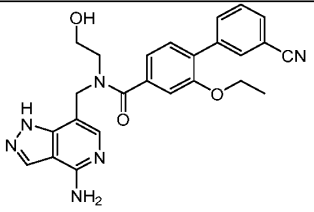
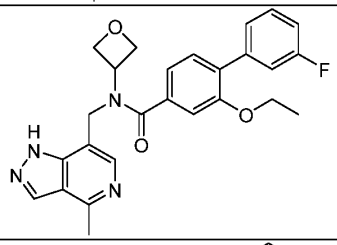
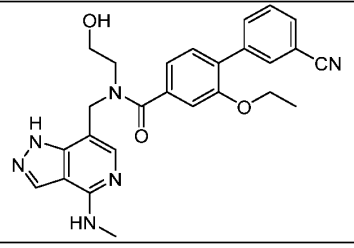
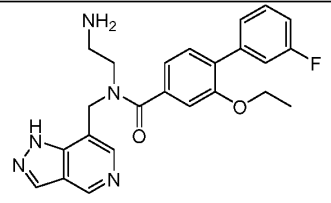
In another embodiment, m is 0, 1, or 2. In yet another embodiment, m is 0. In still another embodiment, m is 1. In an embodiment, m is 2.

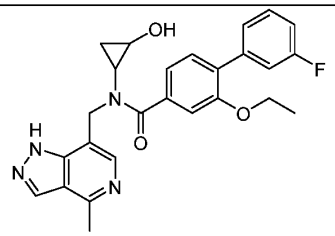
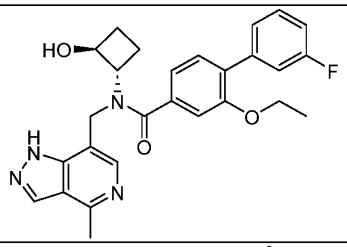
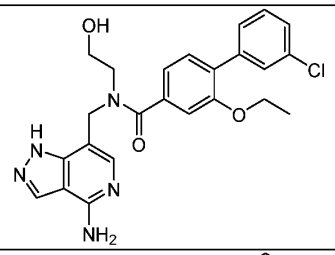
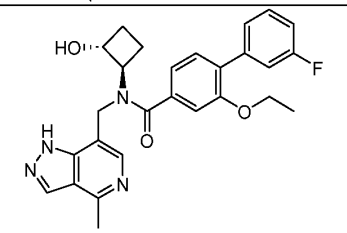
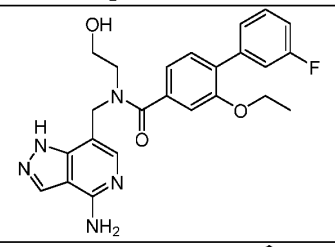
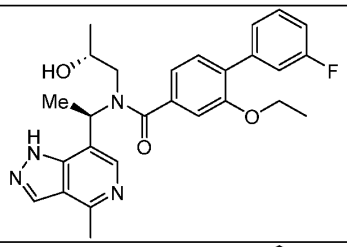
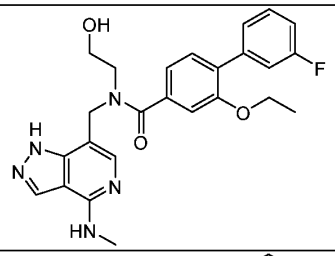
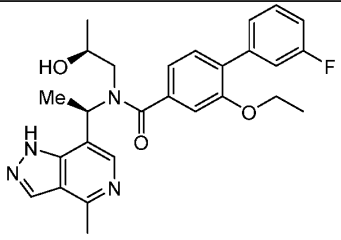
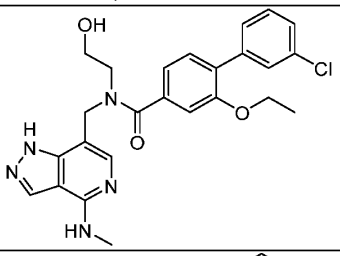
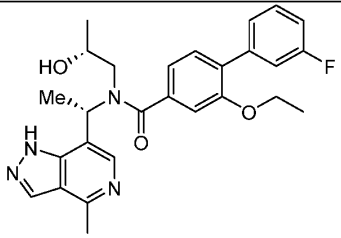
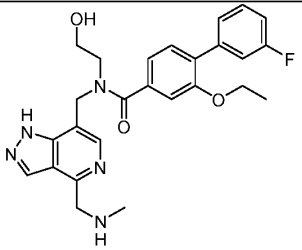
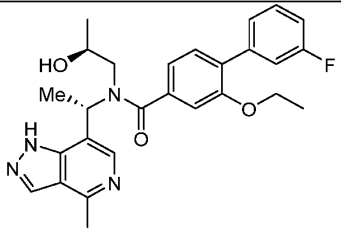
In another embodiment, n is 0, 1, or 2. In yet another embodiment, n is 0. In still another embodiment, n is 1. In an embodiment, n is 2.

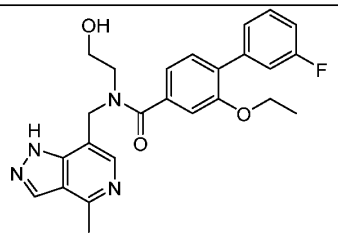
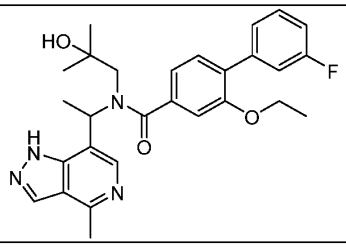
In another embodiment, p is 0, 1, or 2. In yet another embodiment, p is 0. In still another embodiment, p is 1. In an embodiment, p is 2.

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

Table 2

Ex. No.	Structure	Ex. No.	Structure
041		052	
042		053	
043		054	
044		055	

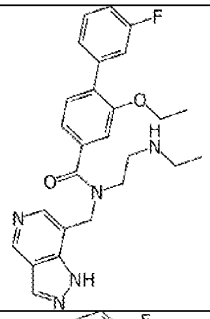
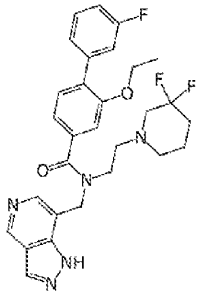
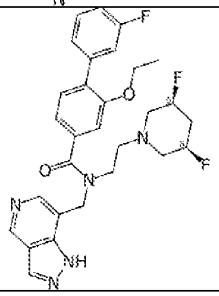
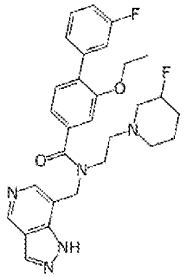
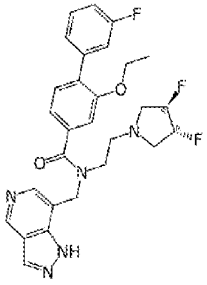
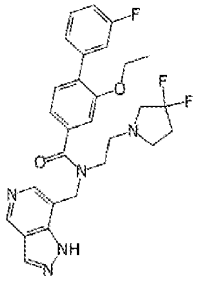
045		056	
046		057	
047		058	
048		059	
049		060	
050		061	

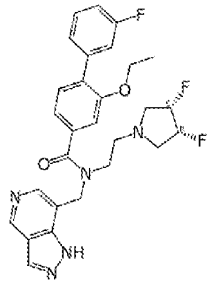
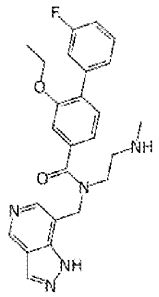
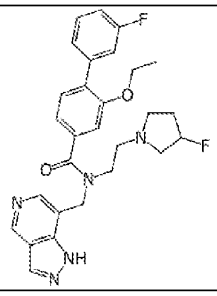
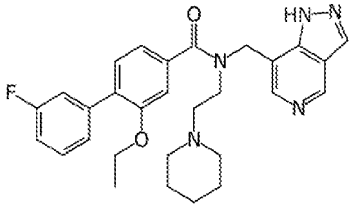
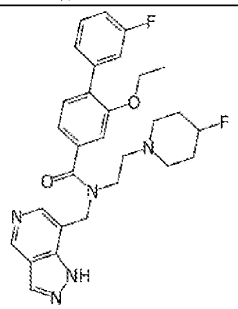
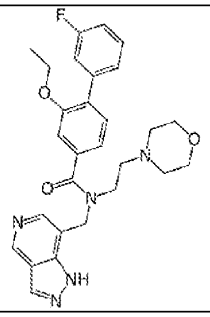
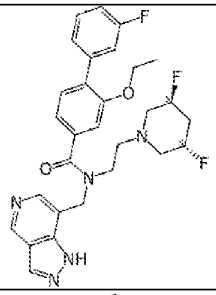
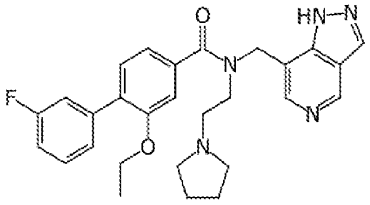
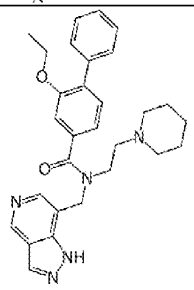
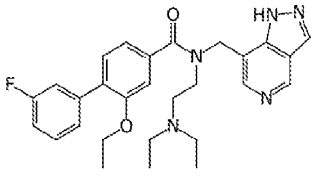
051		062	

or a pharmaceutically acceptable salt thereof.

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

Table 2A

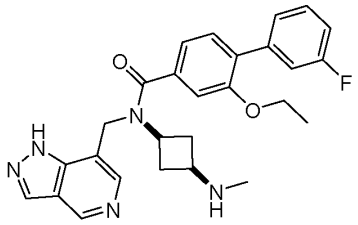
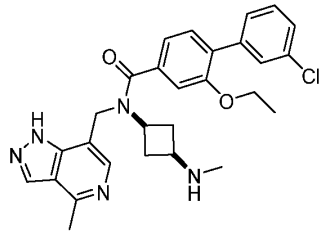
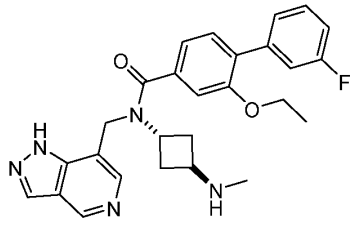
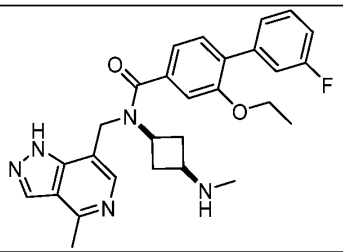
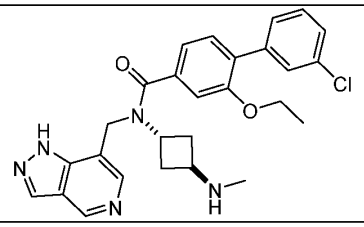
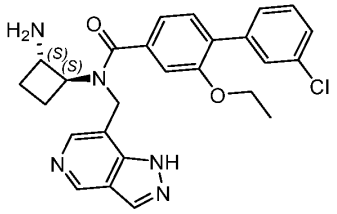
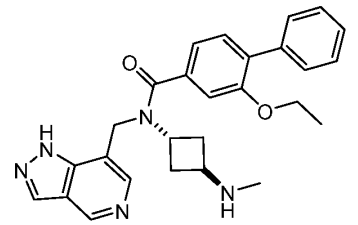
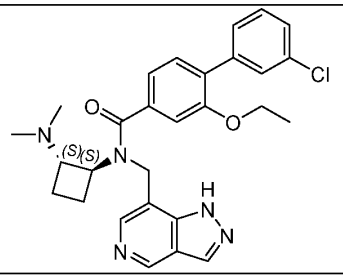
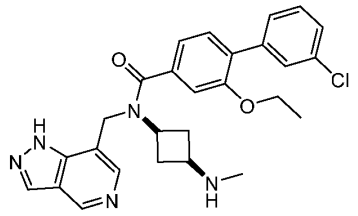
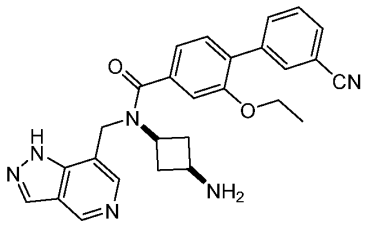
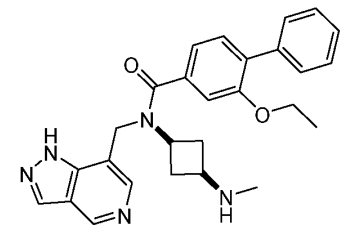
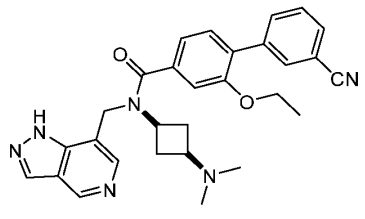
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106		114	
107		115	

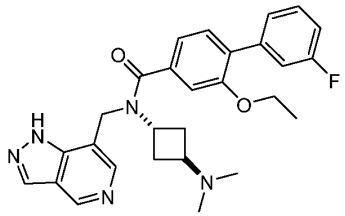
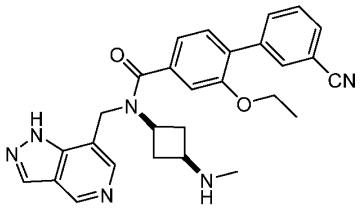
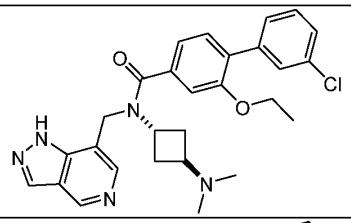
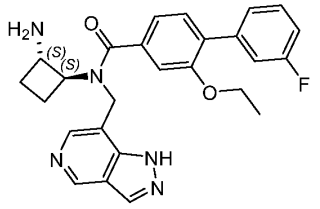
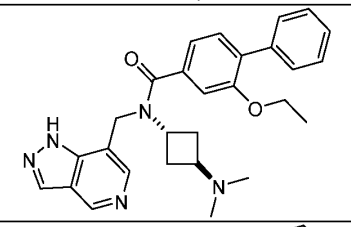
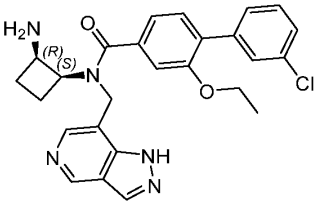
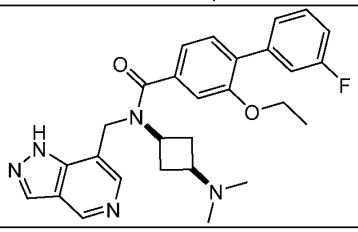
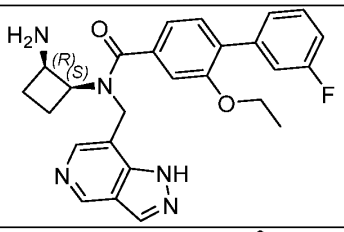
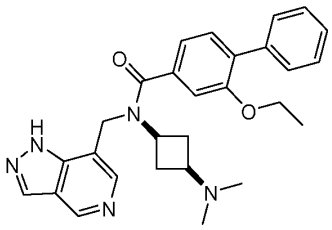
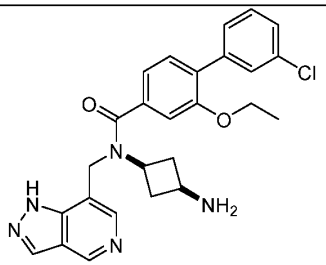
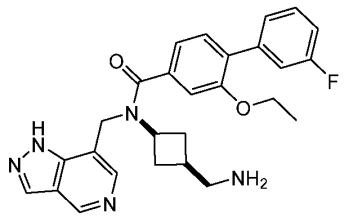
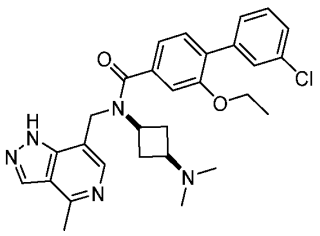
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109		117	
110		118	
111		119	
112		120	

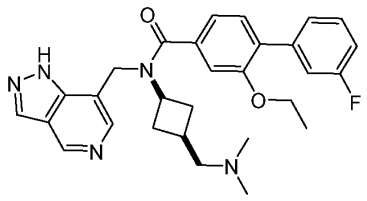
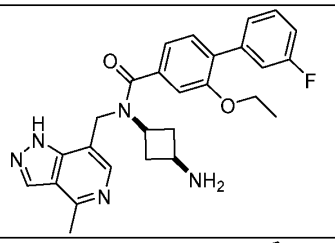
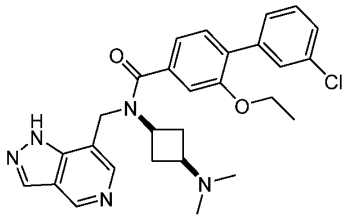
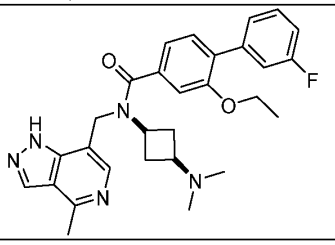
or a pharmaceutically acceptable salt thereof.

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

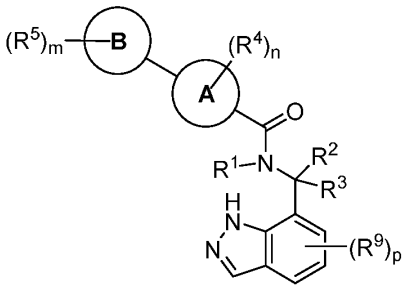
Table 2B

Ex No.	Structure	Ex No.	Structure
234		277	
235		278	
236		287	
237		288	
238		289	
239		290	

240		291	
242		294	
243		295	
244		300	
245		301	
248		302	

249		303	
253		304	

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



(III)

or a pharmaceutically acceptable salt thereof;

wherein

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6}

haloalkyl), NH(C_{1-6} haloalkyl), N(C_{1-6} alkyl)$_2$, N(C_{1-6} haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is independently optionally oxidized and independently optionally substituted by C_{1-6} alkyl; and the nitrogen atom of NH_2, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)(C_{1-6} haloalkyl), NH(C_{1-6} haloalkyl), N(C_{1-6} alkyl)$_2$, and N(C_{1-6} haloalkyl)$_2$ is optionally oxidized and one or more carbon atoms of the alkyl groups on the nitrogen atom are optionally substituted with 1-6 deuterium atoms or C_{1-6} alkoxy;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, NH(C_{1-6} alkyl), N(C_{1-6} 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, NH(C_{1-6} alkyl), and N(C_{1-6} alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, NH(C_{1-6} alkyl), and N(C_{1-6} alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In an embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl; and the nitrogen atom of NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized.

In an embodiment,

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is independently optionally oxidized and independently optionally substituted by C_{1-6} alkyl; and the nitrogen atom of $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized and the carbon atom of the alkyl groups on the nitrogen atom are optionally substituted with 1-6 deuterium atoms or C_{1-6} alkoxy;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In another embodiment,

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, halo, SO_2R^6, or C_{0-3} alkyene-5-10 membered heteroaryl;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

In another embodiment,

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is C_{1-6} alkyl;

R^2 is H;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH or C_{1-6} alkoxy;

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, both of which is substituted by OH;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $NHC(O)C_{1-6}$ alkyl, CN, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $CONH_2$, $CONH(C_{1-6}$ alkyl), CN, and C_{1-6} haloalkyl;

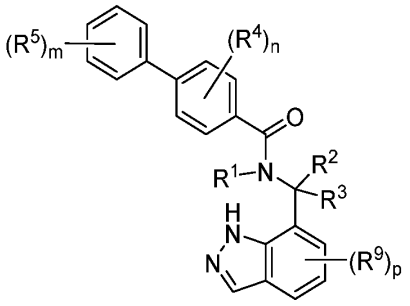
each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

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



(**IIIa**)

or a pharmaceutically acceptable salt thereof.

In still another embodiment, Ring A is phenyl.

In an embodiment, Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl. In another embodiment, Ring B is phenyl. In yet another embodiment, Ring B and R^5 are absent.

In still another embodiment, R^1 is C_{1-6} alkyl. In an embodiment, R^1 is methyl. In another embodiment, R^1 is ethyl. In an embodiment, R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl. In yet another embodiment, R^1 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo. In still another embodiment, R^1 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-3}$ alkyl, $C(O)C_{1-3}$ alkyl, NH_2, NHC_{1-3} alkyl, $N(C_{1-3}$ alkyl$)_2$, and halo. In another embodiment, R^1 is C_{3-6} cycloalkyl optionally substituted with NH_2, NHC_{1-3} alkyl, or $N(C_{1-3}$ alkyl$)_2$.

In another embodiment, R^2 is H.

In yet another embodiment, R^3 is C_{1-6} alkyl substituted by OH or C_{1-3} alkoxy. In still another embodiment, R^3 is C_{1-6} alkyl substituted by OH. In an embodiment, R^3 is C_{1-6} alkyl substituted by C_{1-3} alkoxy. In an embodiment, R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, halo, SO_2R^6, or C_{0-3} alkyene-5-10 membered heteroaryl. In another embodiment, R^3 is C_{1-6} alkyl substituted by 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH. In another embodiment, R^3 is C_{1-6} alkyl substituted by 3-6 membered heterocycloalkyl optionally substituted with one or two halo. In yet another embodiment, R^3 is 3-6 membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl. In an embodiment, R^3 is C_{1-6} alkyl substituted by $N(R^a)_2$. In another embodiment, each R^a is independently H or C_{1-6} alkyl.

In another embodiment, R^2 and R^3, together with the atom to which they are attached, form a ring selected from the group consisting of C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, both of which is substituted by OH. In yet another embodiment, R^2 and R^3, together with the atom to which they are attached, form C_{3-6} cycloalkyl substituted by OH. In still another embodiment, R^2 and R^3, together with the atom to which they are attached, form 3-6 membered heterocycloalkyl substituted by OH.

In an embodiment, each R^4 is independently selected from the group consisting of halo, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, and C_{1-6} haloalkyl. In another embodiment, each R^4 is independently selected from the group consisting of halo, C_{1-3} alkoxy, O-cyclopropyl, and C_{1-3} haloalkyl. In an embodiment, R^4 is C_{1-6} alkoxy.

In yet another embodiment, each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, CN, and $C(O)NH(C_{1-6}$ alkyl). In still another embodiment, each R^5 is independently selected from the group consisting of C_{1-3} alkyl, halo, CN, and $C(O)NH(C_{1-3}$ alkyl). In another embodiment, R^5 is selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, CN, and C_{1-6} haloalkyl.

In an embodiment, each R^9 is independently selected from the group consisting of C_{1-3} alkyl, C_{1-6} alkoxy, C_{1-3} alkyl-OH, and halo.

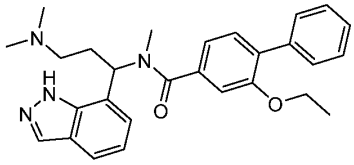
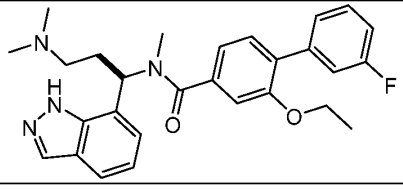
In another embodiment, m is 0, 1, or 2. In yet another embodiment, m is 0. In still another embodiment, m is 1. In an embodiment, m is 2.

In another embodiment, n is 1. In yet another embodiment, n is 0. In still another embodiment, n is 2.

In another embodiment, p is 0, 1, or 2. In yet another embodiment, p is 0. In still another embodiment, p is 1. In an embodiment, p is 2.

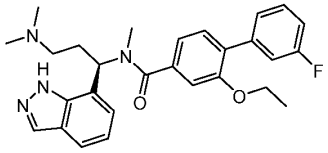
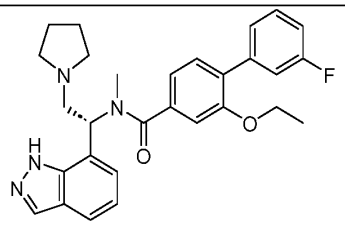
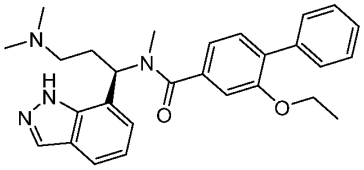
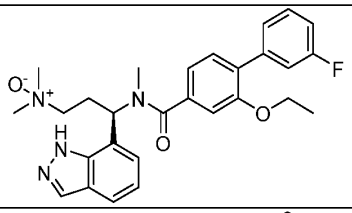
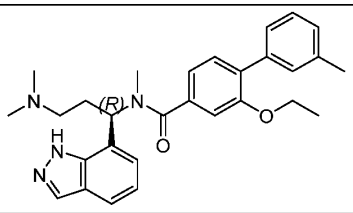
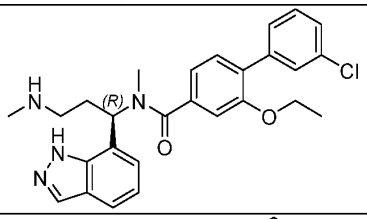
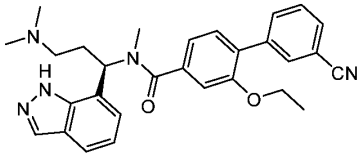
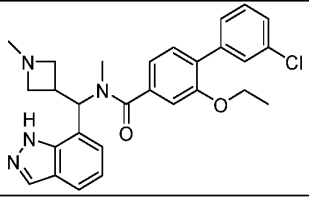
In another embodiment, the compound of Formula I is selected from the group consisting of a compound in Table 3.

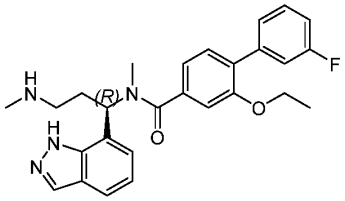
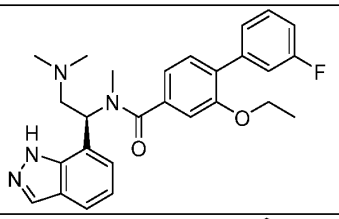
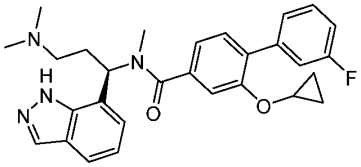
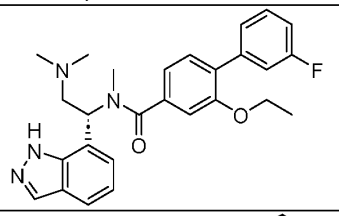
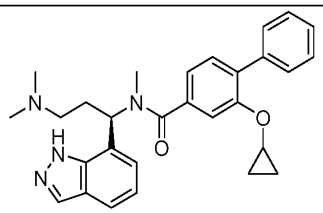
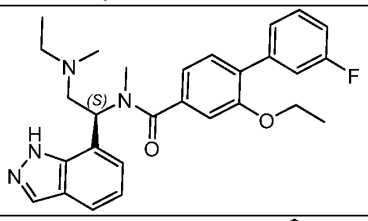
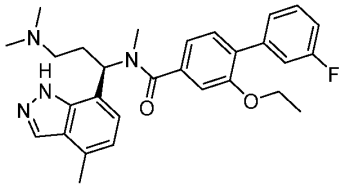
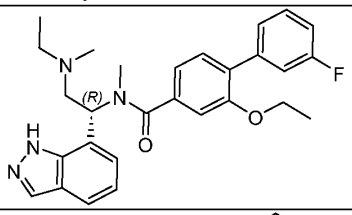
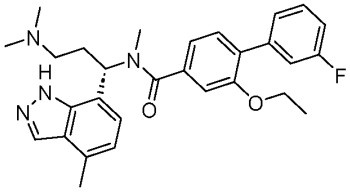
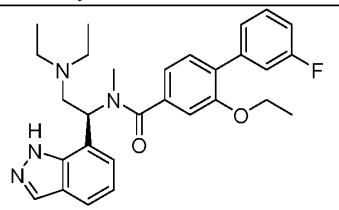
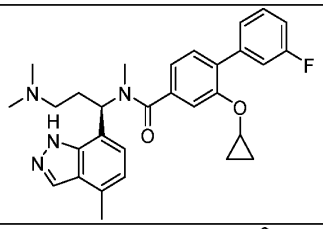
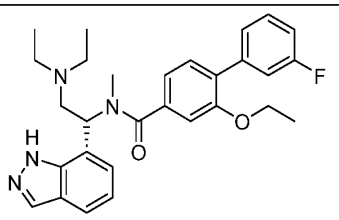
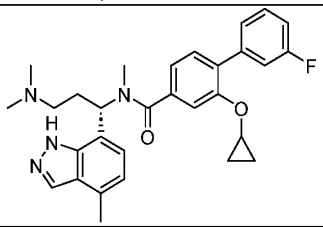
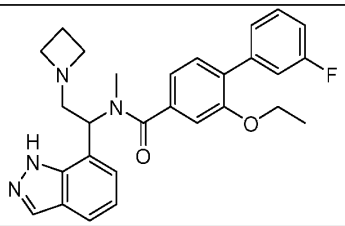
Table 3

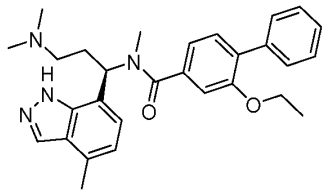
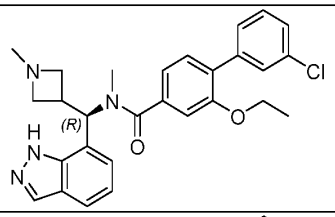
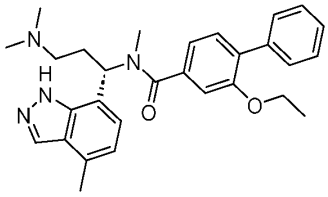
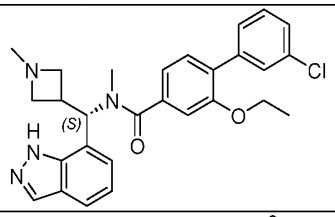
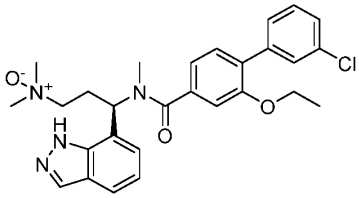
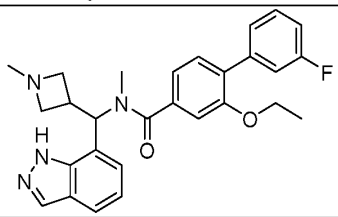
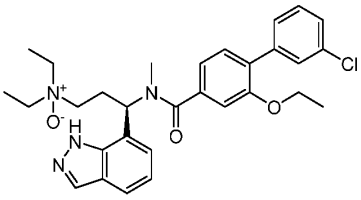
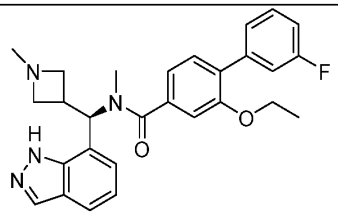
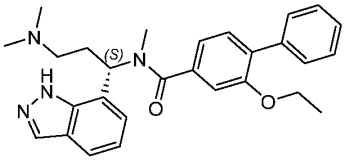
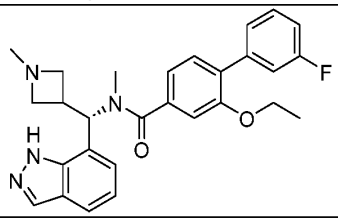
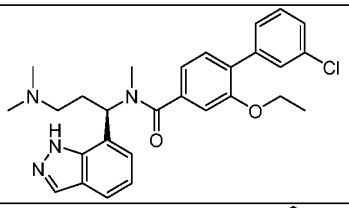
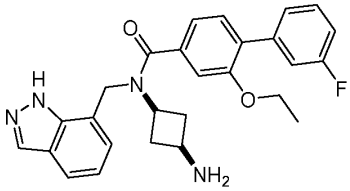
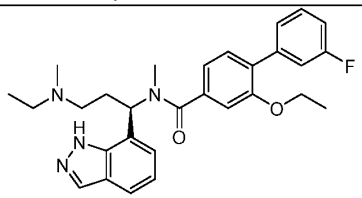
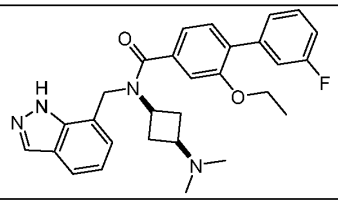
Ex. No.	Structure	Ex. No.	Structure
135		186	

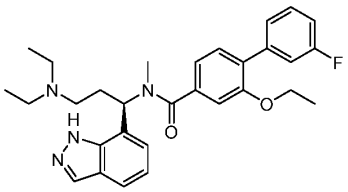
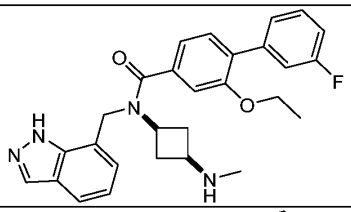
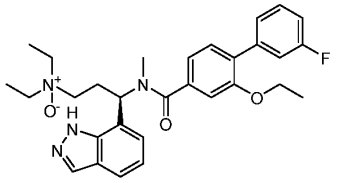
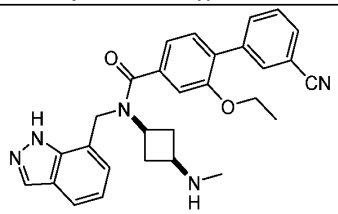
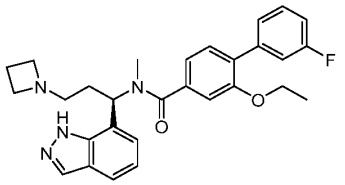
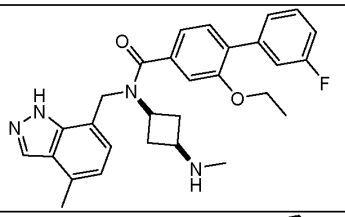
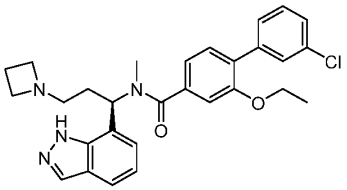
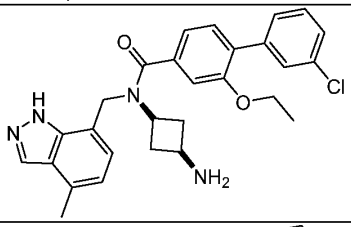
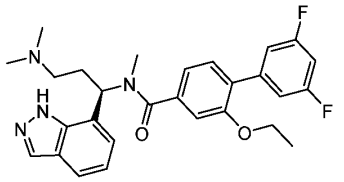
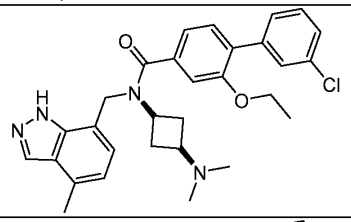
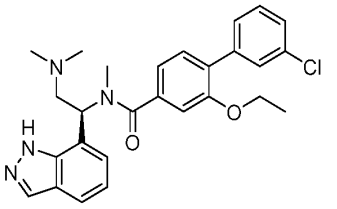
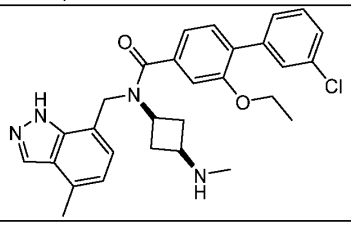
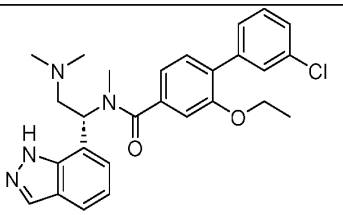
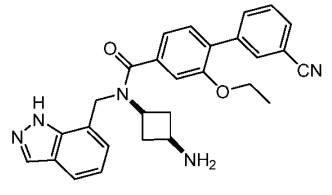
In another embodiment, the compound of Formula I is selected from the group consisting of a compound in Table 3A.

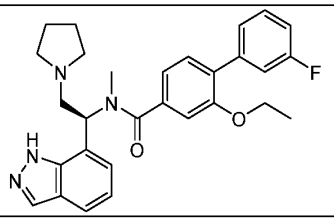
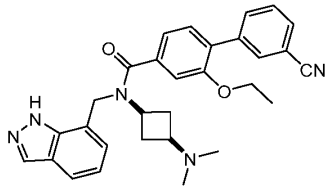
Table 3A

Ex. No.	Structure	Ex. No.	Structure
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194		227	
195		233	
196		241	

197		256	
198		257	
199		258	
200		259	
201		260	
202		261	
203		264	

204		282	
205		283	
206		296	
207		297	
212		298	
213		250	
214		251	

215		252	
216		265	
217		266	
218		284	
219		285	
220		286	
221		292	

222		293	

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).

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 used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

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 subject a therapeutically effective amount of a compound disclosed herein.

In another aspect, provided herein is a method of modulating GLP-1 in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In another aspect, provided herein is a method of treating a disease or disorder associated with GLP-1 activity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the disease or disorder associated with GLP-1 activity is obesity. In an embodiment, the obesity is dietary-induced obesity.

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

In an embodiment, the obesity-related comorbidity is selected from the group consisting of diabetes, heart failure, metabolic dysfunction-associated steatohepatitis (MASH), and a renal disease.

In another aspect, provided herein is a method of treating obesity-related disease, disorder, or comorbidity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein and a GLP-1 modulator.

In an embodiment, the GLP-1 modulator is selected from the group consisting of semaglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

In another aspect, provided herein is a method of treating inflammation in a subject in need thereof, comprising administering to the subject 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 subject 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 subject 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 subject 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, hypertrigliceridemia, 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 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 (αSMA), 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/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 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 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 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 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 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.

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.

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

In an embodiment, the ocular disease is an age-related eye disease (ARED). In an embodiment, the ocular disease is retinal and optic nerve injury. In another embodiment, the ocular disease is age-related macular degeneration (AMD). In an embodiment, the age-related macular degeneration is non-neovascular geographic atrophic (“dry”) AMD. In an embodiment, the age-related macular degeneration is neovascular exudative (“wet”) AMD.

In another embodiment, the ocular disease is diabetic retinopathy. In another embodiment, the ocular disease is diabetic macular edema (DME). In another embodiment, the ocular disease is geographic atrophy. In another embodiment, the geographic atrophy is in the back of the eye. In an embodiment, the ocular disease is retinal disease.

In an embodiment, the ocular disease is dry eye. In an embodiment, the ocular disease is severe dry eye. In an embodiment, the ocular disease is Sjogren's syndrome dry eye (SSDE). In an embodiment, the ocular disease is non-Sjogren's syndrome dry eye (NSSDE).

In an embodiment, the ocular disease is glaucoma. In an embodiment, the ocular disease is cataracts.

In an embodiment, the ocular disease is not an age-related eye disease. In an embodiment, the ocular disease is selected from a corneal ulcer, a non-healing ocular burn, uveitis, a persistent corneal defect, inflammatory keratitis, retinitis pigmentosa, and retinopathy of prematurity.

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

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). In an embodiment, the inflammatory disorder is diabetes-associated atherosclerosis. In another embodiment, the inflammatory disorder is kidney injury in diabetic nephropathy. In an embodiment, the inflammatory disorder is low-grade inflammation. In an embodiment, the inflammatory disorder is graft versus host disease (GvHD).

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

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.

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 term 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 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 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 in a subject in need thereof, comprising administering to the subject 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, 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 an embodiment, the age-related disorder is an ischemic stroke concomitant with diabetes.

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

In an embodiment, the obesity-related comorbidity is selected from the group consisting of diabetes, heart failure, metabolic dysfunction-associated steatohepatitis (MASH), and a renal disease.

In another aspect, provided herein is a method of treating a metabolic condition in a subject in need thereof, comprising administering to the subject 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 an embodiment, the metabolic condition is insulin resistance. In an embodiment, the metabolic condition is an ischemic stroke concomitant with diabetes.

In yet another aspect, provided herein is a method of treating a neurodegenerative disease in a subject in need thereof, comprising administering to the subject 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.

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 subject 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.

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.

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

In an embodiment, the neurosensory disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), traumatic brain injury, Parkinson's disease, and Alzheimer's disease. In another embodiment, the neurosensory disease is ALS. In yet another embodiment, the neurosensory disease is traumatic brain injury. In still another embodiment, the neurosensory disease is Parkinson's disease. In an embodiment, the neurosensory disease is Alzheimer's disease.

In yet another aspect, provided herein is a method of treating, preventing, or mitigating an adverse effect related to the administration of a T cell engaging agent in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the adverse effect is cytokine release syndrome (CRS). In another embodiment, the adverse effect is fever, hypotension and/or hypoxia.

In yet another embodiment, the adverse effect is an elevated serum level of one of more cytokine(s), particularly one or more cytokine(s) selected from the group consisting of IL-1b, IL-6 and IL-8. In another embodiment, the adverse effect is an elevated serum level of one of more cytokine(s), particularly one or more cytokine(s) selected from the group consisting of IL-1b, IL-6, IL-18, and TNF-α. In another embodiment, the adverse effect is an elevated serum level of one of more cytokine(s), particularly one or more cytokine(s) selected from the group consisting of IL-1b, IL-6, and IL-18.

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.

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.

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.

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 a CD20-expressing cancer. In another embodiment, the cancer is a B-cell cancer.

In yet another embodiment, the cancer is selected from the group consisting of Non-Hodgkin lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), high grade B cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL) and marginal zone lymphoma (MZL).

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.

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

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.

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 lymphotrophic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic 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 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 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, 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 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, 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.

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 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).

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

In an embodiment, the obesity is dietary-induced obesity.

In another aspect, provided herein is a method of treating obesity-mediated metabolic disorders in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In an embodiment, the obesity-mediated metabolic disorder is non-alcoholic fatty liver disease (NAFLD). In another embodiment, the obesity-mediated metabolic disorder is insulin resistance. In yet another embodiment, the obesity-mediated metabolic disorder is obesity-induced inflammation.

In yet another aspect, provided herein is a method of improving lipid metabolism in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In still another aspect, provided herein is a method of reducing hypothalamic gliosis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

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

In another aspect, provided herein is a method of reducing low-density lipoprotein (LDL) cholesterol in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In an embodiment of the methods, the method treats obesity in the subject, e.g., reduces obesity in the subject.

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 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 wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In an embodiment, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is administered orally.

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

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 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 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.

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 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 a 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 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.

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 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 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.

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 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 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 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 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. 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.

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; 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 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; 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; 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 oil; glycols, such a 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 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.

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 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 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 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 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 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.

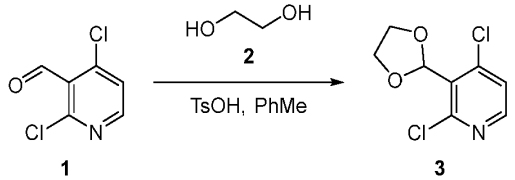
Abbreviations

ACN	acetonitrile
AcOH	acetic acid
DCM	dichloromethane
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EA	ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
EtOH	ethanol
FA	Formic acid
HPLC	high-performance liquid chromatography
LAH	lithium aluminum hydride
LCMS	liquid chromatography-mass spectrometry
m-CPBA	meta-chloroperoxybenzoic acid
MeOH	methanol
NMR	nuclear magnetic resonance
PE	petroleum ether
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
SFC	Supercritical fluid chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	para-Toluenesulfonic acid

Example 1: Synthetic Procedures

Synthesis of Common Intermediates

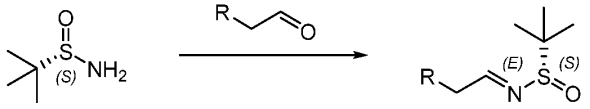
Scheme 1: Synthesis of intermediate **3**



To a solution of starting material **1** (11 g, 62.50 mmol, 1 *eq*) and TsOH (1.08 g, 6.25 mmol, 0.1 *eq*) in toluene (150 mL) was added ethylene glycol (intermediate **2**; 5.82 g, 93.75 mmol, 5.23 mL, 1.5 *eq*). The reaction mixture was stirred at 125°C for 12 h under N_2. TLC showed desired product was formed. TLC (PE:EA =10:1) was not prove that the starting material was reaction complete. The reaction mixture was poured into H_2O (300 mL) and

extracted with EA (3x150 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to give the crude product. The crude product was purified by column silica (PE:EA=1:0–10:1) and concentrated under reduced pressure to give the product (R_f = 0.6; PE:EA =10:1). Intermediate **3** (12.3 g, 50.31 mmol, 80.49% yield, 90% purity) was obtained as light-yellow oil. **NMR:** ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 4.05 - 4.13 (m, 2 H) 4.29 - 4.37 (m, 2 H) 6.43 (s, 1 H) 7.31 (d, *J*=5.26 Hz, 1 H) 8.27 (d, *J*=5.26 Hz, 1 H).

Scheme 2: Synthesis of intermediate (S)-*N*-*tert*-butanesulfinyl imines

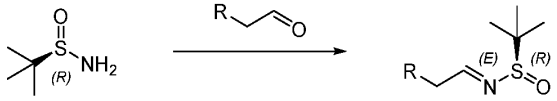


4

6 R = OTBS
7 R = CH_2OTBS

To a solution of starting material **4** (9 g, 74.26 mmol, 1 *eq*) in DCM (800 mL) was added $MgSO_4$ (178.77 g, 1.49 mol, 20 *eq*) and the corrseponding aldehyde (25.89 g, 148.51 mmol, 28.29 mL, 2 *eq*), then the mixture was stirred at 25 °C for 12 h. LCMS showed the starting material was consumed completely and desired mass was detected. The crude mixture was filtered, and the filtrate was concentrated under reduced pressure.

Scheme 3: Synthesis of intermediate (R)-*N*-*tert*-butanesulfinyl imines

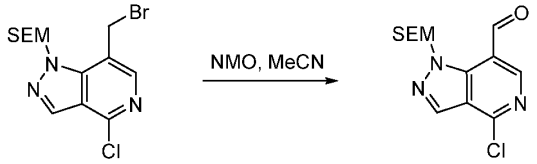


5

8 R = OTBS
9 R = CH_2OTBS

To a solution of starting material **5** (9 g, 74.26 mmol, 1 *eq*) in DCM (800 mL) was added $MgSO_4$ (178.77 g, 1.49 mol, 20 *eq*) and the corresponding aldehyde (25.89 g, 148.51 mmol, 28.29 mL, 2 *eq*), then the mixture was stirred at 25 °C for 12 h. LCMS showed the starting material was consumed completely and desired mass was detected. The crude mixture was filtered, and the filtrate was concentrated under reduced pressure.

Scheme 4: Synthesis of intermediate 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine-7-carbaldehyde (**27**):

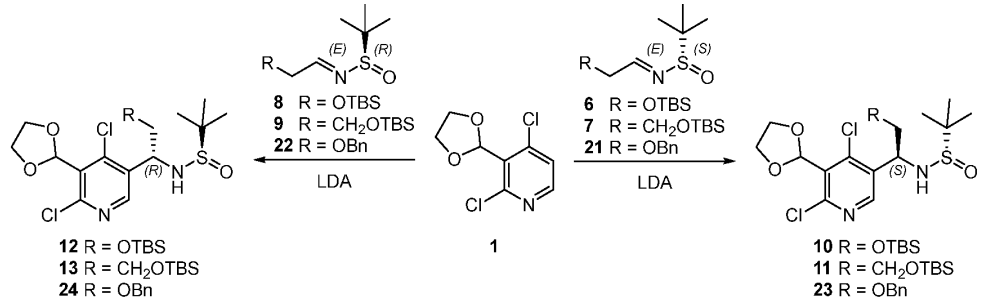


int-26 **int-27**

To a solution of intermediate **26** (7-(bromomethyl)-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine, 10 g, 26.54 mmol, 1 *eq*) in MeCN (100 mL) was added NMO (9.33 g, 79.63 mmol, 8.40 mL, 3 eq) at 0 °C, the mixture was

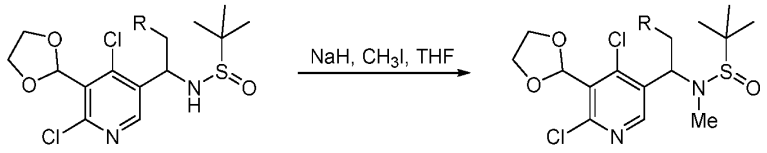
stirred at 0 °C for 2 h. TLC (PE: EtOAc =10:1; UV) showed starting material was consumed up and new spots were formed. The reaction mixture was concentrated to give a crude product. The crude product was purified by silica gel chromatography (8% EtOAc in PE, R_f = 0.30) to give a product. Intermediate **27** (5.3 g, 15.30 mmol, 57.63% yield, 90% purity) was obtained as yellow oil. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 10.25 (s, 1H), 8.70 (s, 1H), 8.31 (s, 1H), 6.20 (s, 2H), 4.12 (q, J = 7.2 Hz, 1H), 3.57 - 3.50 (m, 2H), 2.05 (s, 1H), 1.26 (t, J = 7.2 Hz, 1H), 0.91 - 0.80 (m, 2H), -0.01 - -0.16 (m, 9H).

General Procedure 1 (GP1): Michael addition to imine



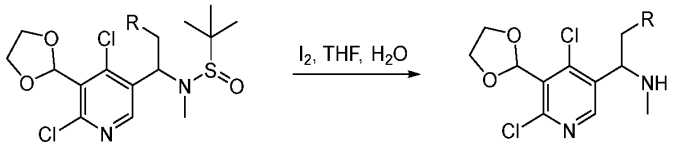
To a solution of starting material **1** (1 g, 4.54 mmol, 1 *eq*) in THF (20 mL) was added LDA (2 M, 1.5 *eq*) at -70 °C under N_2, then stirred at -70°C for 0.5 h. Then the corresponding sulfinamide (1.5 *eq*) in THF (10 mL) was added dropwise and the reaction was stirred for 1 h under N_2. The reaction progress was monitored by LCMS. Upon completion, the reaction mixture was poured into a sat. aq. NH_4Cl solution (150 mL), the mixture was extracted with EtOAc (3x100 mL), the combined organic phases were washed with brine (100mL), dried over anhydrous Na_2SO_4, and concentrated to give a crude product. The crude material was purified by flash silica gel chromatography.

General Procedure 2 (GP2): Sulfinamide *N*-methylation



To a solution of compound **5** (730 mg, 1.47 mmol, 1 *eq*) in THF (10 mL) was added NaH (88.02 mg, 2.20 mmol, 60% purity, 1.5 *eq*) in ten batches at 0 °C under N_2, and stirred for 30 min at 0 °C. Then the reaction was added CH_3I (416.50 mg, 2.93 mmol, 182.68 µL, 2 *eq*) at 0°C and stirred for 1 h at 25°C under N_2. LCMS showed starting material was remained and desire product was detected. The mixture was poured into sat. aq. NH_4Cl solution (50 mL) at 0 °C and the mixture was extracted with EtOAc (3x50 mL), then washed with brine (2x50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a residue. The residue was purified by column chromatography on silica and concentrated under reduced pressure.

General Procedure 3 (GP3): Cleavage of Ellman auxiliary



To a solution of the corresponding sulfinamide (6.1 g, 11.92 mmol, 1 *eq*) in THF (0.2 M) and H_2O (0.2 M) was added I_2 (0.2 *eq*). The reaction mixture was stirred at 50 °C for 12 h. LCMS showed the starting material was consumed completely. The mixture was poured in sat. aq. Na_2SO_3 and extracted with EtOAc (3x100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by silica column chromatography.

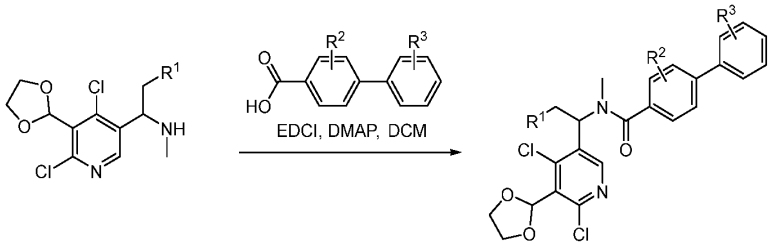
General Procedure 4 (GP4): Silyl protection of hydroxyl group



R = OH, CH_2OH R = OTBS, CH_2OTBS

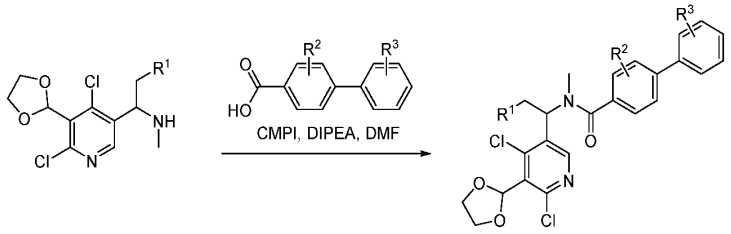
To a solution of the starting alcohol (1 *eq*) in DCM (0.1 M) was added imidazole (3 *eq*) and *tert*-Butyldimethylsilyl chloride (2 *eq*), the mixture was stirred at 20 °C for 12 h. The reaction was monitored by LCMS. Upon completion, the mixture was filtered, and the filtrate was concentrated to give a crude product. The crude product was purified by silica gel chromatography to give desire product.

General Procedure 5 (GP5): Secondary amine coupling



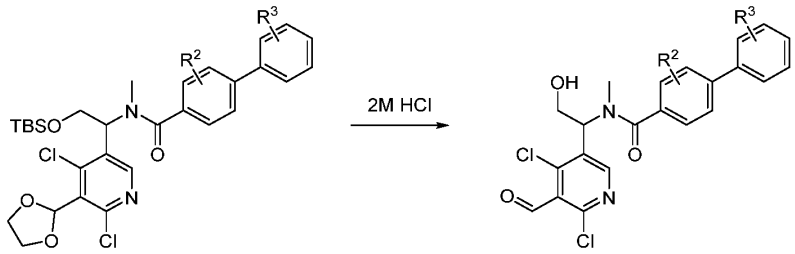
To a solution of the secondary amine (1 *eq*), carboxylic acid (1.1 *eq*), and EDCI (1.5 *eq*) in DCM (0.1 M) was added DMAP (0.1 *eq*), then stirred at 20 °C for 2 h. The reaction was monitored by LCMS. After completion, the reaction was concentrated under reduced to give a crude product. The crude product was purified by preparative-TLC.

Optionally, the following procedure can be utilized:



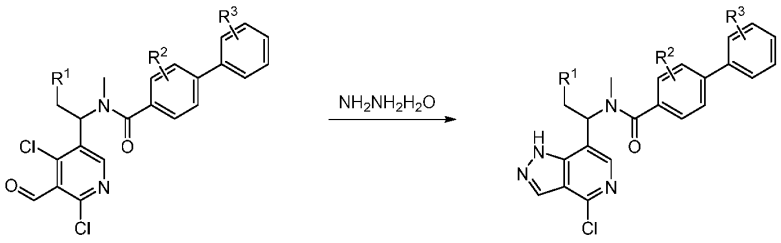
To a solution of the secondary amine (1.0 *eq*) and the carboxylic acid (1.0 *eq*) in DMF (0.25 M) was added CMPI (1.5 *eq*) (or other coupling agent such as HCTU, HATU or the like) and DIPEA (3 *eq*). The mixture was stirred at 50 °C for 12 h. After desired completion as tracked by LCMS. The mixture was poured into H_2O and extracted with EtOAc. The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude residue.

General Procedure 6 (GP6): Global deprotection 1



To a solution of silyl protected alcohol (100 mg, 153.93 µmol, 1 *eq*) in THF (0.03 M; or other applicable solvent) was added HCl (1–150 *eq*). Additionally, other acids can be used in conjuction with HCl, on their own. Examples of other acids include, but are not limited to, TsOH, MsOH, H_2SO_4, HNO_3, or similar (0.01–20 *eq*). The reaction mixture was stirred in the range of 0–90 °C for 1–24 h. The reaction mixture was adjusted to pH = 7 with sat. aq. Na_2CO_3 and extracted with EtOAc (3x50 mL). The combined organic layers were dried over Na_2SO_4, then concentrated under reduced pressure to give a crude residue.

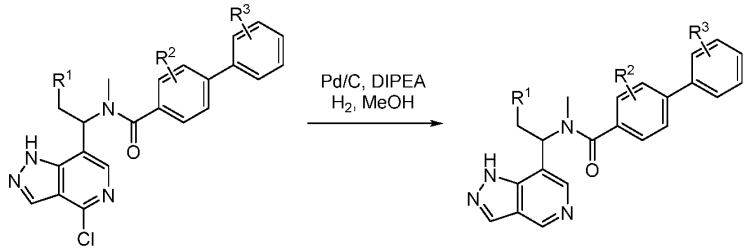
General Procedure 7 (GP7): Annulation reaction (Pyrazole synthesis)



To a solution of the corresponding aldehyde (1 *eq*) in dioxane (0.03 M) was added hydrazine hydrate (98% purity, 2 *eq*), the mixture was stirred at 20 °C for 0.5 h, then stirred at 70 °C for 2 h. The reaction mixture was added into water (10 mL) at 20 °C and extracted with EtOAc (3x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated

under reduce pressure to afford a residue. The crude product was purified by prep-TLC.

General Procedure 8 (GP8): Hydrodechlorination (HDC)

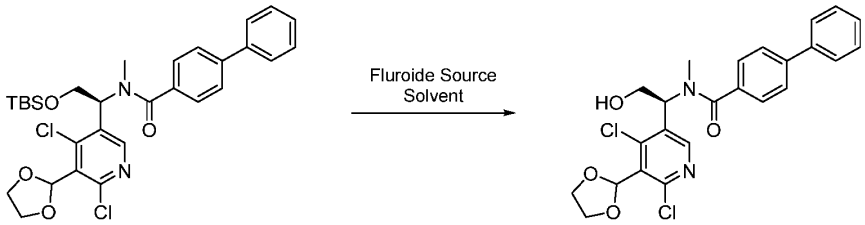


To a solution of the corresponding 4-chloro-pyrazolopyridine (1 *eq*), DIPEA (1 *eq*) in MeOH (0.06 M) was added Pd/C (10% purity, 0.0441 *eq*). The reaction mixture was stirred at 30 °C for 1 h under H_2 (15 psi). The reaction mixture was filtered with diatomite and the filtrate was concentrated to afford the crude residue.

Optional **GP8** when starting materials contain other aryl chloride moieties:

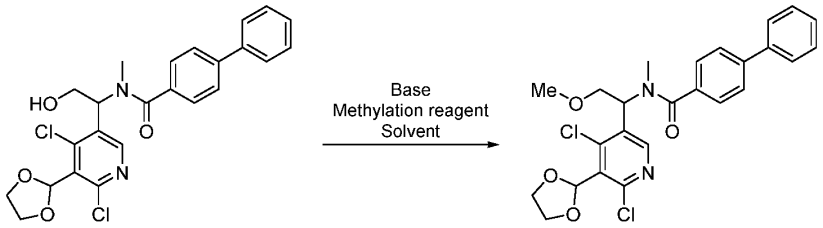
To a solution of the corresponding 4-chloro-pyrazolopyridine (1 *eq*) in THF (0.25 M) was added $Pd(dppf)Cl_2$ (0.1 *eq*), TMEDA (1.7 *eq*), and $NaBH_4$ (1.7 *eq*) under N_2 atmosphere. The mixture was stirred at 20 °C for 2 h. After completion, as judged by LCMS, the mixture was poured into NH_4Cl, the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine (x5) dried over Na_2SO_4 (or similar drying agent). The solvent was removed *in vacuo* to afford the crude residue.

General Procedure 9 (GP9): Silyl Deprotection



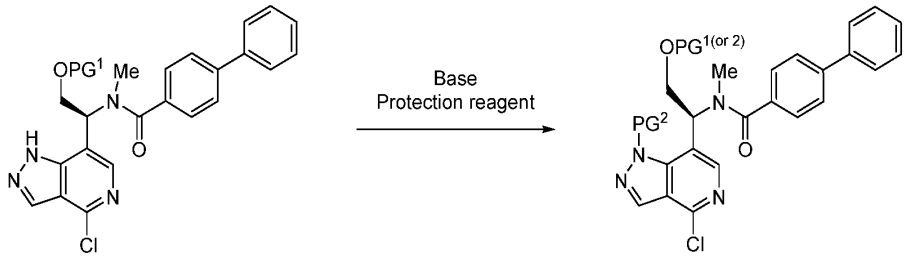
To a solution of the silyl protected compound (1 *eq*) in a solvent (solvent options: MeCN, Et_2O, dioxane, MeOH, EtOH, *i*-PrOH, THF, DCM, DMF, or similar) at a concentration of 0.01–0.5 M, was added a fluoride ion source (1–20 *eq*, examples: TBAF, NH_4F, HF, pyridine·HF, CsF, $LiBF_4$, or similar). The reaction was stirred at 20–80 °C, for 1–20 h, until starting material was consumed. A standard aqueous work-up was performed. The solvent was removed in vacuo to afford the crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether/ethyl acetate to give the desired product.

General Procedure 10 (GP10): Ether synthesis



To a solution of the hydroxy containing compound (1 *eq*) in a solvent (solvent options: MeCN, Et_2O, dioxane, MeOH, EtOH, *i*-PrOH, THF, DCM, DMF, or similar) was added a base (1–5 *eq*, base options: MeLi, t-BuLi, PhLi, NaOMe, LiOMe, NaOEt, NaO*t*-Bu, LiO*t*-Bu, NaH, or similar) at -78 – 25 °C. The reaction was stirred until consumption of starting material, and then quenched by pouring into ice sat. aq. NH_4Cl. The mixture was extracted with organic solvent (x3) and the combined organic phases were washed with brine. The organic phase was dried over sodium sulfate (or similar drying agent) and concentrated under reduced pressure to remove solvent. The resulting crude compound was purified by silica gel column chromatography (PE:EA, or similar applicable solvent system).

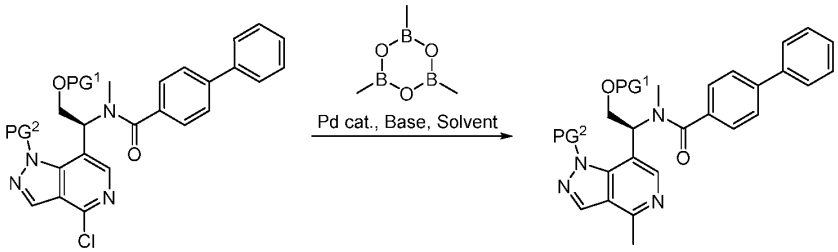
General Procedure 11 (GP11): Heteroaryl *N*-protection



To a solution of the starting material (1 *eq*) in DMF (or other applicable solvent) was added a base (1.5 *eq*; base options: *t*-BuOLi, MeLi, t-BuLi, PhLi, NaOMe, LiOMe, NaOEt, NaO*t*-Bu, NaH, or similar) at 0 °C under N_2 atmosphere. The reaction was stirred at 0 °C for 0.5–2 h. Then SEM-Cl (or other protection reagent such as: MEM chloride, MOM chloride, BOM chloride, or similar) was added to the reaction and the resulting mixture was stirred at 20–30 °C for 1–6 h. The reaction mixture was quenched with NH_4Cl under N2 and mixture was extracted with ethyl acetate (x3), the organic phases were combined and washed with brine (x3), then dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude product. The crude product was purified by flash silica gel chromatography.

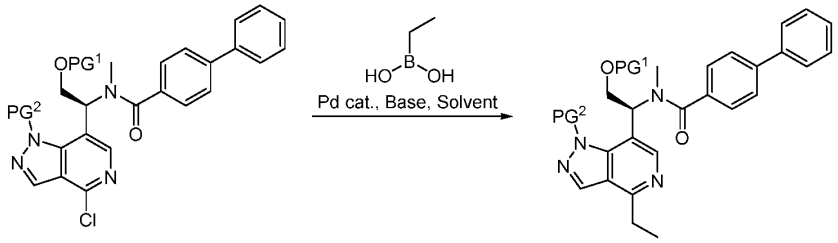
General Procedure 12 (GP12): Suzuki-Miyaura Alkylation

Methylation:



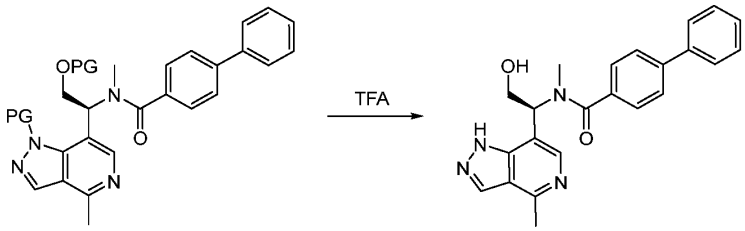
To a solution of the starting material (1 *eq*) and trimethylboroxine (5 *eq*) in 1,4-dioxane (~0.1 M; or other applicable solvent) was added $Pd(dppf)Cl_2$ (0.1 *eq*) (or other palladium catalyst such as: $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, RuPhos Pd G3, Pd/C, or similar) and K_2CO_3 (3 *eq*), the mixture was stirred at 40–120 °C for 1–24 h. The reaction is monitored by LCMS, tracking consumption of starting material. After the reaction mixture was cooled to room temperature, the mixture was filtered through celite®, and the filtrate was concentrated to give a crude product. The crude product was purified by flash silica gel chromatography.

Ethylation:



To a solution of the starting material (1 *eq*) and ethylboronic acid (3 *eq*) in 1,4-dioxane (~0.1 M; or other applicable solvent) was added $Pd(dppf)Cl_2$ (0.1 *eq*) (or other palladium catalyst such as: $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, RuPhos Pd G3, Pd/C, or similar) and K_2CO_3 (3 *eq*), the mixture was stirred at 40–120 °C for 1–24 h. The reaction is monitored by LCMS, tracking consumption of starting material. After the reaction mixture was cooled to room temperature, the mixture was filtered through celite®, and the filtrate was concentrated to give a crude product. The crude product was purified by flash silica gel chromatography.

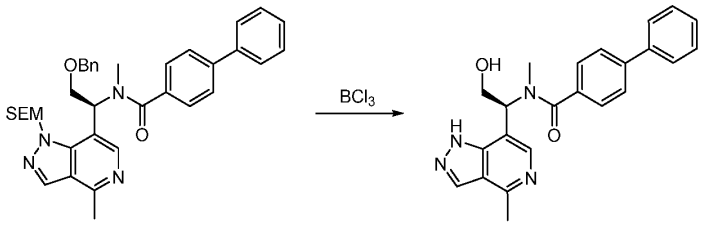
General Procedure 13 (GP13): Global Deprotection 2



To a solution of the starting compound (1 *eq*) in DCM (or other applicable solvent) was added TFA (50–150 *eq*). The reaction mixture was stirred at 20–100 °C for 2–24 h. The reaction mixture was concentrated to give a crude residue. The residue was dissolved in a

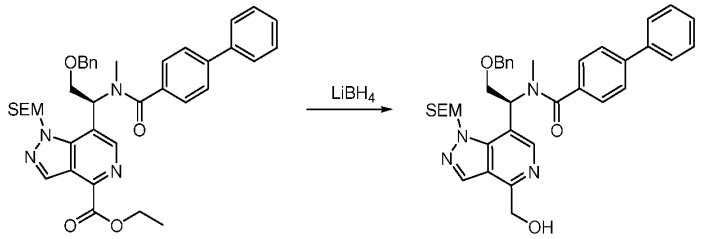
protic solvent and treated with Et_3N ($NH_3 \cdot H_2O$, or similar base) to adjust to pH = 8. The resulting mixture was quenched by pouring into H_2O. The mixture was extracted with EtOAc (×3), the combined organic phases were washed with brine and dried over anhydrous sodium sulfate (or another drying agent). The solution was concentrated under reduced pressure to remove the solvent. The crude material can be purified by prep-TLC, column chromatography, or prep-HPLC before an optional following step.

General Procedure 14 (GP14): Global Deprotection 3



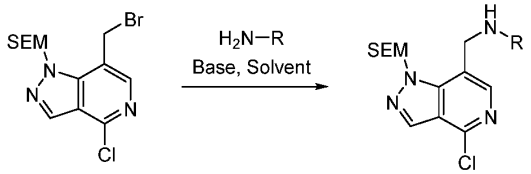
To a solution of the starting compound (1 *eq*) in DCM (or other applicable solvent) was added BCl_3 (3 *eq*) at 0 °C. The reaction mixture was stirred at 0–20 °C for 2–24 h under N_2 atmosphere. The reaction was quenched with sat. aq. $NaHCO_3$, the resulting mixture was extracted with DCM (x2) and the organic phases were washed with brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The crude material can be purified by prep-TLC, column chromatography, or prep-HPLC before an optional following step.

General Procedure 15 (GP15): Reduction



To a solution of the starting compound (1 *eq*) in EtOH (0.1 M) was added $LiBH_4$ (or $NaBH_4$) in THF (2 M, 5 *eq*) at 0°C. The reaction mixture was stirred at 20-30 °C for 1-6 hr under N_2 atmosphere. Upon desired completion the reaction mixture was poured into water and extracted with EA (x3). The combined organic phases were dried with Na_2SO_4 and concentrated to give the crude product.

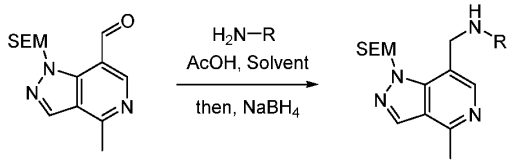
General Procedure 16 (GP16): Amination



int-26

To a solution of **int-26** (1 *eq*) and the corresponding amine (1.5 *eq*) in DMF or other applicable solvent (0.2 M) was added K_2CO_3 or another similar base (2 *eq*). The mixture was stirred at 20-50 °C for 2-20 h. The reaction was tracked by LCMS. After the reaction was completed, the reaction mixture was poured into H_2O solution at 0 °C, and extracted with EtOAc (x 2), the combined organic phase was washed with brine (x 3), dried over anhydrous Na_2SO_4, and concentrated to give a crude product. The residue was purified by silica gel chromatography and concentrated.

General Procedure 17 (GP17): Reductive amination

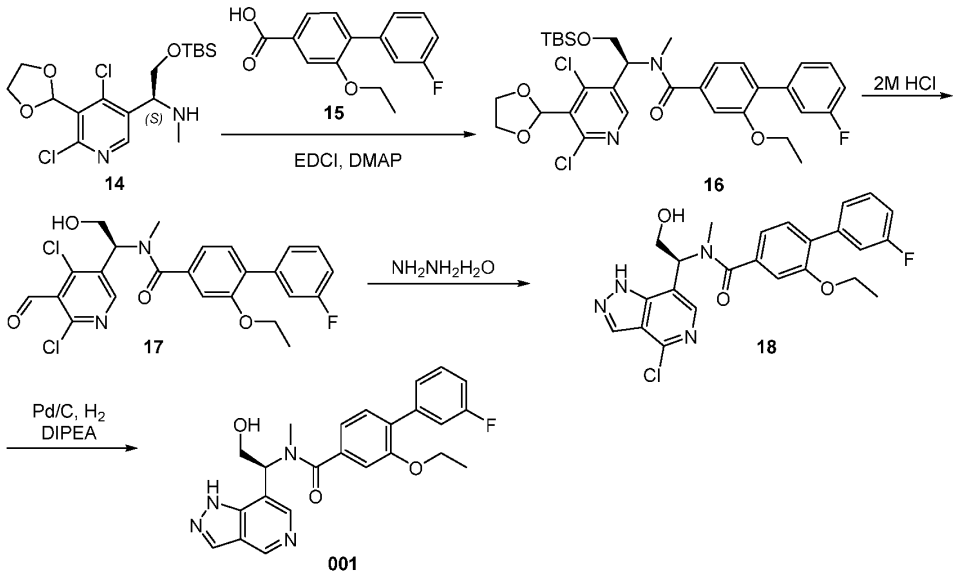


int-28

To a solution of **int-28** (1 *eq*) in MeOH (0.2 M) was added the corresponding amine (2 *eq*) and AcOH (0.1 *eq*). The reaction was stirred at 25°C for 1.5 h. Then $NaBH_4$ (3 *eq*) was added at 0 °C. The reaction was stirred at 25 °C for 0.5 h under N_2. Upon completion the mixture was poured into sat. aq. NH_4Cl at 20°C and extracted with DCM (x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The crude product was purified by flash silica gel chromatography.

Synthesis of Compounds 001–040 (C-substituted):

Synthesis of Compound **001**:



*Synthesis of Intermediate **16**:*

Intermediate **14** was synthesized, starting from **int-1**, via **GP1** through **GP3**

Intermediate **15** is commercially available.

Following **GP4**, the crude product was isolated and then purified by prep-TLC (Petroleum ether: Ethyl acetate = 1:1). Int-**16** (100 mg, 128.53 µmol, 34.91% yield, 83.5% purity) was obtained as yellow oil. **LCMS:** t_R = 0.718 min, m/z =649.3[M+H]$^+$

*Synthesis of Intermediate **17**:*

Following **GP5**, int-**17** (80 mg, 81.41 µmol, 52.89% yield, 50% purity) was obtained as yellow solid and used for next step without purification. **LCMS:** t_R = 0.516 min, m/z = 491.1 (M+H$^+$)

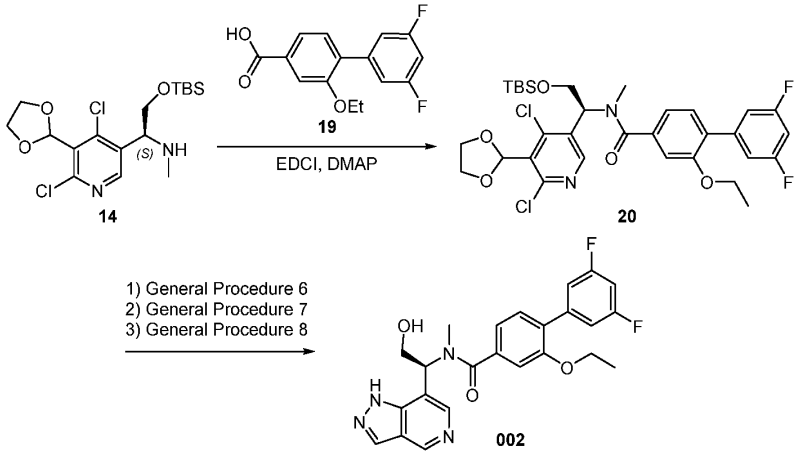
*Synthesis of Intermediate **18**:*

Following **GP7**, the crude product was purified by prep-TLC (PE:EA = 1:1). Int-**18** (50 mg, 104.29 µmol, 64.05% yield, 97.8% purity) was obtained as white oil. **LCMS:** t_R = 0.500 min, m/z = 469.1 [M+H]$^+$

*Synthesis of Compound **001**:*

Following **GP8**, the crude product was purified by prep-HPLC (column: Phenomenex luna C18, 150x25mm, 10um; mobile phase: A=Water+0.1%FA, B=Acetonitrile, 15%–45% B; gradient time: 1 min; flow rate: 60 mL/min). Compound **001** (2.08 mg, 4.79 µmol, 7.48% yield, 100% purity) was obtained as white solid. **LCMS:** t_R = 0.433 min, m/z = 435.2 [M+H]$^+$ **^{1}H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.00 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.27 - 7.15 (m, 3H), 7.15 (s, 2H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.94 - 6.91 (m, 1H), 4.33 - 4.29 (m, 1H), 3.95 (dt, *J* = 6.7, 13.4 Hz, 2H), 2.78 (s, 2H), 1.29 - 1.22 (m, 2H). **SFC** = 100% ee

Synthesis of Compound **002**:



*Synthesis of Intermediate **20**:*

Following a similar scheme to the synthesis of Compound **001**, intermediate **20** was synthesized via **GP1-GP5**. The residue was purified by silica gel column chromatography

(PE:EA =3:1). Compound **8** (550 mg, 617.85 μmol, 83.90% yield, 75% purity) was obtained as yellow oil. **LCMS**: t_R = 0.731 min; m/z = 667.2$[M+H]^+$.

Synthesis of Compound 002:

Following **GP6-GP8**, crude **002** was isolated and purified by prep-HPLC: (column: Phenomenex luna C18, 150x25mm, 10um; mobile phase: A=Water+0.1%FA, B=Acetonitrile, 19%–49% B; gradient time: 15 min; flow rate: 60 mL/min) The combined fractions were concentrated and lyophilized to afford the final product. Compound **002** (10.26 mg, 22.00 μmol, 42.84% yield, 97% purity) was obtained as pink solid. **LCMS:** t_R = 0.337 min; m/z=453.1$[M+H]^+$ **^{1}H NMR** (400 MHz, Chloroform-*d*) δ = 9.58 - 8.91 (m, 1H), 8.57 - 8.13 (m, 2H), 7.26 (br d, *J* = 7.5 Hz, 1H), 7.15 - 6.99 (m, 4H), 6.74 (br t, *J* = 8.6 Hz, 1H), 6.20 (br s, 1H), 4.67 - 4.34 (m, 2H), 4.17 - 3.82 (m, 2H), 2.86 (br s, 3H), 1.33 (br t, *J* = 6.7 Hz, 3H).

Synthesis of Compound 003:

Following a similar scheme to the synthesis of Compound **002**, compound **003** was synthesized via **GP5-GP8**. The residue was purified by pre-HPLC (column: C18 150×30mm; mobile phase: A=Water+0.1%FA, B=Acetonitrile; gradient: 25%–55% B over 1 min). The combined fractions were lyophilized. Compound **003** (8.32 mg, 18.37 μmol, 29.56% yield, 99% purity) was obtained as an off-white solid. **LCMS**: t_R = 0.478 min; m/z=449.2 $[M+H]^+$ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.16 - 9.11 (m, 1H), 8.37 (s, 1H), 8.30 (s, 1H), 7.33 - 7.29 (m, 1H), 7.15 - 7.04 (m, 4H), 6.89 - 6.83 (m, 1H), 6.31 - 6.15 (m, 1H), 4.53 (br t, *J* = 10.3 Hz, 1H), 4.47 - 4.40 (m, 1H), 4.11 - 3.97 (m, 2H), 2.90 (s, 3H), 2.38 (s, 3H), 1.35 (br t, *J* = 6.9 Hz, 3H). **SFC**: 100% ee

Synthesis of Compound 004:

Following a similar procedure to the synthesis of Compound **002**, starting from int-**14**, compound **004** was synthesized via **GP5-GP8**. The residue was purified by two separate methods:

Method 1: prep-HPLC (column: C18 150×30mm; mobile phase: A=water+0.1%FA, B=Acetonitrile; gradient: 25%–55% B over 7 min).

Method 2: pre-HPLC (column: Waters Xbridge 150x25mm, 5um; mobile phase: A=water(NH_4HCO_3). B=Acetonitrile; gradient: 32%-62% B over 9 min).

The combined fractions from prep-HPLC were lyophilized. Compound **004** (2.92 mg, 6.40 μmol, 16.36% yield, 98.9% purity) was obtained as white solid. **LCMS**: Rt=0.485 min , m/z=451.1 $[M+H]^+$ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.27 - 11.99 (m, 1H), 9.05 (s, 1H), 8.24 (s, 1H), 8.20 (s, 1H), 7.46 (s, 1H), 7.35 - 7.31 (m, 1H), 7.27 - 7.22 (m, 3H), 7.08 - 7.05 (m, 1H), 7.04 - 7.01 (m, 1H), 6.17 - 6.09 (m, 1H), 4.54 - 4.43 (m, 1H), 4.35 (dd, *J* = 5.4, 11.4 Hz, 1H), 4.06 - 3.91 (m, 2H), 2.83 (s, 3H), 1.31 - 1.26 (m, 3H). **SFC:** 100% ee

Synthesis of Compound 005:

Following a similar procedure to the synthesis of Compound **002**, starting from int-**14**,

compound **005** was synthesized via **GP5-GP8**. The crude compound **005** was purified by prep-HPLC (column: Phenomenex Luna C18 150x25mm, 10um; mobile phase: [water(FA)-ACN]; gradient: 15%-45% B over 9 min) and the fractions were lyophilized to give the product. Compound **005** (10.52 mg, 25.26 µmol, 17.84% yield, 100% purity) was obtained as a white solid. **LCMS:** t_R = 0.435 min, m/z =417.2 $[M+H]^+$ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.13 - 11.62 (m, 1H), 8.30 - 8.07 (m, 2H), 7.76 (s, 1H), 7.67 (br d, J = 7.9 Hz, 1H), 7.55 (br d, J = 7.8 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.09 - 6.94 (m, 2H), 6.49 - 6.21 (m, 1H), 4.12 - 3.90 (m, 2H), 3.86 (br t, J = 5.6 Hz, 2H), 2.78 (s, 3H), 2.72 (s, 3H), 2.60 - 2.46 (m, 1H), 2.44 - 2.30 (m, 1H), 1.28 (t, J = 6.9 Hz, 3H)

Synthesis of Compound 006:

(S)-3'-chloro-2-cyclopropoxy-N-(2-hydroxy-1-(1H-pyrazolo[4,3-c]pyridin-7-yl)ethyl)-N-methyl-[1,1'-biphenyl]-4-carboxamide

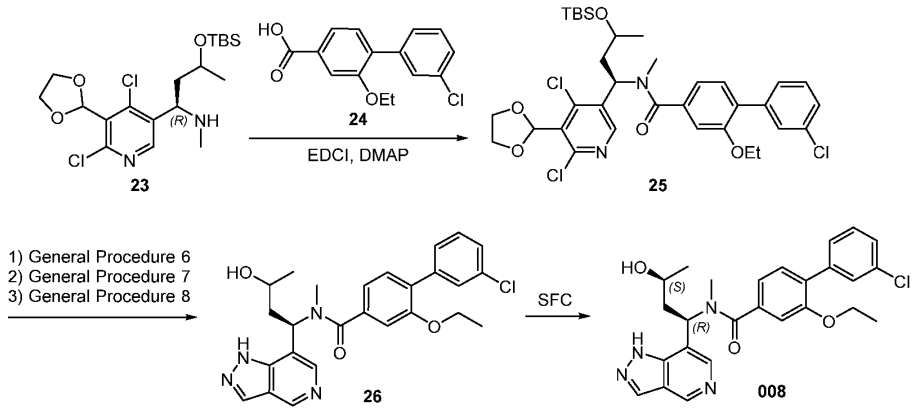
Following a similar procedure to the synthesis of Compound **002**, starting from int-**14**, compound **006** was synthesized via **GP5-GP7**. The final step in the synthesis of compound **006** is as follows:

To a solution of the penultimate compound (40 mg, 80.42 µmol, 1 *eq*) in AcOH (1 mL) was added Zn (52.59 mg, 804.23 µmol, 10 *eq*), the mixture was stirred at 30 °C for 2 h under N_2 atmosphere. The reaction mixture was filtered under N_2 and the filtrate was basified with 1M NaOH. The crude residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*7um;mobile phase: [water(FA)-ACN]; gradient: 23%-53% B over 10 min) and lyophilized to afford compound **006** (8.51 mg, 18.33 µmol, 22.79% yield, 99.7% purity) as an off-white solid. **LCMS**: t_R =0.465 min, m/z=463.2$[M+H]^+$ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.17 (s, 1H), 8.36 (s, 1H), 8.31 (s, 1H), 7.52 (d, *J* = 1.1 Hz, 1H), 7.47 (d, *J* = 1.2 Hz, 1H), 7.39 - 7.32 (m, 4H), 7.23 - 7.18 (m, 1H), 6.24 (br dd, *J* = 5.9, 9.2 Hz, 1H), 4.65 - 4.56 (m, 1H), 4.47 (dd, *J* = 5.2, 11.4 Hz, 1H), 3.85 - 3.75 (m, 1H), 2.96 (s, 3H), 0.88 - 0.73 (m, 4H).

Synthesis of Compound 007:

General procedure 1 (**GP1**), was used to synthesize int-**11**. Int-**11** was subjected to **GP2-GP8**. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 150x25mm, 10um; mobile phase: [water (FA)-ACN]; gradient: 17%-47% B over 15 min). The product was concentrated and lyophilized to afford compound **007** (13.86 mg, 30.90 µmol, 31.09% yield, 100% purity) as an off-white solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.37 (t, J=6.94 Hz, 3 H) 2.44 - 2.67 (m, 2 H) 2.81 (s, 3 H) 3.86 - 3.98 (m, 2 H) 4.00 - 4.13 (m, 2 H) 6.48 (br dd, J=10.63, 4.75 Hz, 1 H) 7.01 - 7.09 (m, 3 H) 7.27 - 7.31 (m, 2 H) 7.33 (d, J=8.13 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 8.27 (s, 1 H) 8.42 (br s, 1 H) 9.12 (br s, 1 H). **LCMS:** t_R = 0.459 min, m/z= 449.1 $[M+H]^+$

Synthesis of Compound 008:



Intermediate **23** was synthesized, starting from **int-1**, via **GP1** through **GP3**

Intermediate **24** is commercially available.

Following a similar procedure to the synthesis of Compound **002**, starting from int-**23**, compound **008** was synthesized via **GP5-GP8**. In addition to the proceeding procedures, the diastereomeric mixture of compound **008** (20 mg, 41.76 µmol, 1 eq) was purified by SFC (column: DAICEL CHIRALPAK AS (250mmx30mm, 10um); mobile phase: [CO_2:*i*-PrOH(0.1%NH_3H_2O)]; B% = 30%, isocratic elution mode). After SFC, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized. Compound **008** (11.23 mg, 23.45 µmol, 56.15% yield) was obtained as white solid. **LCMS:** t_R = 0.487 min, m/z= 479.2 $[M+H]^+$ **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.25 - 11.73 (m, 1H), 9.14 (br dd, *J* = 2.1, 9.9 Hz, 1H), 8.59 - 8.31 (m, 1H), 8.29 (s, 1H), 7.52 (s, 1H), 7.39 (s, 1H), 7.36 - 7.29 (m, 3H), 7.09 - 7.02 (m, 2H), 6.57 (br d, *J* = 11.1 Hz, 1H), 4.13 - 3.97 (m, 3H), 2.78 (s, 3H), 2.60 (br s, 1H), 2.20 - 2.12 (m, 1H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.36 (t, *J* = 6.9 Hz, 3H)

Synthesis of Compound 009:

Following a similar procedure to the synthesis of Compound **002**, starting from int-**13**, compound **009** was synthesized via **GP2-GP8**. The crude compound **009** was purified by prep-HPLC (column: C18 150x30mm; mobile phase: [water (FA)-ACN]; gradient: 20%-50% B over 7 min), but LCMS showed the product contained impurities, Re-purified by prep-HPLC (column: C18 150×30mm; mobile phase: [water (FA)-ACN]; gradient: 22%-52% B over 7 min). The product was concentrated and lyophilized to give the product. Compound **009** (47.64 mg, 104.10 µmol, 50.27% yield, 98% purity) was obtained as white solid. **LCMS:** t_R = 0.464 min, m/z= 449.2 $[M+H]^+$ **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.37 (t, J=6.94 Hz, 3 H) 2.43 - 2.52 (m, 1 H) 2.59 - 2.69 (m, 1 H) 2.81 (s, 3 H) 3.91 - 3.98 (m, 2 H) 4.01 - 4.12 (m, 2 H) 6.48 (br dd, J=10.51, 4.63 Hz, 1 H) 7.01 - 7.10 (m, 3 H) 7.28 - 7.31 (m, 2

H) 7.33 (d, J=8.25 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 8.27 (s, 1 H) 8.42 (s, 1 H) 9.13 (s, 1 H). **SFC** = 96% ee

Synthesis of Compound 010:

Following a similar procedure to the synthesis of Compound **009**, starting from int-**13**, compound **009** was synthesized via **GP2-GP8**. An additional silyl deprotection step **GP9** was employed between **GP5** and **GP6**, utilizing $LiBF_4$ (10 *eq*) in ACN:H_2O (20:1; 0.8 M). The crude compound **010** product was purified by Prep-HPLC (column: Phenomenex luna C18 150x25mm, 10um; mobile phase: [water(FA)-ACN]; gradient: 18%-48% B over 9 min) to give compound **010** (42.85 mg, 99.54 µmol, 54.16% yield, 100% purity) as white solid. **LCMS:** Rt =0.431min, m/z=431.1$[M+H]^+$ **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.10 (br s, 1H), 8.39 (br s, 1H), 8.25 (s, 1H), 7.50 (d, J = 7.5 Hz, 2H), 7.43 - 7.34 (m, 2H), 7.34 - 7.27 (m, 2H), 7.08 - 7.01 (m, 2H), 6.45 (br dd, J = 4.8, 10.3 Hz, 1H), 4.12 - 3.95 (m, 2H), 3.95 - 3.84 (m, 2H), 2.79 (s, 3H), 2.60 (tdd, J = 4.9, 9.8, 14.5 Hz, 1H), 2.43 (dt, J = 5.9, 13.1 Hz, 1H), 1.31 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 011:

Following a similar procedure to the synthesis of Compound **009**, starting from int-**13**, compound **009** was synthesized via **GP2-GP8**. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25mm, 5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 30%-60% B over 9 min), lyophilized. Compound **011** (19.75 mg, 44.15 µmol, 26.01% yield, 100% purity) was obtained as an off-white solid. **LCMS**: t_R = 0.457 min, m/z= 461.2 $[M+H]^+$ **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.19 - 11.86 (m, 1H), 9.13 (s, 1H), 8.43 (s, 1H), 8.27 (s, 1H), 7.46 (s, 1H), 7.40 - 7.28 (m, 2H), 7.24 - 7.15 (m, 2H), 7.11 (br d, J = 7.8 Hz, 1H), 7.03 (dt, J = 1.9, 8.5 Hz, 1H), 6.53 - 6.45 (m, 1H), 3.96 (br t, J = 5.7 Hz, 2H), 3.76 (br dd, J = 3.3, 5.3 Hz, 1H), 2.83 (s, 3H), 2.73 - 2.58 (m, 1H), 2.55 - 2.41 (m, 1H), 0.89 - 0.65 (m, 4H). **SFC**: 100% ee

Synthesis of Compound 012:

Following a similar procedure as compound **011**, **GP2–8** were utilized in the synthesis of compound **012**.

The crude product was purified by prep-HPLC (column: Waters Xbridge 150x25mm, 5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 35%-65% B over 9 min), then lyophilized for 12 h. Compound **012** (30.65 mg, 63.94 µmol, 34.06% yield, 99.5% purity) was obtained as white solid. **LCMS:** t_R = 0.477 min, m/z = 477.2 $[M+H]^+$ **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.09 (br s, 1H), 9.14 (s, 1H), 8.44 (s, 1H), 8.29 (s, 1H), 7.45 (d, J = 6.4 Hz, 2H), 7.34 - 7.29 (m, 5H), 6.51 (br d, J = 4.5 Hz, 1H), 6.48 (br d, J = 4.4 Hz, 1H), 3.96 (t, J = 5.9 Hz, 2H), 3.77 (br d, J = 3.3 Hz, 1H), 2.84 (s, 3H), 2.70 - 2.61 (m, 1H), 2.53 - 2.45 (m, 1H), 0.86 - 0.71 (m, 4H). **SFC:** 100% ee

Synthesis of Compound 013:

Following a similar procedure to compound **002**, compound **013** was synthesized starting from **int-10** utilizing the following steps, in order: **GP2–5**, **GP9–10**, **GP6–GP8**; to afford the residue of crude compound **013**.

The residue was purified by prep-HPLC (column: Waters Xbridge 150x25mm, 5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 40%–70% B over 9 min), combined fractions were lyophilized. Compound **013** (44.69 mg, 96.62 µmol, 57.37% yield, 100% purity) was obtained as a white solid. **LCMS**: t_R = 0.466 min, m/z=463.1 $[M+H]^+$ **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.17 (br s, 1H), 9.12 (s, 1H), 8.40 (s, 1H), 8.26 (s, 1H), 7.41 - 7.33 (m, 2H), 7.32 - 7.28 (m, 2H), 7.13 - 7.07 (m, 2H), 7.04 (br d, *J* = 2.0 Hz, 1H), 6.43 - 6.34 (m, 1H), 4.14 - 4.00 (m, 2H), 3.66 (br t, *J* = 5.7 Hz, 2H), 3.42 (s, 3H), 2.82 (s, 3H), 2.72 - 2.61 (m, 1H), 2.54 - 2.43 (m, 1H), 1.37 (t, *J* = 6.9 Hz, 3H). **SFC**: 100% ee

Synthesis of Compound 014:

Following a similar procedure to compound **002**, compound **014** was synthesized starting from **int-10** utilizing the following steps, in order: **GP2-5**, **GP9-10**, **GP6-GP8**; to afford the residue of crude compound **014**.

The residue was purified by preparative HPLC (column: YMC-Actus Triart C18 150 x 30mm x 7um; mobile phase: [water (FA)-ACN]; gradient: 28%–58% B over 10 min) and lyophilized. Compound **014** (9.04 mg, 19.19 µmol, 38.33% yield, and 98.7% purity) was obtained as yellow solid. **LCMS:** t_R = 0.500 min, m/z= 465.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.23 (br d, *J* = 2.0 Hz, 1H), 8.46 (s, 2H), 7.54 (s, 1H), 7.41 (s, 1H), 7.33 (br d, *J* = 4.0 Hz, 3H), 7.16 - 7.05 (m, 2H), 6.38 (br s, 1H), 4.35 (s, 1H), 4.11 (br d, *J* = 4.9 Hz, 2H), 4.07 - 4.00 (m, 1H), 3.56 (s, 3H), 2.89 (s, 3H), 1.37 (t, *J* = 6.9 Hz, 3H)

Synthesis of Compound 015:

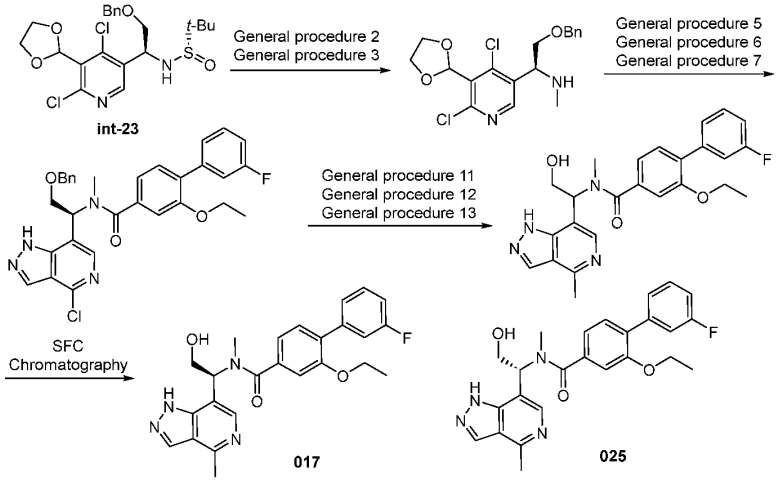
Following a similar procedure to compound **002**, compound **015** was synthesized starting from **int-11** utilizing the following steps, in order: **GP2-5**, **GP9-10**, **GP6-GP8**; to afford the residue of crude compound **015**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm x 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 40%–70% B over 9 min), lyophilized. Compound **015** (44.69 mg, 96.62 µmol, 57.37% yield, 100% purity) was obtained as a white solid.. **LCMS**: t_R = 0.466 min, m/z=463.1 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.17 (br s, 1H), 9.12 (s, 1H), 8.40 (s, 1H), 8.26 (s, 1H), 7.41 - 7.33 (m, 2H), 7.32 - 7.28 (m, 2H), 7.13 - 7.07 (m, 2H), 7.04 (br d, *J* = 2.0 Hz, 1H), 6.43 - 6.34 (m, 1H), 4.14 - 4.00 (m, 2H), 3.66 (br t, *J* = 5.7 Hz, 2H), 3.42 (s, 3H), 2.82 (s, 3H), 2.72 - 2.61 (m, 1H), 2.54 - 2.43 (m, 1H), 1.37 (t, *J* = 6.9 Hz, 3H). **SFC**: 100% ee

Synthesis of Compound 016:

Following a similar procedure to compound **002**, compound **016** was synthesized starting from **int-11** utilizing the following steps, in order: **GP2-5**, **GP9-10**, **GP6-GP8**; to

afford the residue of crude compound **015**. The crude product was purified by prep-HPLC(column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water(FA)-ACN]; gradient: 28%-58% B over 9 min) to give compound **016** (44.46 mg, 92.82 μmol, 39.00% yield, 100% purity) as white solid. **LCMS**: Rt =0.485min, m/z=479.1 $[M+H]^+$ **NMR**: ^1H NMR (400 MHz, CHLOROFORM-d) δ = 12.21 (br s, 1H), 9.16 (s, 1H), 8.44 (s, 1H), 8.30 (s, 1H), 7.58 (s, 1H), 7.46 (td, J = 1.9, 6.6 Hz, 1H), 7.41 - 7.34 (m, 3H), 7.17 - 7.11 (m, 2H), 6.43 (br dd, J = 4.8, 10.2 Hz, 1H), 4.19 - 4.03 (m, 2H), 3.70 (t, J = 5.9 Hz, 2H), 3.46 (s, 3H), 2.86 (s, 3H), 2.77 - 2.66 (m, 1H), 2.59 - 2.48 (m, 1H), 1.41 (t, J = 7.0 Hz, 3H)

Synthesis of Compound 017:



The synthesis of compound **017** was completed starting from **int-23**. The starting material was subjected **GP2-3**, followed by **GP5-7**. The resulting compound was subjected to **GP11-13**. Finally, the product was purified by SFC (column: DAICEL CHIRALPAK IK (250mm x 30mm, 10um); mobile phase: [CO_2:MeOH (0.1%NH_3H_2O)]; B%: 35%, isocratic elution mode), After SFC, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized. Compound **017** (8.26 mg, 17.75 μmol, 53.08% yield, 96.4% purity) was obtained as a white solid. **LCMS:** t_R = 0.417min, 449.2 $[M+H]^+$ (ESI pos). **NMR:** ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.49 - 8.34 (m, 1H), 8.14 (br s, 1H), 7.21 (br d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.05 - 6.94 (m, 1H), 6.92 - 6.89 (m, 1H), 6.76 - 6.65 (m, 1H), 4.90 - 4.66 (m, 1H), 4.63 - 4.35 (m, 3H), 3.71 (q, *J* = 7.1 Hz, 2H), 2.73 (s, 3H), 2.34 (br s, 3H), 1.07 - 0.99 (m, 4H). **SFC**: 100% ee

Synthesis of Compound 018:

Following a similar procedure to compound **017**, compound **018** was synthesized starting from **int-23** utilizing the following steps: **GP2-3**, **GP5-7**, then **GP11-13**. The crude product was purified by prep-TLC (DCM:MeOH = 10:1) to give the crude product (R_f = 0.5). Then, the still crude product was re-purified by prep-TLC (DCM:MeOH = 10:1) to give the

crude product (R_f = 0.5). The product was finally purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um; mobile phase: [water (FA)-ACN]; gradient: 12%-42% B over 9 min) and lyophilized to afford the desired product. Compound **018** (8.05 mg, 17.08 µmol, 9.89% yield, 99% purity) was obtained as a white. **LCMS:** t_R = 0.433 min, m/z =467.3 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.34 - 8.27 (m, 1H), 8.23 (s, 1H), 7.61 (dd, J = 1.3, 7.9 Hz, 1H), 7.56 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.12 (br dd, J = 2.0, 8.5 Hz, 2H), 6.89 - 6.76 (m, 1H), 4.67 (dd, J = 4.3, 11.2 Hz, 1H), 4.49 (br d, J = 11.1 Hz, 1H), 4.40 (dd, J = 4.4, 7.5 Hz, 1H), 4.12 (d, J = 7.0 Hz, 2H), 2.89 (s, 3H), 2.44 (s, 3H), 1.42 (t, J = 6.9 Hz, 3H)

Synthesis of Compound 019:

Following a similar procedure to compound **017**, compound **019** was synthesized starting from **int-23** utilizing the following steps: **GP2-3**, **GP5-7**, then **GP11-13**. The final crude product was purified by SFC (column: DAICEL CHIRALPAK IC (250mm x 30mm, 10um); mobile phase: [CO_2-ACN/*i*-PrOH (0.1% NH_3H_2O)]; B%: 25%, isocratic elution mode), and concentrated under reduced pressure to give the product. Compound **019** (30.12 mg, 64.13 µmol, 74.55% yield, 99% purity) was obtained as yellow solid. **LCMS:** t_R = 0.451 min, m/z = 465.1 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.38 (t, J=6.94 Hz, 3 H) 2.50 (s, 3 H) 3.02 (s, 3 H) 4.08 (q, J=6.92 Hz, 2 H) 4.59 - 4.66 (m, 2 H) 4.72 - 4.80 (m, 1 H) 7.33 - 7.36 (m, 3 H) 7.41 - 7.45 (m, 1 H) 7.52 (s, 1 H) 7.54 - 7.57 (m, 2 H) 8.38 (s, 1 H) 8.52 (s, 1 H)

Synthesis of Compound 020:

Following a similar procedure to compound **017**, compound **020** was synthesized starting from **int-23** utilizing the following steps: **GP2-3**, **GP5-7**, then **GP11-13**. The crude compound **020** (45 mg, 94.08 µmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 30mm, 10um); mobile phase: [CO_2:*i*-PrOH (0.1%NH_3H_2O)]; B%: 45%, isocratic elution mode) to afford the desired product. Compound **020** (7.4 mg, 16.85 µmol, 17.91% yield, and 98% purity) was obtained as a white off-solid. **LCMS:** t_R = 0.453 min, m/z= 431.2 $[M+H]^+$.**NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.55 - 11.89 (m, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 7.52 (d, J = 7.3 Hz, 2H), 7.43 - 7.37 (m, 2H), 7.36 - 7.30 (m, 2H), 7.15 - 7.07 (m, 2H), 6.15 (br dd, J = 5.4, 8.4 Hz, 1H), 4.57 - 4.45 (m, 1H), 4.45 - 4.36 (m, 1H), 4.08 - 3.96 (m, 2H), 2.89 (s, 3H), 2.83 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 021:

Following a similar procedure to compound **017**, compound **021** was synthesized starting from **int-23** utilizing the following steps: **GP2-3**, **GP5-7**, then **GP11-13**. The crude compound **021** (51 mg, 110.27 µmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 50mm, 10um); mobile phase: [CO_2:*i*-PrOH (0.1%NH_3H_2O)]; B%: 30%, isocratic elution mode). The eluent was concentrated to remove organic solvents and

the residual aqueous solution was lyophilized to afford the desired product. Compound **021** (18.93 mg, 40.11 µmol, 36.38% yield, 98% purity) was obtained as an off-white solid. **LCMS**: t_R = 0.458 min, m/z= 463.3 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.18 (s, 1H), 8.12 (s, 1H), 7.52 (dd, J = 1.3, 7.9 Hz, 1H), 7.46 (s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.08 - 7.02 (m, 2H), 6.81 (br d, J = 9.4 Hz, 1H), 4.55 (dd, J = 4.3, 11.1 Hz, 1H), 4.44 - 4.35 (m, 1H), 4.32 - 4.25 (m, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.77 (s, 3H), 2.33 (d, J = 3.8 Hz, 6H), 1.32 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 022:

Following a similar procedure to compound **017**, compound **022** was synthesized starting from **int-23** utilizing the following steps: **GP2-3**, **GP5-7**, then **GP11-13**. The crude compound **022** (35 mg, 76.00 µmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 30mm, 10um); mobile phase: [CO_2:*i*-PrOH (0.1%NH_3H_2O)]; B%: 50%, isocratic elution mode). The eluent was concentrated to remove organic solvents and the residual aqueous solution was lyophilized to afford the desired product. Compound **022** (18.93 mg, 40.11 µmol, 36.38% yield, 98% purity) was obtained as an off-white solid. **LCMS**: t_R = 0.453 min, m/z= 461.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.51 - 11.98 (m, 1H), 8.26 (s, 1H), 8.22 (s, 1H), 7.49 (s, 1H), 7.38 - 7.28 (m, 2H), 7.24 - 7.16 (m, 3H), 7.03 (t, J = 8.2 Hz, 1H), 6.18 - 6.13 (m, 1H), 4.57 - 4.51 (m, 1H), 4.45 - 4.40 (m, 1H), 3.77 (br s, 1H), 2.96 - 2.91 (m, 3H), 2.89 (s, 3H), 0.87 - 0.69 (m, 5H). **SFC**: 100% ee.

Synthesis of Compound 023:

Compound **023** was synthesized starting from **int-11** utilizing the following procedures in order: **GP2-7**, **GP4**, **GP11-13**. The crude product was purified by Prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um; mobile phase: [water(FA)-ACN]; gradient: 20%-50% B over 15 min) to afford compound **023** (20.78 mg, 27.69 µmol, 19.91% yield, 100% purity) was obtained as white solid. **LCMS:** t_R = 0.457min, m/z=475.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.34 (s, 2H), 7.49 (d, J = 1.3 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.27 - 7.19 (m, 2H), 7.15 (dd, J = 1.5, 7.7 Hz, 1H), 7.09 - 7.01 (m, 1H), 6.52 - 6.44 (m, 1H), 4.03 - 3.95 (m, 2H), 3.83 - 3.76 (m, 1H), 2.99 (s, 3H), 2.87 (s, 3H), 2.70 - 2.62 (m, 1H), 2.53 - 2.45 (m, 1H), 0.87 - 0.73 (m, 4H)

Synthesis of Compound 024:

Following a similar procedure to compound **023**, compound **024** was synthesized starting from **int-11** utilizing the following procedures in order: **GP2-7**, **GP4**, **GP11-13**. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um; mobile phase: [water(FA)-ACN]; gradient: 12%-42% B over 9 min) the resulting solution was concentrated and lyophilized to afford the product. Compound **024** (16.33 mg, 32.93 µmol, 14.70% yield, 99% purity) was obtained as a white solid. **LCMS:** t_R = 0.484 min, m/z = 491.1 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.59 - 11.44 (m, 1H),

8.39 - 8.17 (m, 2H), 7.44 (s, 2H), 7.34 - 7.28 (m, 4H), 7.10 (dd, J = 1.3, 7.7 Hz, 1H), 6.50 - 6.38 (m, 1H), 3.94 (br t, J = 5.2 Hz, 2H), 3.76 (br d, J = 3.4 Hz, 1H), 2.87 (s, 3H), 2.82 (s, 3H), 2.68 - 2.55 (m, 1H), 2.52 - 2.41 (m, 1H), 0.87 - 0.68 (m, 4H).

Synthesis of Compound 025:

Following the identical procedure for the synthesis of compound **017**, compound **025** was synthesized starting from **int-23**. The starting material was subjected **GP2-3**, followed by **GP5-7**. The resulting compound was then subjected to **GP11-13** resulting in an enantiomeric mixture of compound **017** and **025**. The crude enantiomers were separated by SFC (column: DAICEL CHIRALPAK IK (250mm x 50mm, 10um); mobile phase: [CO_2-EtOH (0.1%NH_3H_2O)]; B%: 25%, isocratic elution mode), and concentrated under reduced pressure to give the product. Compound **025** (69.20 mg, 152.75 µmol, 22.84% yield, 99% purity) was obtained as white solid. **LCMS**: t_R = 0.458 min, m/z = 449.1 $[M+H]^+$. **NMR**: ^1H NMR (400 MHz, DMSO-*d*6) δ ppm 1.21 - 1.36 (m, 3 H) 2.79 (br s, 3 H) 2.91 - 3.09 (m, 3 H) 4.09 (br s, 2 H) 5.16 - 5.40 (m, 1 H) 5.92 (br d, J=8.88 Hz, 1 H) 7.04 - 7.11 (m, 1 H) 7.13 - 7.20 (m, 2 H) 7.32 - 7.40 (m, 3 H) 7.42 - 7.47 (m, 1 H) 8.15 - 8.30 (m, 1 H) 8.54 (br s, 1 H).

Synthesis of Compound 026:

Following a similar procedure to compound **023**, compound **026** was synthesized starting from **int-13** utilizing the following procedures in order: **GP2-7**, **GP4**, **GP11-13**. The crude product was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water (NH_4OH)-ACN]; gradient: 20%-50% B over 10 min) to afford compound **026** (15.03 mg, 33.81 µmol, 46.60% yield, 100% purity) as yellow solid. **LCMS:** t_R =0.456min, m/z=445.2 $[M+H]^+$. **NMR**: ^1H NMR (400 MHz, CHLOROFORM-d) δ = 12.27 - 11.86 (m, 1H), 8.23 - 8.17 (m, 2H), 7.47 - 7.43 (m, 2H), 7.35 - 7.30 (m, 2H), 7.28 - 7.24 (m, 2H), 7.01 - 6.97 (m, 2H), 6.35 (br dd, J = 4.5, 10.3 Hz, 1H), 4.02 - 3.91 (m, 2H), 3.89 - 3.82 (m, 2H), 2.84 (br s, 3H), 2.73 (s, 3H), 2.58 - 2.47 (m, 1H), 2.41 - 2.33 (m, 1H), 1.27 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 027:

Following a similar procedure to compound **023**, compound **027** was synthesized starting from **int-13** utilizing the following procedures in order: **GP2-7**, **GP4**, **GP11-13**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 35%-65% B over 9 min) then concentrated and lyophilized to give the product. Compound **027** (14.37 mg, 29.40 µmol, 89.56% yield, 98% purity) was obtained as a brown solid. **LCMS:** t_R = 0.460 min, m/z =479.3 $[M+H]^+$. **NMR:** ^1H NMR (400 MHz, CHLOROFORM-d) δ = 12.13 - 11.62 (m, 1H), 8.30 - 8.07 (m, 2H), 7.76 (s, 1H), 7.67 (br d, J = 7.9 Hz, 1H), 7.55 (br d, J = 7.8 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.09 - 6.94 (m, 2H), 6.49 - 6.21 (m, 1H), 4.12 - 3.90 (m, 2H), 3.86 (br t, J = 5.6

Hz, 2H), 2.78 (s, 3H), 2.72 (s, 3H), 2.60 - 2.46 (m, 1H), 2.44 - 2.30 (m, 1H), 1.28 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 028:

Following a similar procedure to compound **023**, compound **028** was synthesized starting from **int-13** utilizing the following procedures in order: **GP2-7**, **GP4**, **GP11-13**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um;mobile phase: [water(NH_3H_2O)-ACN]; gradient: 22%-52% B over 9 min) and lyophilized to give the product. Compound **028** (17 mg, 36.21 μmol, 79.93% yield, 100% purity) was obtained as a white solid. **LCMS:** t_R = 0.442 min, m/z = 470.2 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.13 - 11.62 (m, 1H), 8.30 - 8.07 (m, 2H), 7.76 (s, 1H), 7.67 (br d, J = 7.9 Hz, 1H), 7.55 (br d, J = 7.8 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.09 - 6.94 (m, 2H), 6.49 - 6.21 (m, 1H), 4.12 - 3.90 (m, 2H), 3.86 (br t, J = 5.6 Hz, 2H), 2.78 (s, 3H), 2.72 (s, 3H), 2.60 - 2.46 (m, 1H), 2.44 - 2.30 (m, 1H), 1.28 (t, J = 6.9 Hz, 3H)

Synthesis of Compound 029:

Following a similar procedure to compound **023**, compound **029** was synthesized starting from **int-13** utilizing the following procedures in order: **GP2-7**, **GP4**, **GP11-13**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 32%-62% B over 9 min), lyophilized. Compound **029** (5.32 mg, 11.21 μmol, 19.37% yield, 100% purity) was obtained as an off-white solid. **LCMS**: t_R =0.465 min, m/z=475.3 $[M+H]^+$ **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.22 - 11.98 (m, 1H), 8.28 (br d, *J* = 9.1 Hz, 2H), 7.46 (s, 1H), 7.39 - 7.29 (m, 2H), 7.25 - 7.16 (m, 3H), 7.11 (br d, *J* = 7.4 Hz, 1H), 7.07 - 7.00 (m, 1H), 6.49 - 6.41 (m, 1H), 3.95 (br t, *J* = 5.6 Hz, 2H), 3.77 (br d, *J* = 3.0 Hz, 1H), 2.90 (s, 3H), 2.83 (s, 3H), 2.67 - 2.56 (m, 1H), 2.51 - 2.40 (m, 1H), 0.85 - 0.69 (m, 4H). **SFC**: 100% ee.

Synthesis of Compound 030:

Following a similar procedure to compound **017**, compound **030** was synthesized starting from **int-23**. The starting material was subjected **GP2-3**, **GP5-7**, then **GP11-13**. The final crude product was pre-purified by prep-HPLC (column: Phenomena Luna C18 150 x 25mm, 10um; mobile phase: [water (FA)-ACN]; gradient: 15%-45% B over 9 min). Compound **030** (32 mg, 65.14 μmol, 8.90% yield, 97% purity) was obtained as a white solid. The product was then purified by SFC (column: DAICEL CHIRALPAK IK (250mm x 30mm, 10um); mobile phase: [CO_2-ACN/*i*-PrOH (0.1% NH_3H_2O)]; B%: 25%, isocratic elution mode). Compound **030** (18.15 mg, 38.09 μmol, 56.72% yield, 100% purity) was obtained as a white solid. **LCMS:** t_R = 0.472 min, m/z= 477.3 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.28 (s, 1H), 8.18 (s, 1H), 7.51 (dd, J = 1.3, 7.9 Hz, 1H), 7.45 (d, J = 1.1 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.06 - 7.00 (m, 2H), 6.80 (br d, J = 9.5 Hz, 1H), 4.68 - 4.58 (m, 1H), 4.55

- 4.47 (m, 1H), 4.45 - 4.40 (m, 1H), 4.00 (q, J = 7.0 Hz, 2H), 3.13 (q, J = 7.6 Hz, 2H), 2.39 (s, 3H), 2.32 (s, 3H), 1.40 (t, J = 7.6 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 031:

Following a similar procedure to compound **017**, compound **031** was synthesized starting from **int-23**. The starting material was subjected **GP2-3**, **GP5-7**, **GP11-12**, then **GP14**. The resulting crude compound was pre-purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um; mobile phase: [water(FA)-ACN]; gradient: 12%-42% B over 9 min) and lyophilized. Compound **031** (20 mg, 43.24 μmol, 29.53% yield) was obtained as white solid. The product was further purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 30mm, 10um); mobile phase: [CO_2:*i*-PrOH (0.1%NH_3H_2O)]; B%: 35%, isocratic elution mode). After SFC, the eluent was concentrated to remove organic solvents and the residual aqueous solution was lyophilized. Compound **031** (30.67 mg, 66.31 μmol, 87.63% yield, and 100% purity) was obtained as white solid. **LCMS:** t_R = 0.467 min, m/z= 463.2 ($M+H^+$). **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.42 - 12.07 (m, 1H), 8.26 (d, *J* = 18.1 Hz, 2H), 7.33 (br d, *J* = 7.8 Hz, 2H), 7.31 - 7.26 (m, 2H), 7.17 - 7.08 (m, 2H), 7.07 - 6.99 (m, 1H), 6.15 (br dd, *J* = 6.1, 8.4 Hz, 1H), 4.52 (br d, *J* = 10.0 Hz, 1H), 4.41 (dd, *J* = 5.6, 11.3 Hz, 1H), 4.06 (br dd, *J* = 7.1, 13.9 Hz, 2H), 3.21 (q, *J* = 7.6 Hz, 2H), 2.91 (s, 3H), 1.47 (t, *J* = 7.6 Hz, 3H), 1.36 (t, *J* = 6.9 Hz, 3H)

Synthesis of Compound 032:

Following a similar procedure to compound **017**, compound **032** was synthesized starting from **int-23**. The starting material was subjected **GP2-3**, **GP5-7**, **GP11-12**, then **GP14**. The crude product was pre-purified by prep-HPLC (column: Phenomenex luna C18 150 x 40mm, 15um; mobile phase: [water(FA)-ACN]; gradient: 20%-50% B over 15 min) the eluent was concentrated and then lyophilized for 12 h. The isolated product was purified further by SFC (column: Phenomenex-Cellulose-2 (250mm x 30mm, 10um); mobile phase: [CO_2-EtOH (0.1%NH_3H_2O)]; B%: 25%, isocratic elution mode). After SFC, the eluent was concentrated to remove organic solvents and the residual aqueous solution was lyophilized. Compound **032** (38.02 mg, 77.00 μmol, 73.07% yield, 96.1% purity) was obtained as brown gum. **LCMS:** 0.469min, 475.2 $[M+H]^+$ ESI pos **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.40 - 12.07 (m, 1H), 8.29 (s, 1H), 8.25 (s, 1H), 7.50 (s, 1H), 7.38 - 7.29 (m, 2H), 7.26 - 7.15 (m, 4H), 7.09 - 6.98 (m, 1H), 6.16 (br d, *J* = 8.9 Hz, 1H), 4.60 - 4.51 (m, 1H), 4.42 (dd, *J* = 5.6, 11.3 Hz, 1H), 3.78 (br s, 1H), 3.22 (q, *J* = 6.8 Hz, 2H), 2.94 (s, 3H), 1.49 (t, *J* = 7.5 Hz, 4H), 0.86 - 0.70 (m, 4H)

Synthesis of Compound 033:

Following a similar procedure to compound **017**, compound **033** was synthesized starting from **int-23**. The starting material was subjected **GP2-3**, **GP5-7**, **GP11-12**, then **GP14**. The crude product was pre-purified by prep-HPLC (column: Phenomenex luna C18

150 x 40mm, 15um; mobile phase: [water (FA)-ACN]; gradient: 22%-52% B over 15 min.) then lyophilized for 12 h. The resulting compound was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 30mm, 10um); mobile phase: [CO_2-EtOH (0.1%NH_3H_2O)]; B%: 35%, isocratic elution mode) the eluent was then concentrated and lyophilized to afford the desired product. Compound **033** (43.04 mg, 84.08 µmol, 60.36% yield, 96.3% purity) was obtained as white solid and by LCMS and ^{1}H-NMR. **LCMS:** t_R = 0.474 min, m/z = 493.2 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ =12.22 (br s, 1H), 8.25 (d, J = 11.3 Hz, 2H), 7.49 (s, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.01 - 6.95 (m, 2H), 6.78 (tt, J = 2.3, 8.9 Hz, 1H), 6.16 (br dd, J = 5.4, 9.0 Hz, 1H), 4.57 - 4.50 (m, 1H), 4.45 - 4.38 (m, 1H), 3.77 (br d, J = 3.2 Hz, 1H), 3.18 (q, J = 7.6 Hz, 2H), 2.92 (s, 3H), 1.46 (t, J = 7.6 Hz, 3H), 0.85 - 0.69 (m, 4H). **SFC:** 100% ee.

Synthesis of Compound 034:

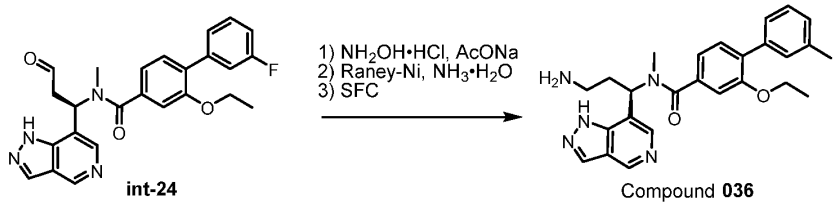
Following an identical procedure to compound **019**, the intermediate isolated after **GP11**, was subject to a modified **GP12**, wherein the solvent is EtOH and under performed under CO atmosphere at 50 psi. The result product was subjected to **GP15**, then **GP13** to afford the crude product. The crude material was pre-purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um; mobile phase: [water (FA)-ACN]; gradient: 15%-45% B over 9 min), and the product was concentrated and lyophilized to give the product. This material was then purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 30mm, 10um); mobile phase: [CO_2-EtOH (0.1%NH_3H_2O)]; B%:40%, isocratic elution mode), and concentrated under reduced pressure to give the product. Compound **034** (46.79 mg, 96.32 µmol, 66.17% yield, 99% purity) was obtained as yellow solid. **LCMS:** t_R = 0.448 min, m/z = 481.1 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.40 (t, J=7.00 Hz, 3 H) 2.44 (s, 3 H) 4.10 (q, J=7.00 Hz, 2 H) 4.40 - 4.53 (m, 2 H) 4.66 (dd, J=11.07, 4.31 Hz, 1 H) 5.13 (s, 2 H) 7.34 - 7.39 (m, 3 H) 7.43 - 7.47 (m, 1 H) 7.55 (d, J=1.50 Hz, 1 H) 7.57 (s, 1 H) 7.61 (dd, J=7.88, 1.50 Hz, 1 H) 8.23 (s, 1 H) 8.33 (s, 1 H).

Synthesis of Compound 035:

Following a similar procedure to compound **034**, compound **035** was isolated and pre-purified before final purification by SFC (column: DAICEL CHIRALPAK IK(250mm x 30mm, 10um); mobile phase: [CO_2-EtOH(0.1%NH_3H_2O)]; B%:35%, isocratic elution mode) and lyophilized to give the product. Compound **035** (41.71 mg, 88.90 µmol, 41.71% yield, 99% purity) was obtained as a white solid. **LCMS:** t_R = 0.427 min, m/z =465.3 $[M+H]^+$ **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 11.90 - 11.41 (m, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.61 (dd, J = 1.4, 7.9 Hz, 1H), 7.55 (d, J = 1.1 Hz, 1H), 7.43 - 7.30 (m, 4H), 7.07 (br d, J = 1.1 Hz, 1H), 5.12 (s, 2H), 4.64 (br d, J = 4.3 Hz, 1H), 4.53 - 4.44 (m, 1H), 4.43 - 4.35 (m, 1H), 4.10 (q, J = 6.9 Hz, 2H), 2.43 (s, 3H), 1.40 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 036:

Starting from **int-11**, the material was subjected to **GP2-8**, followed by oxidation with DMP (1.5 *eq*) in DCM (0.25 M) at 0 °C and stirred for 2 hr. The reaction was filtered, and the filtrate was concentrated to give the crude material which was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1, R_f = 0.7). **Int-24** (25 mg, 50.40 µmol, 64.58% yield, 90% purity) was obtained as a colorless oil. **LCMS:** Rt = 0.457 min, m/z= 447.2 ($M+H^+$).



int-24 Compound **036**

Int-24 (197 mg, 441.24 µmol, 1 *eq*) in EtOH (5 mL) was treated with $NH_2OH.HCl$ (45.99 mg, 661.85 µmol, 1.5 *eq*) and AcONa (54.29 mg, 661.85 µmol, 1.5 *eq*). The reaction mixture was stirred at 40 °C for 12h under N_2. Then the reaction mixture was poured into saturated ice-water (30 mL) and extracted by EA (50 mL x3). The combined organic phase was dried with Na_2SO_4 and concentrated to give the crude product. The crude product was used directly in the next step without further purification. To the crude material (162 mg, 351.04 µmol, 1 eq) in AcOH (2 mL) was added Zinc metal (114.77 mg, 1.76 mmol, 5 eq), the mixture was stirred at 25°C for 12 h under N_2. After 12 h, zinc (229.54 mg, 3.51 mmol, 10 eq) was added again and the reaction was stirred at 25°C for 2 h under N_2. The reaction mixture was filtered, and the filter liquor was basified with 1M (NaOH). The filter cake was basified with 1M (NaOH). The crude product was pre-purified by prep-HPLC (column: Phenomena Luna C18 150 x 25mm, 10um; mobile phase: [water (FA)-ACN]; gradient: 8%-38% B over 9 min), and the product was concentrated and lyophilized to give the semi-purified product. This material was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 30mm, 10um); mobile phase: [CO_2-EtOH (0.1%NH_3H2O)]; B%:60%, isocratic elution mode). Compound **036** (10.85 mg, 23.28 µmol, 65.10% yield, and 96% purity) was obtained as a yellow solid. **LCMS:** t_R = 0.419 min, m/z= 448.3 $[M+H]^+$. **NMR:** ^1H NMR (400 MHz, CHLOROFORM-d) δ = 9.03 (br s, 1H), 8.47 - 8.09 (m, 2H), 7.31 - 7.20 (m, 3H), 7.04 - 6.89 (m, 3H), 6.34 (br dd, J = 2.0, 3.5 Hz, 1H), 4.04 - 3.91 (m, 2H), 3.06 - 2.86 (m, 2H), 2.79 - 2.63 (m, 3H), 2.60 - 2.49 (m, 1H), 2.33 (br d, J = 3.5 Hz, 1H), 2.09 - 1.87 (m, 1H), 1.28 (br t, J = 6.9 Hz, 3H), 1.19 (br d, J = 5.0 Hz, 2H).

Synthesis of Compound 037:

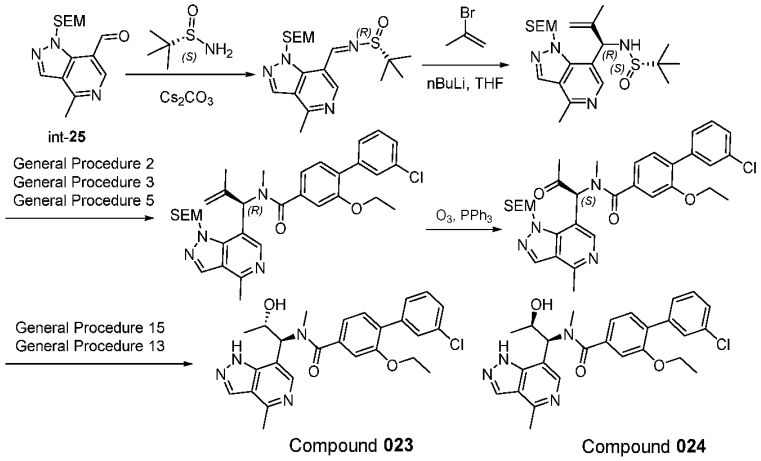
To a solution of intermediate **24** (20 mg, 44.80 µmol, 1 eq) in MeOH (2 mL) was added $MeNH_2$ (2 M, 67.19 µL, 3.00 eq), the reaction mixture was stirred at 20 °C for 2 hr. Then $NaBH_4$ (3.39 mg, 89.59 µmol, 2 eq) was added to the solution slowly at 0 °C, the reaction mixture was stirred at 20 °C for 1 hr. After the reaction was completed, the reaction

mixture was poured into NH_4Cl (3 mL) at 0°C, filtered, the filtrate was concentrated under reduced pressure to give a residue. Then the solution was triturated in DCM/MeOH=10:1) and collected by filtration, the filtrate was concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters X bridge 150 x 25mm, 5um; mobile phase: [water (NH_4OH)-ACN]; gradient: 18%-48% B over 10 min). Compound **037** (4.74 mg, 10.27 μmol, 22.93% yield, and 100% purity) was obtained as a white solid. **LCMS:** t_R = 0.565 min, m/z= 462.3 $[M+H]^+$. **NMR:** ^1H NMR (400 MHz, CHLOROFORM-d) δ = 9.09 (br s, 1H), 8.38 - 8.20 (m, 2H), 7.46 - 7.33 (m, 4H), 7.10 - 7.03 (m, 3H), 4.27 - 3.94 (m, 4H), 3.84 (br s, 2H), 3.45 - 3.16 (m, 1H), 3.01 (s, 3H), 2.37 - 2.27 (m, 4H), 1.41 - 1.37 (m, 3H).

Synthesis of Compound 038:

To a solution of Intermediate **24** (60 mg, 134.39 μmol, 1 eq) in MeOH (1.5 mL) was added dimethylamine (2 M, 1.5 mL, 22.32 eq), the reaction mixture was stirred at 20 °C for 11 h. Then $NaBH_4$ (10.17 mg, 268.77 μmol, 2 eq) was added to the solution slowly at 0 °C, the reaction mixture was stirred at 20 °C for 1 h. After the reaction was completed, the reaction mixture was poured into NH_4Cl (10 mL) at 0°C, filtered, the filtrate was concentrated under reduced pressure to give a residue. Then the solution was triturated in DCM/MeOH=10:1) and collected by filtration, the filtrate was concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC(column: Phenomenex luna C18 150 x 25mm, 10um;mobile phase: [water(FA)-ACN]; gradient:5%-35% B over 9 min) and lyophilized to give the product. Compound **038** (10.74 mg, 19.97 μmol, 14.86% yield, 97% purity, FA) was obtained as a yellow solid. **LCMS:** t_R = 0.417 min, m/z =476.3 $[M+H]^+$ **NMR:** ^1H NMR (400 MHz, CHLOROFORM-d) δ = 9.14 (br s, 1H), 8.45 (br s, 1H), 8.34 - 8.18 (m, 1H), 7.45 - 7.29 (m, 4H), 7.20 - 6.97 (m, 3H), 6.31 (br s, 1H), 4.28 - 3.91 (m, 2H), 2.88 (br s, 3H), 2.69 (br d, J = 11.3 Hz, 2H), 2.49 (br s, 6H), 1.49 - 1.31 (m, 3H)

Synthesis of Compound 023 & 024:



To a solution of int-**25** (2 g, 6.86 mmol, 1 eq), int-**4** (914.97 mg, 7.55 mmol, 1.1 eq) in DCM (30 mL) was added Cs_2CO_3 (2.68 g, 8.24 mmol, 1.2 eq), the reaction was stirred at 20 °C for 12 h. TLC (PE:EtOAc=0:1;UV&DNP) showed starting material was consumed up and new spot was formed. The reaction was filtered and concentrated to give a crude product. The crude product was purified by silica gel chromatography (50% EtOAc in PE, R_f=0.60).

To a solution of 2-bromoprop-1-ene (827.75 mg, 6.84 mmol, 607.74 µL, 1.2 eq) in THF (20 mL) was added *n*-BuLi (2.5 M, 5.47 mL, 2.4 eq) at -70 °C under N_2 protected, then stirred at -70 °C for 0.5 h, then a solution of the purified compound from the prior step (2.5 g, 5.70 mmol, 1 eq) in THF (5 mL) was added dropwise to this reaction, the reaction was stirred at -70 °C for 1 h. LCMS showed starting material was consumed up and desire product was detected. The solution was slowly poured into saturated aqueous NH_4Cl (300 mL) at 0°C under N_2. The layers were separated, the aqueous layer was extracted in EtOAc (100 mL x 3), the combined organics were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuo to give the crude residue. The crude product was purified by silica gel chromatography (7% EtOAc in MeOH, R_f=0.10) to give a product.

The product was subjected to **GP2**, **GP3**, and **GP5** to give the intermediate amide product. The product (140 mg, 231.31 µmol, 1 eq) was dissolved in DCM (3 mL) and MeOH (3 mL) was treated with ozone (11.10 mg, 231.31 µmol, 1 eq) at -70 °C for 0.5 h, then the mixture was purged with nitrogen 3 times, PPh_3 (121.34 mg, 462.63 µmol, 2 eq) was dissolved in DCM (1 mL) was added dropwise to the mixture at -70 °C. The mixture was warmed to 20 °C and stirred at 20 °C for 1 h. TLC (PE: EtOAc=0:1; UV) showed starting material was consumed up and new spots were formed. The reaction was concentrated to give a crude product. The crude product was purified by silica gel chromatography (35% EtOAc in PE, Rf=0.80) to give a product. This product was subjected to **GP15** followed by **GP13** and the resulting crude mixture was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 32%-62% B over 15 min) and lyophilized.

Compound **023** (2.13 mg, 4.45 µmol, 10.84% yield, and 100% purity) was obtained as white solid. **LCMS:** t_R = 0.493 min, m/z =479.3 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.27 - 11.88 (m, 1H), 8.35 - 8.04 (m, 2H), 7.55 - 7.45 (m, 1H), 7.43 - 7.35 (m, 1H), 7.30 (br d, *J* = 3.8 Hz, 2H), 7.19 (br s, 1H), 7.14 - 6.90 (m, 2H), 5.77 - 5.38 (m, 1H), 4.99 - 4.63 (m, 1H), 4.19 - 3.82 (m, 2H), 2.91 (br d, *J* = 14.9 Hz, 3H), 2.86 - 2.74 (m, 3H), 1.38 (br d, *J* = 13.0 Hz, 3H), 1.35 - 1.23 (m, 3H)

Compound **024** (5.08 mg, 10.61 µmol, 25.85% yield, and 100% purity) was obtained as white solid. **LCMS:** t_R = 0.502 min, m/z =479.3 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.16 - 11.85 (m, 1H), 8.39 (br s, 1H), 8.23 (s, 1H), 7.53 (s, 1H), 7.40 (s, 1H), 7.32 (br d, *J* = 5.9 Hz, 3H), 7.06 - 7.00 (m, 2H), 5.94 - 5.69 (m, 1H), 5.07 - 4.75 (m,

1H), 4.05 (br dd, *J* = 6.9, 12.9 Hz, 2H), 2.85 (s, 3H), 2.83 (s, 3H), 1.57 - 1.52 (m, 3H), 1.36 (t, *J* = 6.9 Hz, 3H).

Synthesis of Compound 163

Compound **163** was prepared following the procedure for Compound **145** using Compound **098** as starting material. Compound **163** (64.95 mg, 127.85 µmol, 57.19% yield, 100% purity) was obtained as a white solid. **LCMS**: RT=0.527 min, m/z=508.1 [M+H]+ **^{1}H NMR** (400 MHz, METHANOL-d4) δ = 9.14 (s, 1H), 8.52 (br s, 1H), 8.42 (s, 1H), 8.34 - 8.21 (m, 1H), 7.53 (br s, 1H), 7.44 - 7.30 (m, 4H), 7.15 (br s, 2H), 6.35 (br s, 1H), 4.08 (br s, 2H), 3.79 - 3.55 (m, 2H), 3.38 (br s, 6H), 3.14 - 2.99 (m, 1H), 2.89 (br s, 4H), 1.32 (br s, 3H).

Synthesis of Compound 164

Compound **164** was prepared following the procedure for Compound **145** using Compound **091** as starting material. Compound **164** (33 mg, 67.68 µmol, 45.60% yield, 98.5% purity) was obtained as off-white solid. **LCMS**: Rt =0.459min, m/z=488.1(M+H+). **^{1}H NMR**:(400 MHz, CHLOROFORM-d) δ = 9.12 (s, 1H), 8.50 (br s, 1H), 8.26 (s, 1H), 7.33 (br s, 3H), 7.30 (br d, J = 7.6 Hz, 1H), 7.18 - 7.09 (m, 3H), 6.30 (br s, 1H), 4.06 (br dd, J = 7.2, 11.2 Hz, 2H), 3.58 (br s, 2H), 3.42 - 3.33 (m, 6H), 3.18 (br dd, J = 2.0, 3.2 Hz, 2H), 2.91 (br s, 3H), 2.39 (s, 3H), 1.35 (br t, J = 6.4 Hz, 3H).

Synthesis of Compound 165

Compound **165** was prepared following the procedure for Compound **145** using Compound **102** as starting material. Compound **165** (53.24 mg, 103.01 µmol, 50.22% yield, 97.43% purity) as a white solid. **LCMS**: Rt =0.471min, m/z=504.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.16 (br s, 1H), 8.51 (br s, 1H), 8.34 (br s, 1H), 8.28 (s, 1H), 7.52 (s, 1H), 7.39 - 7.31 (m, 2H), 7.25 - 7.15 (m, 3H), 7.03 (dt, J = 2.0, 8.4 Hz, 1H), 6.28 (br dd, J = 5.2, 10.2 Hz, 1H), 3.90 - 3.81 (m, 2H), 3.65 (br dd, J = 6.6, 11.6 Hz, 1H), 3.55 (s, 3H), 3.45 (s, 3H), 3.33 (m, 1H), 2.95 (s, 3H), 2.84 - 2.76 (m, 1H), 0.87 - 0.69 (m, 4H).

Synthesis of Compound 166

Compound **166** was prepared following the procedure for Compound **145** using Compound **096** as starting material. Compound **166** (43.06 mg, 90.56 µmol, 27.63% yield, 99.6% purity) was obtained as off-white solid. **LCMS**: RT=0.419 min, m/z= 474.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.06 (s, 1H), 8.43 (s, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.34 - 7.29 (m, 2H), 7.28 - 7.24 (m, 2H), 7.10 - 7.05 (m, 2H), 6.20 (dd, J = 4.4, 9.2 Hz, 1H), 4.08 - 3.89 (m, 2H), 3.85 - 3.76 (m, 1H), 3.62 (dd, J = 7.2, 10.4 Hz, 1H), 3.48 (s, 3H), 3.39 (s, 3H), 3.19 (d, J = 10.4 Hz, 1H), 2.84 (s, 3H), 2.69 (t, J = 12.0 Hz, 1H), 1.26 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 041–062 (*N*-substituted):

Synthesis of Compound 041:

Compound **041** was synthesized starting from int-**26**. Intermediate **26** was subjected to **GP16**, **GP5**, **GP8**, and finally **GP13** resulting in crude **041**. The crude product was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um;mobile phase: [water(NH_4HCO_3)-ACN]; gradient:20%-50% B over 15 min) lyophilization for 12 h. Compound **041** (31.85 mg, 72.94 µmol, 21.72% yield, 99.5% purity) was obtained as white solid. **LCMS:** t_R = 0.447min, 456.1 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.02 (br s, 1H), 12.08 - 11.93 (m, 1H), 9.05 (br s, 1H), 8.31 (br s, 1H), 8.20 (s, 1H), 7.32 - 7.21 (m, 4H), 7.03 - 6.99 (m, 2H), 6.98 - 6.94 (m, 1H), 5.08 (s, 2H), 3.97 (br d, *J* = 6.6 Hz, 2H), 3.84 (br s, 2H), 3.44 (br s, 2H), 1.29 (t, *J* = 6.9 Hz, 3H), 1.19 (br s, 1H).

Synthesis of Compound 042:

Compound **042** was synthesized by following a similar procedure to compound **041**. Intermediate **26** was subjected to **GP16**, **GP5**, **GP8**, and finally **GP13** resulting in crude **042**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 25%-55% B over 15 min) and lyophilization to give 20 mg product. Then the product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN]; gradient:18%-48% B over 9 min) and lyophilization. Compound **042** (14.35 mg, 31.82 µmol, 44.26% yield, 100% purity) was obtained as yellow gum. **LCMS:** t_R = 0.455min, m/z=451.2 $[M+H]^+$. **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.32 - 11.97 (m, 1H), 8.45 - 8.23 (m, 1H), 7.56 (s, 1H), 7.46 - 7.41 (m, 1H), 7.37 - 7.32 (m, 3H), 7.29 (s, 3H), 7.14 - 7.06 (m, 2H), 5.20 (br s, 2H), 4.07 (q,M*J* = 6.6 Hz, 2H), 3.97 - 3.82 (m, 2H), 3.52 (br s, 2H), 1.38 (t, *J* = 6.9 Hz, 3H)

Synthesis of Compound 043:

Compound **043** was synthesized by following a similar procedure to compound **041**. Intermediate **26** was subjected to **GP16**, **GP5**, then a modified protocol of **GP8** was used. The modified protocol utilized the following conditions: tert-butyl carbamate (5 *eq*) and Cs_2CO_3 (2 *eq*) and $Pd(OAc)_2$ (0.1 *eq*) and Xantphos (0.2 *eq*). The reaction mixture was stirred at 100°C for 12h under N_2. After isolation of the product finally **GP13** was utilized resulting in crude **043**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(ammonia hydroxide v/v)-ACN]; gradient: 10%-40% B over 10 min) and lyophilization. Compound **043** (13.12 mg, 28.74 µmol, 11.51% yield, 100% purity) was obtained as white solid. **LCMS**: t_R = 0.438 min, m/z = 457.3 $[M+H]^+$. **NMR**: ^{1}H NMR (METHANOL-d4, 400MHz): δ = 8.25 (br s, 1H), 7.79-7.96 (m, 2H), 7.65-7.76 (m, 2H), 7.53-7.64 (m, 1H), 7.32-7.47 (m, 1H), 7.18-7.33 (m, 1H), 6.98-7.17 (m, 1H), 4.95-4.96 (m, 1H), 4.96 (br s, 2H), 4.20-4.25 (m, 1H), 4.04-4.21 (m, 1H), 3.69-3.82 (m, 2H), 3.41-3.55 (m, 1H), 1.33 ppm (br d,*J*=17.5 Hz, 3H).

Synthesis of Compound 044:

Compound **044** was synthesized by following a similar procedure to compound **043**. Intermediate **26** was subjected to **GP16**, **GP5**, then a modified protocol of **GP8** was used. The modified protocol utilized DMSO as the solvent, and the following reagents: methanamine-hydrochloride (3 *eq*), rac-(2S)-pyrrolidine-2-carboxylic acid (0.2 *eq*), CuI (0.2 *eq*) and K_2CO_3 (2 *eq*). The reaction mixture was stirred at 100 °C for 12 h under N_2. The isolated product was subjected to **GP13** resulting in crude **044**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient: 13%-43% B over 10 min) and lyophilization. Compound **044** (20.72 mg, 41.70 µmol, 49.70% yield, 94.7% purity) was obtained as white solid. **LCMS:** t_R = 0.411 min, m/z = 471.2 $[M+H]^+$. **NMR**: ^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 11.90 (br s, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 7.74 (d, *J*=7.9 Hz, 1H), 7.58-7.65 (m, 1H), 7.47-7.54 (m, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 7.06-7.14 (m, 2H), 5.11 (br d, *J*=1.8 Hz, 1H), 4.93 (s, 2H), 4.04 (q, *J*=6.8 Hz, 2H), 3.86 (br t, *J*=5.2 Hz, 2H), 3.49 (br d, *J*=5.1 Hz, 2H), 3.19 (br d, *J*=3.3 Hz, 3H), 1.33 ppm (t, *J*=6.9 Hz, 3H).

Synthesis of Compound 045:

Compound **045** was synthesized starting from intermediate **28**. Int-**28** was subjected to **GP17** (amine = 2-(benzyloxy)cyclopropan-1-amine), **GP5**, then finally **GP14** resulting in the crude residue of compound **045**. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150 x 30mm, 7um; mobile phase: [water(FA)-ACN]; gradient: 20%-50% B over 10 min). The eluent was lyophilized to afford compound **045** (73 mg, 158.52 µmol, 27.68% yield, 100% purity) as white solid. **LCMS**: t_R = 0.440 min, m/z = 461.3 $[M+H]^+$. **NMR**: ^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 8.44 (s, 1H), 8.26 (s, 1H), 7.34-7.42 (m, 2H), 7.28-7.33 (m, 2H), 7.11-7.17 (m, 2H), 7.01-7.08 (m, 1H), 5.19 (d, *J*=14.3 Hz, 1H), 4.82 (d, *J*=14.4 Hz, 1H), 4.07 (q,*J*=6.9 Hz, 2H), 3.12 (br dd, *J*=6.0, 4.0 Hz, 1H), 2.89 (s, 4H), 1.38 (t, *J*=7.0 Hz, 3H), 1.00 (td, *J*=7.9, 4.2 Hz, 1H), 0.57-0.70 ppm (m, 1H)

Synthesis of Compound 046:

Compound **046** was synthesized by following a similar procedure to compound **043**. Intermediate **26** was subjected to **GP16**, **GP5**, then a modified protocol of **GP8** was used. The modified protocol utilized NH_2Boc (5 *eq*) in dioxane (0.05 M) was added Cs_2CO_3 (3 *eq*) and Xantphos Pd G_4 (0.1 *eq*), the mixture was stirred at 100 °C for 12 h under N_2. The isolated product was subjected to **GP13** resulting in crude **046**. The residue was purified by pre-HPLC (column: Waters Xbridge 150 x 25mm, 5um;mobile phase: [water(NH_4HCO_3)-ACN];gradient:28%-58% B over 9 min), lyophilized. The residue was purified by SFC (column: DAICEL CHIRALPAK IC(250mm x 30mm,10um); mobile phase: [CO_2-ACN/i-PrOH(0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode), lyophilized. Compound **046** (26.95 mg, 56.86 µmol, 24.10% yield, 98.3% purity) was obtained as an off-white solid. **LCMS**: t_R =

0.461 min, m/z=466.1 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.07 (s, 1H), 7.81 - 7.66 (m, 1H), 7.54 (s, 1H), 7.41 (br d, *J* = 6.9 Hz, 1H), 7.32 (br t, *J* = 5.8 Hz, 3H), 7.07 (br d, *J* = 6.5 Hz, 2H), 5.48 - 5.35 (m, 1H), 4.96 (br s, 2H), 4.08 - 4.00 (m, 2H), 3.87 (br s, 2H), 3.54 - 3.43 (m, 2H), 1.35 (br t, *J* = 6.9 Hz, 3H).

Synthesis of Compound 047:

Compound **047** was synthesized by following a similar procedure to compound **047** where the sole modification was the choice of acid used during the secondary amine coupling reaction (**GP5**). The resulting crude residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 22%-52% B over 9 min), lyophilized. Compound **047** (32.84 mg, 73.06 µmol, 37.10% yield, 100% purity) was obtained as a white solid, **LCMS**: t_R = 0.445 min, m/z = 450.1 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.44 - 11.59 (m, 1H), 8.05 (s, 1H), 7.76 (s, 1H), 7.41 - 7.28 (m, 4H), 7.12 - 6.96 (m, 3H), 5.28 - 5.11 (m, 2H), 4.97 (s, 2H), 4.04 (q, *J* = 6.6 Hz, 2H), 3.88 (br s, 2H), 3.53 - 3.42 (m, 2H), 1.35 (t, *J* = 6.9 Hz, 3H).

Synthesis of Compound 048:

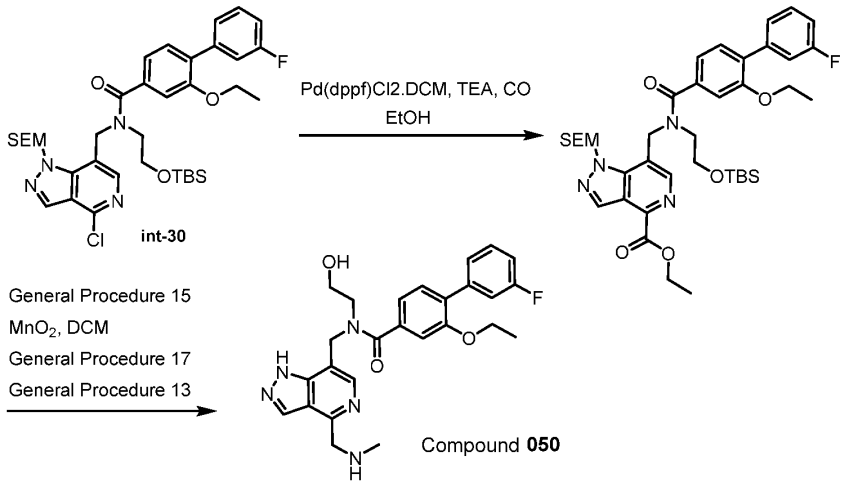
Compound **048** was synthesized by following a similar procedure to compound **043**. Intermediate **26** was subjected to **GP16**, **GP5**, then a modified protocol of **GP8** was used. The modified protocol utilized methanamine-hydrochloride (5 *eq*) in DMSO (0.05 M) was added K_2CO_3 (3 *eq*) and CuI (0.2 *eq*), and L-Proline (0.2 *eq*) the mixture was stirred at 100 °C for 12 h under N_2. The isolated product was subjected to **GP13** resulting in crude **048**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 28%-58% B over 9 min), lyophilized. Compound **048** (13.89 mg, 29.97 µmol, 25.69% yield, 100% purity) was obtained as a white solid. **LCMS**: t_R = 0.447 min, m/z = 464.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.06 (s, 1H), 7.81 (s, 1H), 7.40 - 7.29 (m, 4H), 7.10 - 7.00 (m, 3H), 5.54 - 5.25 (m, 1H), 4.95 (s, 2H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.87 (br t, *J* = 5.2 Hz, 2H), 3.51 (br d, *J* = 5.0 Hz, 2H), 3.22 (br s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H).

Synthesis of Compound 049:

Compound **049** was synthesized by following a similar procedure to compound **047** where the sole modification was the choice of acid used during the secondary amine coupling reaction (**GP5**). The resulting residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient: 23%-53% B over 10 min) and lyophilization. Compound **049** (27.15 mg, 53.29 µmol, 48.26% yield, 94.2% purity) was obtained as white solid. **LCMS:** t_R = 0.469 min, m/z = 480.3$[M+H]^+$. **NMR**: ^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 11.73-12.28 (m, 0.5H), 8.03 (s, 0.9H), 7.80 (s, 1.0H), 7.53 (s, 1.1H), 7.37-7.44 (m, 1.1H), 7.29-7.34 (m, 3.0H), 7.00-7.11 (m, 2.1H), 5.12-

5.22 (m, 1.0H), 4.91-4.92 (m, 1.0H), 4.93 (s, 2.0H), 4.03 (q, *J*=6.6 Hz, 2.0H), 3.86 (br t, *J*=5.1 Hz, 2.1H), 3.45-3.57 (m, 2.1H), 3.20 (d, *J*=4.5 Hz, 3.0H), 1.34 ppm (t, *J*=7.0 Hz, 4.0H).

Synthesis of Compound 050:



Compound **050** was synthesized using common intermediate **30** from the synthesis of compound **041**. Intermediate **30** was subjected to a modified **GP12** where the starting material (int-**30**, 1 *eq*) was dissolved in EtOH (0.1 M) and treated with Et_3N (3 *eq*), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.05 *eq*), then degassed and stirred at 80 °C for 12 h under CO (1 *eq*, 50 PSI) atmosphere. The isolated product was then subjected to **GP15**, followed by MnO_2 (20 *eq*) in DCM (0.05 M) for 12 h, then **GP17**, and finally **GP13**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um;mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 18%-48% B over 15 min) and lyophilization. Compound **050** (13.51 mg, 28.29 µmol, 20.43% yield, 100% purity) was obtained as white solid. **LCMS:** t_R = 0.438 min, m/z = 478.2 $[M+H]^+$. **NMR**: ^1H NMR (CHLOROFORM-d, 400MHz): δ = 8.24-8.43 (m, 2H), 7.27-7.40 (m, 4H), 6.92-7.13 (m, 3H), 5.03-5.21 (m, 2H), 4.27 (s, 2H), 3.97-4.09 (m, 2H), 3.77-3.91 (m, 2H), 3.40-3.56 (m, 2H), 2.57-2.67 (m, 2H), 1.34 ppm (br t, *J*=6.9 Hz, 3H)

Synthesis of Compound 051:

Compound **051** was synthesized by following a similar procedure to compound **041**. Intermediate **26** was subjected to **GP16**, **GP5**, **GP12**, and finally **GP13**. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150 x 25mm,10um; mobile phase: [water(FA)-ACN]; gradient: 18%-48% B over 9 min), and the product was concentrated and lyophilized to give the product. Compound **051** (43.11 mg, 96.12 µmol, 33.31% yield, 100% purity) was obtained as white solid. **LCMS**: t_R = 0.451min, m/z = 449.2 $[M+H]^+$. **NMR**: ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.36 (t, J=6.88 Hz, 3 H) 2.93 (s, 3 H) 3.52 (br s, 2 H) 3.91 (br d, J=4.00 Hz, 2 H) 4.00 - 4.11 (m, 2 H) 5.16 (s, 2 H) 7.02 - 7.09 (m, 3 H) 7.28 - 7.38 (m, 4 H) 8.30 (s, 1 H) 8.41 (br s, 1 H).

Synthesis of Compound 052:

Compound **052** was synthesized by following a similar procedure to compound **041**. Intermediate **26** was subjected to **GP16**, **GP4**, **GP5**, **GP12**, and finally **GP13**. The crude product was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um;mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 30%-60% B over 9 min) to give the product compound **052** (66.36 mg, 143.48 μmol, 48.60% yield, 100% purity) as white solid. **LCMS**: t_R = 0.453min, m/z = 463.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.32 - 8.24 (m, 1H), 8.22 (s, 1H), 7.40 - 7.27 (m, 4H), 7.13 - 7.00 (m, 3H), 5.13 (br d, J = 15.0 Hz, 1H), 4.85 (br d, J = 14.5 Hz, 1H), 4.40 (br d, J = 2.8 Hz, 1H), 4.04 (br d, J = 6.0 Hz, 2H), 3.77 (br t, J = 10.3 Hz, 1H), 3.66 - 3.54 (m, 1H), 2.81 (s, 3H), 1.34 (br t, J = 6.7 Hz, 3H), 1.27 - 1.12 (m, 3H)

Synthesis of Compound 053:

Compound **053** was synthesized by following a similar procedure to compound **041**. Intermediate **26** was subjected to **GP16**, **GP4**, **GP5**, **GP12**, **GP13**. The resulting product was then oxidized with DMP (1.5 *eq*) in DCM (0.25 M) at 0 °C and stirred for 2 hr. The reaction was filtered, and the filtrate was concentrated to give the crude material which was purified by flash chromatography. Finally, the resulting oxidized product was subjected to Grignard conditions. The starting material was dissolved in THF and treated with MeMgBr (3 M, 579.08 μL, 5 *eq*) at 0°C. The reaction was stirred at 25 °C for 2 h under N_2. The reaction was quenched with sat. aq. NH_4Cl at 0 °C and extracted with EA (x 3). The organic phases were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The crude product was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 25%-55% B over 15 min). Compound **053** (20.81 mg, 42.58 μmol, 12.25% yield, 97.5% purity) was obtained as white solid. **LCMS**: t_R = 0.459min, m/z = 477.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 11.75 (br dd, *J* = 5.1, 7.3 Hz, 1H), 8.44 - 8.35 (m, 1H), 8.23 (s, 1H), 7.40 - 7.33 (m, 1H), 7.32 - 7.28 (m, 2H), 7.28 - 7.27 (m, 1H), 7.07 - 7.00 (m, 1H), 6.92 - 6.78 (m, 1H), 5.41 (br s, 1H), 5.53 - 5.33 (m, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.40 (br s, 2H), 2.89 (br s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.30 - 1.17 (m, 5H).

Synthesis of Compound 054:

Compound **054** was synthesized starting from intermediate **28**. Int-**28** was subjected to **GP17**, **GP5**, then finally **GP13** resulting in the crude residue of compound **054**. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um; mobile phase: [water(FA)-ACN]; gradient: 18%-48% B over 9 min) and lyophilization for 12 hr. Compound **054** (10.62 mg, 22.74 μmol, 6.92% yield, 98.6% purity) was obtained as white solid. **LCMS**: t_R = 0.449min, m/z = 461.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.24 (s, 1H), 7.94 - 7.83 (m, 1H), 7.41 - 7.34 (m, 1H), 7.34 - 7.28 (m, 1H), 7.29 - 7.28

(m, 1H), 7.07 - 7.03 (m, 1H), 6.84 - 6.80 (m, 2H), 5.18 - 5.07 (m, 1H), 5.02 (br s, 1H), 4.90 (br s, 1H), 5.06 - 4.78 (m, 1H), 4.20 (br s, 1H), 3.93 (br d, *J* = 7.0 Hz, 2H), 2.90 (br s, 3H), 1.33 (t, *J* = 6.8 Hz, 4H).

Synthesis of Compound 055:

Compound **055** was synthesized by following a similar procedure to compound **041**. Intermediate **26** was subjected to **GP16**, **GP5**, **GP8**, and finally **GP13** resulting in crude **055**. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm, 5um;mobile phase: [water(NH_4HCO_3)-ACN];gradient:25%-55% B over 9 min), and lyophilized to afford compound **055** (12.03 mg, 27.20 µmol, 18.05% yield, 98% purity) which was obtained as a brown gum. **LCMS**: t_R = 0.406 min, m/z = 434.2 $[M+H]^+$. **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.11 (br d, *J* = 3.1 Hz, 1H), 8.25 (br s, 2H), 7.39 - 7.28 (m, 4H), 7.03 (br t, *J* = 7.0 Hz, 3H), 5.03 (br s, 2H), 4.09 - 3.95 (m, 2H), 3.59 - 3.33 (m, 2H), 3.00 (br s, 2H), 1.35 (br t, *J* = 6.7 Hz, 3H).

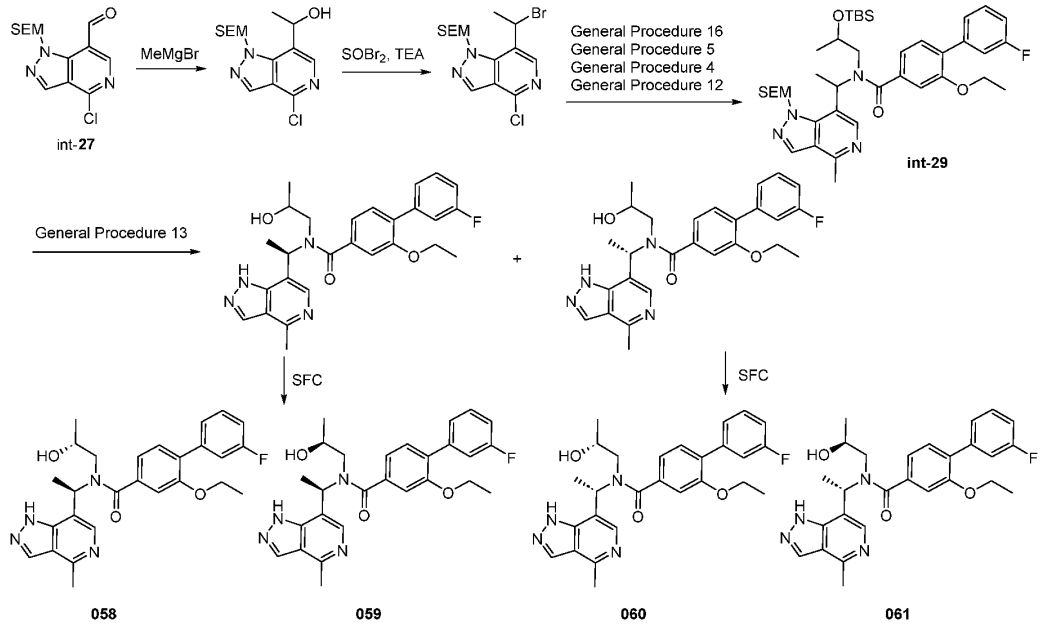
Synthesis of Compound 056 & 057:

Compounds **056** and **057** were synthesized by following a similar procedure to compound **054**. Intermediate **28** was subjected to **GP17**, **GP5**, and finally **GP13** resulting in the crude mixture of **056** and **057**. The product was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 50mm, 10um); mobile phase: [CO_2-i-PrOH (0.1%NH_3H_2O)]; B%: 32%, isocratic elution mode). After SFC, the eluents were concentrated to remove organic solvents and the residual aqueous solutions were lyophilized.

Compound 056 (23.7 mg, 49.10 µmol, 23.30% yield, 98.3% purity) was obtained as off-white solid. **LCMS:** t_R = 0.472 min, m/z =4 75.3$[M+H]^+$ **NMR:** ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.50 - 11.97 (m, 1H), 8.23 - 8.14 (m, 2H), 7.45 - 7.31 (m, 5H), 7.14 - 7.03 (m, 3H), 5.42 - 5.24 (m, 1H), 4.92 - 4.76 (m, 1H), 4.67 - 4.52 (m, 1H), 4.39 - 4.26 (m, 1H), 4.19 - 4.03 (m, 3H), 2.59 - 2.42 (m, 3H), 2.25 - 2.10 (m, 2H), 1.85 - 1.80 (m, 1H), 1.82 - 1.79 (m, 1H), 1.55 - 1.44 (m, 2H), 1.39 (t, J = 6.8 Hz, 4H) **SFC**: 100% ee.

Compound **057** (38.37 mg, 79.81 µmol, 37.87% yield, 98.7% purity) was obtained as off-white solid. **LCMS:** t_R = 0.467 min, m/z = 475.3 $[M+H]^+$. **^{1}H NMR:** (400 MHz, CHLOROFORM-d) δ = 12.48 - 12.13 (m, 1H), 8.12 (s, 1H), 8.18 - 8.11 (m, 1H), 7.44 - 7.28 (m, 5H), 7.13 - 7.02 (m, 3H), 5.43 - 5.19 (m, 1H), 4.87 - 4.68 (m, 1H), 4.60 (br s, 1H), 4.33 (br s, 1H), 4.08 (quin, J = 6.7 Hz, 2H), 2.38 (br s, 3H), 2.16 (br s, 1H), 1.87 - 1.79 (m, 2H), 1.52 - 1.43 (m, 1H), 1.38 (t, J = 6.9 Hz, 3H), 1.26 (br d, J = 4.8 Hz, 1H).

Synthesis of Compound 058, 059, 060, and 061:



Compound **058–061** were synthesized using the synthetic procedure shown above. Int-**27** (1 *eq*) in THF (0.2M) was treated with MeMgBr (3 M, 3 *eq*) at -70 °C and stirred for 2 h. The resulting crude product was purified by silica gel chromatography. The purified product was dissolved in DCM and treated with Et_3N (2 *eq*) and then $SOBr_2$ (2 eq) at 0 °C. The reaction was stirred at 20 °C for 12 h under N_2 atmosphere. The crude product was purified by silica gel chromatography. The isolated compound was then subject to **GP16**, **GP5**, **GP4**, then **GP12** to afford int-**29**. Intermediate **29** was then subject to **GP13** followed by purification by SFC to afford the 4 corresponding products.

Compound 058: LCMS: t_R = 0.461 min, m/z = 477.3 $[M+H]^+$. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.23 (s, 1H), 8.18 - 8.06 (m, 1H), 7.41 - 7.32 (m, 1H), 7.30 - 7.24 (m, 4H), 7.07 - 6.99 (m, 1H), 6.90 (br s, 2H), 3.99 (br s, 2H), 3.79 - 3.36 (m, 4H), 2.89 (br s, 3H), 1.93 (br d, J = 6.8 Hz, 3H), 1.34 (br t, J = 6.9 Hz, 3H), 1.04 (br s, 2H). **SFC:** 100% ee.

Compound 059: LCMS: t_R = 0.467 min, m/z = 477.3 $[M+H]^+$. **^{1}H NMR:** (400 MHz, CHLOROFORM-d) δ = 8.23 (s, 1H), 8.33 - 8.08 (m, 1H), 7.37 - 7.34 (m, 1H), 7.39 - 7.25 (m, 4H), 7.06 - 7.01 (m, 1H), 6.94 (br s, 2H), 4.00 (br s, 2H), 3.53 (br s, 3H), 3.41 (br s, 1H), 2.88 (br s, 3H), 1.93 (br d, J = 7.0 Hz, 3H), 1.35 (t, J = 6.9 Hz, 3H), 0.97 (br s, 2H). **SFC:** 97.95% ee.

Compound 060: LCMS: t_R = 0.464 min, m/z = 477.3 $(M+H^+)$ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.30 (br s, 2H), 7.38 - 7.35 (m, 1H), 7.39 - 7.34 (m, 1H), 7.33 - 7.27 (m, 1H), 7.38 - 7.24 (m, 4H), 7.12 (br s, 1H), 7.06 - 7.00 (m, 1H), 5.80 - 5.57 (m, 1H), 4.03 (br s, 3H), 3.87 - 3.50 (m, 2H), 3.47 - 3.35 (m, 1H), 2.99 (br s, 3H), 1.97 (br d, J = 6.7 Hz, 3H), 1.40 - 1.31 (m, 3H), 1.04 (br s, 1H), 1.08 - 0.99 (m, 1H). **EE:** 99.56%.

Compound 061: LCMS: t_R = 0.474 min, m/z = 477.3 $[M+H]^+$ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.27 (s, 1H), 8.41 - 8.22 (m, 1H), 7.38 - 7.31 (m, 1H), 7.41 - 7.31 (m, 1H), 7.31 - 7.26 (m, 4H), 7.13 (br s, 1H), 7.06 - 7.00 (m, 1H), 5.71 (br s, 1H), 4.03 (br s, 3H), 3.61 (br s, 2H), 3.46 - 3.31 (m, 1H), 3.00 - 2.90 (m, 1H), 2.94 (br s, 2H), 1.96 (br d, J = 6.7 Hz, 3H), 1.38 - 1.26 (m, 3H), 1.08 - 1.01 (m, 1H), 1.03 (br s, 1H). **SFC:** 99.10% ee.

Synthesis of Compound 062:

Compound **062** was synthesized starting from int-**29** (above). Intermediate **29** was dissolved in DCM (0.1 M) and treated with DMP (3 *eq*) at 0 °C. The reaction was stirred for 1.5 h. The reaction was worked-up and the crude product was purified by prep-HPLC. The purified product was then dissolved in THF (0.15 M) and treated with MeMgBr (3 M, 5 *eq*) at 0 °C. The mixture was stirred at 20 °C for 2 h. The reaction was quenched with sat. NH4Cl (50 mL)at 0 °C and extracted with EA (x3). The organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by preparative HPLC (column: Waters Xbridge 150 x 25mm, 5um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient:36%-66% B over 9 min), LCMS showed the product was not clean and therefore was re-purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm, 10um;mobile phase: [water(FA)-ACN]; gradient: 15%-45% B over 9 min). Compound **062** (1.62 mg, 3.30 µmol, 2.09% yield, 100% purity) was obtained as white solid. **LCMS:** t_R = 0.475 min, m/z= 491.3 $[M+H]^+$. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.35 - 8.19 (m, 2H), 7.34 (dd, *J* = 6.0, 8.0 Hz, 2H), 7.24 (br s, 3H), 7.08 - 6.97 (m, 2H), 6.85 (br s, 1H), 4.12 - 3.90 (m, 2H), 2.84 (br s, 2H), 1.96 (br d, *J* = 7.0 Hz, 3H), 1.32 (br s, 6H), 1.25 (br s, 3H).

Synthesis of Compound 063

Compound **063** was prepared in a similar manner to the scheme shown for Compound **067** using 2-fluoroethan-1-amine. Compound **063** was isolated as a white solid (76.02 mg, 146.33 µmol, 32.67% yield, 95% purity). **LCMS**: RT= 0.432 min, m/z= 494.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.38 - 11.58 (m, 1H), 9.04 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 7.32 - 7.24 (m, 2H), 7.23 - 7.19 (m, 2H), 7.01 - 6.92 (m, 3H), 6.32 (br dd, J = 5.3, 10.0 Hz, 1H), 4.56 (t, J = 4.8 Hz, 1H), 4.45 (t, J = 4.8 Hz, 1H), 3.98 (br dd, J = 7.2, 15.4 Hz, 2H), 2.96 (br d, J = 4.6 Hz, 1H), 2.92 - 2.83 (m, 3H), 2.74 (s, 3H), 2.58 - 2.43 (m, 1H), 2.39 - 2.27 (m, 1H), 1.29 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 064

Compound **064** was prepared in a similar manner to the scheme shown for Compound **067** using bis(2-fluoroethyl)amine. Compound **064** was isolated as a white solid (87.64 mg, 164.73 µmol, 38.13% yield, 98.5% purity). **LCMS**: Rt =0.422 min, m/z=540.2[M+H]+ **HPLC**: Rt =1.131 min. **1HNMR**: (400 MHz, CHLOROFORM-d) δ = 12.26 (br d, J = 1.2 Hz, 1H), 9.13 (s, 1H), 8.43 (s, 1H), 8.29 (s, 1H), 7.41 - 7.28 (m, 4H), 7.10 - 7.02

(m, 3H), 6.37 (br dd, J = 4.4, 10.0 Hz, 1H), 4.64 (t, J = 4.8 Hz, 2H), 4.52 (t, J = 4.8 Hz, 2H), 4.14 - 3.99 (m, 2H), 3.02 (t, J = 4.8 Hz, 2H), 2.98 - 2.87 (m, 4H), 2.83 (s, 3H), 2.62 - 2.50 (m, 1H), 2.44 - 2.33 (m, 1H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 066

Compound **066** was prepared according to the scheme shown for Compound **067** using ethylmethyl amine instead of **2**. Compound **066** (17.45 mg, 35.29 µmol, 10.50% yield, 99% purity) was obtained as a white solid. **LCMS**: RT= 0.408 min, m/z= 409.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.03 (s, 1H), 8.36 (s, 1H), 8.18 (s, 1H), 7.32 - 7.24 (m, 2H), 7.24 - 7.17 (m, 2H), 7.06 - 6.90 (m, 3H), 6.22 (br dd, J = 5.0, 8.5 Hz, 1H), 4.11 - 3.88 (m, 2H), 2.76 (s, 3H), 2.68 - 2.48 (m, 5H), 2.37 (br d, J = 5.1 Hz, 1H), 2.32 (s, 3H), 1.29 (br t, J = 6.8 Hz, 3H), 1.06 (br t, J = 7.0 Hz, 3H).

Synthesis of Compound 069

Compound **069** was prepared in a similar manner to Compound **073** below and was isolated as a white solid (75.5 mg, 154.89 µmol, 35.12% yield, 99% purity). **LCMS**: RT = 0.380 min, m/z=483.3 [M+2+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.34 (br t, J=6.94 Hz, 3 H) 2.54 - 2.66 (m, 1 H) 2.73 (s, 6 H) 2.79 - 2.99 (m, 5 H) 3.14 - 3.26 (m, 1 H) 3.97 - 4.19 (m, 2 H) 6.24 (br dd, J=9.32, 4.94 Hz, 1 H) 7.10 - 7.20 (m, 2 H) 7.32 (d, J=7.63 Hz, 1 H) 7.46 - 7.53 (m, 1 H) 7.60 (br d, J=7.75 Hz, 1 H) 7.74 (br d, J=7.88 Hz, 1 H) 7.82 (s, 1 H) 8.28 (s, 1 H) 8.41 (s, 2 H) 8.45 (s, 1 H) 9.13 (s, 1 H).

Synthesis of Compound 070

Compound **070** was prepared following the procedure provided for **077** using 3-fluoroazetidine HCl instead of **2**. Compound **070** (50.30 mg, 94.48 µmol, 21.09% yield, 94.96% purity) was obtained as a white solid. **LCMS**: RT= 0.408 min, m/z= 506.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.05 (s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 7.33 - 7.25 (m, 2H), 7.22 (br d, J = 7.6 Hz, 2H), 7.04 - 6.90 (m, 3H), 6.23 (br dd, J = 5.5, 9.4 Hz, 1H), 5.26 - 4.97 (m, 1H), 3.99 (br dd, J = 7.2, 17.7 Hz, 2H), 3.77 (br dd, J = 6.3, 14.4 Hz, 2H), 3.29 - 3.16 (m, 2H), 2.77 (br s, 1H), 2.74 (s, 3H), 2.71 (br s, 1H), 2.43 - 2.16 (m, 2H), 1.29 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 073

Compound **073** was prepared following the steps of **GP5-8**. The resulting product was then oxidized with DMP (1.5 *eq*) in DCM (0.25 M) at 0 °C and stirred for 2 hr. The reaction was filtered, and the filtrate was concentrated to give the crude material which was purified by flash chromatography. Compound **073** was then prepared following the scheme shown for compound **076**. Compound **073** (142.34 mg, 274.69 µmol, 44.81% yield, 99.5% purity) was obtained as white solid. **LCMS**: Rt =0.396min, m/z=470.3(M+H+). **^{1}H NMR**: (400 MHz, METHANOL-d4) δ = 9.15 (s, 1H), 8.50 (br s, 2H), 8.42 (s, 1H), 7.47 (br s, 1H), 7.41 -

7.33 (m, 4H), 7.32 - 7.25 (m, 2H), 7.15 (br d, J = 7.2 Hz, 1H), 6.33 (br s, 1H), 3.77 (br s, 1H), 3.41 - 3.33 (m, 1H), 2.95 (br s, 7H), 2.73 (br s, 1H), 3.05 - 2.61 (m, 1H), 0.84 - 0.51 (m, 4H).

Synthesis of Compound 074

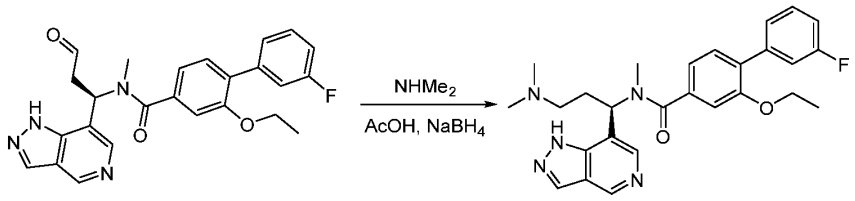
Compound **074** was prepared following the steps of **GP11-13**. The resulting product was then oxidized with DMP (1.5 *eq*) in DCM (0.25 M) at 0 °C and stirred for 2 hr. The reaction was filtered, and the filtrate was concentrated to give the crude material which was purified by flash chromatography. N-methylation was performed by using the oxidized product (190 mg, 429.37 µmol, 1 eq) in DCE (5 mL) was added Me_2NH (2 M, 1.07 mL, 5 eq), AcOH (2.58 mg, 42.94 µmol, 2.46 µL, 0.1 eq) and Molecular sieve 4A (50 mg, 429.37 µmol, 1 eq) stirred at 20°C for 4hr, then added $NaBH(OAc)_3$ (273.00 mg, 1.29 mmol, 3 eq) at 0°C under N_2 and stirred for 12hr. The reaction mixture was poured into water (20 mL) under N_2 and extracted by DCM (20 mL X 3), the organic phase was combined and washed with brine (20 mL X 2), dried with anhydrous Na_2SO_4, filtered and concentrated to give a crude product in vacuo. The residue was purified by prep-HPLC: column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:3%-33% B over 10 min and lyophilization to get the product compound **074** (53.48 mg, 111.92 µmol, 26.07% yield, 98.69% purity) was obtained as a yellow gum. **LCMS**: Rt =0.421 min, m/z=472.3[M+H]+ **HPLC**: Rt =1.040 min **^{1}H NMR** ((400 MHz, CHLOROFORM-d) δ = 8.45 (s, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.46 - 7.31 (m, 4H), 7.16 - 7.10 (m, 2H), 6.22 (br dd, J = 5.6, 9.2 Hz, 1H), 4.14 - 4.03 (m, 2H), 3.04 - 2.95 (m, 1H), 2.86 (s, 6H), 2.81 - 2.69 (m, 2H), 2.61 (s, 6H), 2.58 - 2.47 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 075

Compound **075** was prepared according to the scheme shown for Compound **067** using dimethylamine. A Suzuki-Miyaura Alkylation was then performed according to **GP12** to isolate Compound **075** as a light yellow solid (64.37 mg, 120.18 µmol, 70.45% yield, 100% purity). **LCMS**: RT=0.422 min, m/z=490.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.48 (s, 1H), 8.29 (s, 1H), 8.23 (s, 1H), 7.35 (td, J = 2.9, 7.8 Hz, 2H), 7.31 - 7.27 (m, 2H), 7.15 - 7.08 (m, 2H), 7.03 (s, 1H), 6.21 (br d, J = 3.4 Hz, 1H), 4.18 - 3.98 (m, 2H), 3.01 - 2.89 (m, 1H), 2.88 - 2.82 (m, 6H), 2.79 - 2.64 (m, 2H), 2.57 (s, 6H), 2.54 - 2.47 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 040

Compound **040** was prepared following the steps of **GP4** and **GP11-13**, followed by oxidation with DMP in DCM or IBX in DMSO. The crude was treated and purified in the same manner as Compound **036**. Compound **040** was then prepared according to the following scheme (see also synthesis of Compound 186 below):



7 040

To a solution of compound 7 (60 mg, 134.39 μmol, 1 eq) in MeOH (1.5 mL) was added dimethylamine (2 M, 1.5 mL, 22.32 eq), the reaction mixture was stirred at 20 °C for 11 hr. Then NaBH4 (10.17 mg, 268.77 μmol, 2 eq) was added to the solution slowly at 0 °C, the reaction mixture was stirred at 20 °C for 1 hr. After the reaction was completed, the reaction mixture was poured into NH4Cl(10 mL) at 0°C, filtered, the filtrate was concentrated under reduced pressure to give a residue. Then the solution was triturated in DCM/MeOH=10:1) and collected by filtration, the filtrate was concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:5%-35% B over 9 min) and freeze-dried to give the product. Compound **040** (10.74 mg, 19.97 μmol, 14.86% yield, 97% purity, FA) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.14 (br s, 1H), 8.45 (br s, 1H), 8.34 - 8.18 (m, 1H), 7.45 - 7.29 (m, 4H), 7.20 - 6.97 (m, 3H), 6.31 (br s, 1H), 4.28 - 3.91 (m, 2H), 2.88 (br s, 3H), 2.69 (br d, J = 11.3 Hz, 2H), 2.49 (br s, 6H), 1.49 - 1.31 (m, 3H). **LCMS**: Rt = 0.417 min, m/z =476.3 (M+H+).

Synthesis of Compound 224

Compound **224** was prepared by treating Compound **040** with Lawesson's reagent in toluene. Compound **224** was isolated as a yellow solid (26.34 mg, 51.43 μmol, 48.92% yield, 96% purity). **LCMS**: Rt = 0.425min, m/z=492.2(M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.16 (s, 1H), 8.54 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 7.76 - 7.60 (m, 1H), 7.35 (s, 1H), 7.32 - 7.29 (m, 2H), 7.28 - 7.22 (m, 1H), 7.07 - 6.99 (m, 1H), 6.96 - 6.82 (m, 2H), 4.13 - 3.98 (m, 2H), 3.07 - 2.97 (m, 1H), 2.95 (s, 3H), 2.88 - 2.73 (m, 2H), 2.69 - 2.62 (m, 1H), 2.60 (s, 6H), 1.36 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 039

Compound **039** was prepared in a similar manner to Compound **040** using methylamine instead of dimethylamine and was isolated as a white solid (4.74 mg, 10.27 μmol, 22.93% yield, and 100% purity). **LCMS**: Rt = 0.565 min, m/z= 462.3 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.09 (br s, 1H), 8.38 - 8.20 (m, 2H), 7.46 - 7.33 (m, 4H), 7.10 - 7.03 (m, 3H), 4.27 - 3.94 (m, 4H), 3.84 (br s, 2H), 3.45 - 3.16 (m, 1H), 3.01 (s, 3H), 2.37 - 2.27 (m, 4H), 1.41 - 1.37 (m, 3H).

Compound **145** was prepared using Compound **040** as starting material. To a solution of compound **040** (140 mg, 294.39 µmol, 1 eq) in DCM (3 mL) was added m-CPBA (145.15 mg, 294.39 µmol, 35% purity, 1 eq) at 0°C. The reaction mixture was stirred at 20°C for 4h. The mixture was concentrated to get a residue. The crude product was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 8%-38% B over 10 min and lyophilization. Compound **145** (47.64 mg, 95.12 µmol, 32.31% yield, 98.15% purity) was obtained as a white solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.14 (s, 1H), 8.50 (br s, 1H), 8.41 - 8.31 (m, 1H), 8.28 (s, 1H), 7.35 (br dd, J = 4.0, 7.6 Hz, 2H), 7.30 (br s, 1H), 7.27 - 7.22 (m, 1H), 7.21 - 7.11 (m, 2H), 7.07 - 7.00 (m, 1H), 6.28 (br dd, J = 4.4, 9.6 Hz, 1H), 4.16 - 4.00 (m, 2H), 3.90 (br t, J = 10.0 Hz, 1H), 3.75 - 3.62 (m, 1H), 3.61 - 3.37 (m, 6H), 3.34 - 3.21 (m, 1H), 2.91 (s, 3H), 2.78 (br d, J = 11.8 Hz, 1H), 1.36 (br t, J = 6.8 Hz, 3H). **LCMS**: Rt =0.430min, m/z=492.2(M+H+).

Synthesis of Compound 067

Compound **067** was prepared in a similar manner to Compound **040** using 2-fluoro-N-methylethan-1-amine. Compound **067** (87.64 mg, 164.73 µmol, 38.13% yield, 98.5% purity) as a light yellow solid. **LCMS**: Rt =0.438 min, m/z=524.2[M+H]+ **HPLC**: Rt =1.163 min. **1H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.14 (s, 1H), 8.44 (s, 1H), 8.28 (s, 1H), 7.54 (s, 1H), 7.44 - 7.40 (m, 1H), 7.37 - 7.31 (m, 3H), 7.11 - 7.06 (m, 2H), 6.33 (br dd, J = 4.8, 10.2 Hz, 1H), 4.69 (t, J = 4.4 Hz, 1H), 4.57 (t, J = 4.4 Hz, 1H), 4.16 - 3.98 (m, 2H), 2.95 - 2.89 (m, 1H), 2.87 - 2.75 (m, 6H), 2.65 - 2.53 (m, 1H), 2.47 (s, 3H), 2.43 (br d, J = 7.2 Hz, 1H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 136

Compound **136** was prepared in a similar manner to Compound **067** and was obtained as a white solid (22.62 mg, 47.57 µmol, 45.24% yield). **LCMS**: RT=0.408 min, m/z=476.3 [M+H]+ **^{1}H NMR** (400 MHz, METHANOL-d4) δ = 9.60 (s, 1H), 8.92 (s, 1H), 8.73 (br s, 1H), 7.51 (d, J = 7.2 Hz, 2H), 7.45 - 7.29 (m, 4H), 7.25 - 7.10 (m, 2H), 6.49 (br d, J = 2.2 Hz, 1H), 4.82 (br t, J = 4.3 Hz, 2H), 4.19 - 3.89 (m, 2H), 3.70 - 3.53 (m, 2H), 3.45 (br s, 2H), 3.14 - 2.99 (m, 1H), 2.95 (br s, 3H), 2.86 - 2.64 (m, 1H), 1.33 (br t, J = 6.6 Hz, 3H).

Synthesis of Compound 137

Compound **137** was prepared in a similar manner to Compound **067** and was obtained as an off-white solid (27.60 mg, 52.49 µmol, 11.72% yield, 99.2% purity). **LCMS**: Rt =0.439min, m/z=522.3(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.21 (br s, 1H), 9.15 (s, 1H), 8.45 (s, 1H), 8.29 (s, 1H), 7.44 - 7.30 (m, 4H), 7.12 - 7.03 (m, 3H), 6.36 (br dd, J = 5.6, 9.2 Hz, 1H), 4.62 (br t, J = 5.4 Hz, 1H), 4.50 (br t, J = 5.7 Hz, 1H), 4.18 - 4.00 (m, 2H), 2.85 (s, 3H), 2.69 - 2.56 (m, 4H), 2.54 - 2.41 (m, 2H), 2.35 (s, 3H), 1.97 - 1.82 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H).

Synthesis of Compound 138

Compound **138** was prepared in a similar manner to Compound **067** and was obtained as a brown gum (36.48 mg, 71.71 µmol, 85.99% yield, 99% purity). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.34 (t, J=6.88 Hz, 3 H) 1.78 - 1.94 (m, 2 H) 2.32 (s, 3 H) 2.44 (td, J=13.76, 6.75 Hz, 2 H) 2.54 - 2.65 (m, 4 H) 2.82 (s, 3 H) 3.95 - 4.14 (m, 2 H) 4.40 - 4.64 (m, 2 H) 6.33 (br dd, J=9.01, 5.75 Hz, 1 H) 7.02 - 7.10 (m, 2 H) 7.31 - 7.44 (m, 4 H) 7.53 (d, J=7.50 Hz, 2 H) 8.25 (s, 1 H) 8.42 (s, 1 H) 9.11 (s, 1 H) 12.23 (br s, 1 H). **LCMS**: Rt =0.427min, m/z=504.2(M+H+).

Synthesis of Compound 139

Compound **139** was prepared in a similar manner to Compound **067** and was obtained as an off-white solid (34.01 mg, 69.47 µmol, 14.88% yield). **LCMS**: Rt =0.420 min, m/z=490.2[M+H]+ **HPLC**: Rt =1.080 min. **1H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.06 (s, 1H), 8.51 (s, 1H), 8.41 (s, 1H), 8.24 (s, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.43 - 7.37 (m, 2H), 7.37 - 7.31 (m, 2H), 7.11 - 7.03 (m, 2H), 6.41 - 6.24 (m, 1H), 4.62 (br t, J = 5.6 Hz, 1H), 4.50 (br t, J = 5.6 Hz, 1H), 4.08 - 3.99 (m, 2H), 3.16 - 3.00 (m, 4H), 2.80 (s, 4H), 2.68 - 2.57 (m, 1H), 2.17 - 2.01 (m, 2H), 1.34 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 155

Compound **155** was prepared in a similar manner to Compound **067** and was obtained as a white solid (153.25 mg, 306.76 µmol, 65.72% yield, 98% purity). **LCMS**: Rt=0.392 min, m/z=490.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.41 - 12.04 (m, 1H), 9.14 (s, 1H), 8.45 (s, 1H), 8.29 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.46 - 7.40 (m, 2H), 7.38 (br d, J = 7.7 Hz, 2H), 7.15 - 7.08 (m, 2H), 6.36 (br dd, J = 4.8, 10.0 Hz, 1H), 4.69 (t, J = 4.6 Hz, 1H), 4.57 (t, J = 4.6 Hz, 1H), 4.08 (br dd, J = 7.4, 15.6 Hz, 2H), 2.88 (br s, 1H), 2.86 (s, 3H), 2.81 (br s, 1H), 2.77 (s, 2H), 2.63 - 2.52 (m, 1H), 2.46 (s, 3H), 2.44 - 2.35 (m, 1H), 1.38 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 184

Compound **184** was prepared in a similar manner to Compound **067**. Compound **184** (35.11 mg, 66.64 µmol, 22.67% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt=0.408 min, m/z=522.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 13.03 - 11.15 (m, 1H), 9.14 (s, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 7.43 - 7.34 (m, 2H), 7.32 (br d, J = 7.0 Hz, 2H), 7.14 - 7.01 (m, 3H), 6.35 (br dd, J = 4.9, 9.8 Hz, 1H), 4.66 (t, J = 4.8 Hz, 1H), 4.54 (t, J = 4.8 Hz, 1H), 4.08 (br dd, J = 7.3, 15.8 Hz, 2H), 2.97 - 2.93 (m, 1H), 2.90 - 2.85 (m, 2H), 2.84 (s, 3H), 2.83 - 2.79 (m, 1H), 2.74 (q, J = 7.1 Hz, 2H), 2.59 - 2.50 (m, 1H), 2.43 (br s, 1H), 1.38 (t, J = 6.9 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H).

Synthesis Compound 076

Compound **076** (124.7 mg, 241.27 µmol, 28.77% yield, 97.91% purity) was prepared in a similar manner to Compound **040** and was obtained as a yellow gum. **LCMS**: Rt =0.441 min, m/z=506.2[M+H]+ **HPLC**: Rt =1.138 min. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ =

8.39 (s, 2H), 8.35 (s, 1H), 8.27 (s, 1H), 7.55 (s, 1H), 7.44 - 7.39 (m, 1H), 7.37 - 7.31 (m, 3H), 7.18 - 7.12 (m, 2H), 6.20 (br dd, J = 5.6, 9.2 Hz, 1H), 4.19 - 4.00 (m, 2H), 3.29 - 3.15 (m, 1H), 2.92 (br d, J = 4.4 Hz, 1H), 2.90 - 2.86 (m, 6H), 2.83 (br s, 1H), 2.75 (s, 6H), 2.63 (br dd, J = 6.4, 11.6 Hz, 1H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 068

Compound **068** was prepared in a similar manner to Compound **076** and was isolated as a yellow solid (155.02 mg, 293.98 µmol, 44.92% yield, 99% purity). **LCMS**: Rt =0.412min, m/z=522.5(M+H+) **^{1}H NMR** (400 MHz, METHANOL-d4) δ ppm 1.12 - 1.28 (m, 3 H) 2.56 - 2.66 (m, 1 H) 2.72 (br s, 3 H) 2.78 (br d, J=8.00 Hz, 1 H) 2.89 (br s, 7 H) 3.27 (br s, 2 H) 3.95 (br s, 2 H) 4.97 (s, 2 H) 6.21 (br s, 1 H) 6.95 - 7.09 (m, 2 H) 7.19 - 7.33 (m, 4 H) 7.41 (s, 1 H) 8.25 (s, 2 H) 8.28 (br s, 1 H) 8.52 (s, 1 H).

Synthesis of Compound 096

Compound **096** was prepared in a similar manner to Compound **040**. Compound **096** (6090.70 mg, 12.78 mmol, 89.82% yield, 96% purity) was obtained as an off-white solid. **LCMS**: Rt = 0.405 min, m/z = 458.2 (M+H+).**^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.35 (br t, J=6.88 Hz, 3 H) 2.33 (s, 6 H) 2.37 - 2.42 (m, 1 H) 2.46 - 2.51 (m, 1 H) 2.51 - 2.58 (m, 2 H) 2.82 (s, 3 H) 3.94 - 4.15 (m, 2 H) 6.32 (br d, J=9.13 Hz, 1 H) 7.03 - 7.12 (m, 2 H) 7.30 - 7.37 (m, 2 H) 7.37 - 7.44 (m, 2 H) 7.53 (d, J=7.25 Hz, 2 H) 8.25 (s, 1 H) 8.42 (s, 1 H) 9.10 (s, 1 H).

Synthesis of Compound 135

Compound **135** was prepared in a similar manner to Compound **040**. Compound **135** (16.76 mg, 36.34 µmol, 29.62% yield, 99% purity) was obtained as off-white solid. **LCMS**: RT=0.493 min, m/z=457.3 [M+2+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.35 (t, J=6.88 Hz, 3 H) 2.34 (s, 6 H) 2.36 - 2.48 (m, 2 H) 2.49 - 2.57 (m, 2 H) 2.77 (s, 3 H) 3.95 - 4.14 (m, 2 H) 6.37 (br dd, J=9.07, 5.57 Hz, 1 H) 7.03 - 7.09 (m, 2 H) 7.17 (t, J=7.57 Hz, 1 H) 7.32 - 7.43 (m, 5 H) 7.54 (d, J=7.25 Hz, 2 H) 7.75 (d, J=8.00 Hz, 1 H) 8.11 (s, 1 H) 11.73 - 12.11 (m, 1 H).

Synthesis of Compound 146

Compound **146** was prepared in a similar manner to Compound **076** and was isolated as a white solid (14.62 mg, 32.60 µmol, 4.26% yield, 94% purity). **LCMS**: RT=0.412 min, m/z=422.2 [M+2+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 0.64 - 0.73 (m, 2 H) 0.92 - 1.02 (m, 2 H) 1.45 (br t, J=6.82 Hz, 3 H) 2.18 - 2.29 (m, 1 H) 2.46 - 2.58 (m, 1 H) 2.65 (s, 6 H) 2.76 (br s, 1 H) 2.81 (br s, 3 H) 2.86 (br s, 1 H) 3.00 - 3.12 (m, 1 H) 4.01 - 4.19 (m, 2 H) 6.13 - 6.27 (m, 1 H) 6.81 (d, J=7.75 Hz, 1 H) 6.95 - 7.04 (m, 2 H) 8.26 (s, 1 H) 8.42 (s, 1 H) 8.43 - 8.52 (m, 1 H) 9.12 (s, 1 H).

Synthesis of Compound 149

Compound **149** was prepared in a similar manner to Compounds **008** and **076**. Compound **149** (20.64 mg, 41.31 µmol, 21.37% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt=0.392 min, m/z=495.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.06 (br s, 1H), 8.38 (br s, 2H), 8.20 (s, 1H), 7.68 (s, 1H), 7.53 (s, 2H), 7.42 (br s, 2H), 7.24 (br d, J = 7.6 Hz, 1H), 7.17 - 7.07 (m, 1H), 6.19 (br s, 1H), 3.89 - 3.60 (m, 1H), 3.05 - 2.87 (m, 1H), 2.80 (s, 3H), 2.76 - 2.62 (m, 2H), 2.54 (s, 6H), 2.51 - 2.40 (m, 1H), 0.88 - 0.47 (m, 4H).

Synthesis of Compound 156

Compound **156** was prepared in a similar manner to Compounds **008** and **076** and was obtained as a white solid (113.37 mg, 257.68 µmol, 36.88% yield, 99% purity). **LCMS**: RT=0.413 min, m/z=436.2 [M+2+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.39 (br t, J=6.85 Hz, 3 H) 1.75 - 1.84 (m, 1 H) 1.95 - 2.13 (m, 3 H) 2.27 - 2.36 (m, 2 H) 2.47 - 2.59 (m, 1 H) 2.65 (s, 6 H) 2.76 (br s, 1 H) 2.81 (s, 3 H) 2.83 - 2.90 (m, 1 H) 3.00 - 3.13 (m, 1 H) 3.71 (quin, J=8.53 Hz, 1 H) 3.93 - 4.10 (m, 2 H) 6.16 - 6.25 (m, 1 H) 6.92 (s, 1 H) 7.03 (br d, J=7.58 Hz, 1 H) 7.20 (br d, J=7.70 Hz, 1 H) 8.25 (s, 1 H) 8.42 (br s, 1 H) 8.44 - 8.60 (m, 1 H) 9.11 (s, 1 H).

Synthesis of Compound 158

Compound **158** was prepared in a similar manner to Compounds **008** and **076** and was obtained as a white solid (54.55 mg, 127.50 µmol, 33.09% yield, 99% purity). **LCMS**: RT=0.409 min, m/z=424.3 [M+2+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.19 (br t, J=5.44 Hz, 6 H) 1.42 (br d, J=4.40 Hz, 3 H) 2.53 (br s, 1 H) 2.61 (br d, J=4.16 Hz, 6 H) 2.73 (br s, 2 H) 2.81 (br s, 3 H) 2.93 - 3.06 (m, 1 H) 3.25 - 3.39 (m, 1 H) 3.93 - 4.17 (m, 2 H) 6.22 (br s, 1 H) 6.97 (br s, 1 H) 7.03 (br s, 1 H) 7.16 - 7.24 (m, 1 H) 8.25 (br d, J=4.28 Hz, 1 H) 8.42 (br s, 1 H) 8.48 (br s, 1 H) 9.11 (br s, 1 H).

Synthesis of Compound 161

Compound **161** was prepared in a similar manner to Compounds **008** and **076** and was obtained as a white solid (80.16 mg, 183.19 µmol, 46.77% yield, 100% purity). **LCMS**: RT=0.816 min, m/z = 438.3 [M+H]+ **^{1}H NMR** (400 MHz, DMSO-d6) δ = 9.07 (s, 1H), 8.40 - 8.31 (m, 2H), 8.27 - 8.17 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.88 (s, 1H), 5.89 (br s, 1H), 3.97 (br dd, J = 3.6, 6.3 Hz, 2H), 3.05 (br d, J = 7.0 Hz, 1H), 2.85 (s, 3H), 2.42 - 2.32 (m, 4H), 2.19 (s, 6H), 1.63 - 1.49 (m, 2H), 1.30 (t, J = 6.9 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H).

Synthesis of Compound 162

Compound **162** was prepared in a similar manner to Compounds **008** and **076** and was obtained as an off-white solid (56.03 mg, 115.70 µmol, 12.91% yield, 98.2% purity). **LCMS**: Rt =0.440min, m/z=476.3(M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.12 (s, 1H), 8.50 (br s, 1H), 8.44 (s, 1H), 8.26 (s, 1H), 7.39 - 7.32 (m, 2H), 7.27 (s, 2H), 7.16 -

7.08 (m, 2H), 7.06 - 6.99 (m, 1H), 6.31 - 6.20 (m, 1H), 4.17 - 3.97 (m, 2H), 3.02 - 2.93 (m, 1H), 2.85 (s, 3H), 2.80 - 2.68 (m, 2H), 2.58 (s, 6H), 2.56 - 2.48 (m, 1H), 1.36 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 167

Compound **167** was prepared in a similar manner to Compound **076** using ethanamine instead dimethylamine and $NaBH(OAc)_3$. Compound **167** (112.04 mg, 233.24 µmol, 65.09% yield, 99% purity) was obtained as a white solid. **LCMS**: RT= 0.408 min, m/z= 476.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.04 (s, 1H), 8.65 (s, 1H), 8.41 (s, 1H), 8.22 (s, 1H), 7.40 - 7.29 (m, 2H), 7.26 (br dd, J = 2.2, 6.1 Hz, 2H), 7.11 - 7.02 (m, 3H), 6.32 (br d, J = 4.8 Hz, 1H), 4.10 - 3.97 (m, 2H), 3.12 (br s, 2H), 3.06 - 2.96 (m, 2H), 2.94 - 2.84 (m, 1H), 2.80 (s, 3H), 2.68 (br d, J = 5.9 Hz, 1H), 1.34 (td, J = 6.9, 13.4 Hz, 6H).

Synthesis of Compound 180

Compound **180** was prepared in a similar manner to Compound **076**. Compound **180** (46.23 mg, 111.22 µmol, 49.38% yield, 99% purity) was isolated as a yellow solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.33 (br t, J=6.94 Hz, 3 H) 2.38 - 2.51 (m, 1 H) 2.55 (s, 6 H) 2.62 (br d, J=10.13 Hz, 1 H) 2.69 (s, 3 H) 2.77 (td, J=11.23, 4.94 Hz, 1 H) 2.84 - 2.96 (m, 1 H) 3.96 (dt, J=13.26, 6.75 Hz, 2 H) 5.02 (s, 2 H) 6.14 (br dd, J=9.26, 5.00 Hz, 1 H) 6.84 - 6.96 (m, 3 H) 7.21 - 7.28 (m, 1 H) 8.21 (s, 1 H) 8.25 (s, 1 H) 8.40 (br s, 1 H). **LCMS**: Rt =0.367min, m/z=412.2(M+H+).

Synthesis of Compound 189

Compound **189** was prepared in a similar manner to Compound **040**. Compound **189** (16.02 mg, 33.42 µmol, 67.38% yield, 99% purity) was obtained as a brown gum. **LCMS**: Rt = 0.483 min, m/z = 475.3 (M+H+).**^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.31 - 1.45 (m, 3 H) 2.31 - 2.55 (m, 8 H) 2.57 (br d, J=6.88 Hz, 2 H) 2.71 - 2.96 (m, 3 H) 3.94 - 4.22 (m, 2 H) 6.36 (br dd, J=8.69, 5.44 Hz, 1 H) 6.99 - 7.11 (m, 3 H) 7.18 (t, J=7.63 Hz, 1 H) 7.28 - 7.42 (m, 5 H) 7.76 (d, J=8.13 Hz, 1 H) 8.12 (s, 1 H) 11.83 - 11.95 (m, 1 H).

Synthesis of Compound 227

Compound **227** was prepared by treating Compound **189** with m-CPBA. Compound **227** was isolated as a white solid (29.73 mg, 57.57 µmol, 34.15% yield, 95% purity). **LCMS**: Rt = 0.510 min, m/z =491.1 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.34 (t, J=6.88 Hz, 3 H) 2.69 - 2.80 (m, 1 H) 2.89 (s, 3 H) 3.08 - 3.21 (m, 1 H) 3.47 (s, 3 H) 3.60 (s, 3 H) 3.71 - 3.79 (m, 1 H) 4.02 - 4.14 (m, 3 H) 6.40 (br dd, J=9.82, 5.19 Hz, 1 H) 7.03 (br t, J=7.82 Hz, 1 H) 7.14 - 7.23 (m, 3 H) 7.28 - 7.38 (m, 4 H) 7.44 (br d, J=7.13 Hz, 1 H) 7.76 (d, J=8.13 Hz, 1 H) 8.11 (s, 1 H).

Synthesis of Compound 193

Compound **193** was prepared in a similar manner to Compound **040** using methylamine and $NaBH(OAc)_3$. Compound **193** (6090.70 mg, 12.78 mmol, 89.82% yield,

96% purity) was obtained as a yellow solid. **LCMS**: Rt = 0.400min, m/z=444.3(M+H+).**^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.64 - 9.43 (m, 1H), 8.85 (br s, 1H), 8.61 (br s, 1H), 7.44 - 7.33 (m, 2H), 7.30 - 7.16 (m, 4H), 7.13 - 6.98 (m, 2H), 6.46 - 6.17 (m, 1H), 3.93 (br d, J = 6.6 Hz, 2H), 3.20 (br d, J = 1.6 Hz, 2H), 2.83 (br s, 4H), 2.76 - 2.68 (m, 3H), 2.67 - 2.56 (m, 1H), 1.26 - 1.13 (m, 3H).

Synthesis of Compound 194

Compound **194** was prepared in a similar manner to Compound **040**. Compound **194** (61.46 mg, 133.26 µmol, 74.20% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt 0.475 min, m/z = 457.2 (M+H+)**^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.35 (br t, J=6.82 Hz, 3 H) 2.35 (s, 6 H) 2.37 - 2.49 (m, 2 H) 2.49 - 2.62 (m, 2 H) 2.77 (s, 3 H) 3.96 - 4.17 (m, 2 H) 6.37 (br dd, J=8.69, 5.44 Hz, 1 H) 7.01 - 7.12 (m, 2 H) 7.17 (t, J=7.57 Hz, 1 H) 7.30 - 7.46 (m, 5 H) 7.54 (br d, J=7.38 Hz, 2 H) 7.75 (d, J=8.00 Hz, 1 H) 8.12 (s, 1 H) 11.95 (br s, 1 H)

Synthesis of Compound 195

Compound **195** was prepared in a similar manner to Compound **040**. Compound **195** (50.81 mg, 106.89 µmol, 90.46% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt 0.510min, m/z=471.3(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.97 (br s, 1H), 8.13 (s, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.44 - 7.29 (m, 5H), 7.23 - 7.13 (m, 2H), 7.12 - 7.01 (m, 2H), 6.44 - 6.32 (m, 1H), 4.16 - 3.95 (m, 2H), 2.79 (s, 3H), 2.63 - 2.51 (m, 2H), 2.51 - 2.43 (m, 1H), 2.41 (s, 3H), 2.40 - 2.38 (m, 1H), 2.37 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 196

Compound **196** was prepared in a similar manner to Compound **040**. Compound **196** (108.81 mg, 224.81 µmol, 55.02% yield, 99.5% purity) was obtained as a white solid. **LCMS**: Rt 0.488 min, m/z=482.4, M+H+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.88 (br s, 1H), 8.12 (s, 1H), 7.85 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 7.8 Hz, 1H), 7.55 - 7.48 (m, 1H), 7.38 (d, J = 7.1 Hz, 1H), 7.31 (br d, J = 7.9 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 - 7.05 (m, 2H), 6.37 (br dd, J = 5.6, 9.0 Hz, 1H), 4.18 - 3.98 (m, 2H), 2.77 (s, 3H), 2.57 - 2.50 (m, 2H), 2.48 - 2.37 (m, 2H), 2.35 (s, 6H), 1.36 (br t, J = 6.9 Hz, 3H). **13C NMR**: (101 MHz, CHLOROFORM-d) δ = 172.52 (br s, 1C), 155.91 (br s, 1C), 139.84 - 138.31 (m, 1C), 136.94, 134.79, 133.84, 133.09, 130.99 - 129.84 (m, 1C), 128.80, 123.75 (br d, J = 46.4 Hz, 1C), 120.61 (br d, J = 48.5 Hz, 1C), 119.70 - 118.63 (m, 1C), 111.99 (br d, J = 43.5 Hz, 1C), 64.42, 56.79, 51.04 (br s, 1C), 45.83, 31.95 (br s, 1C), 27.16 (br s, 1C), 14.55.

Synthesis of Compound 197

Compound **197** was prepared in a similar manner to Compound **040** using methylamine and $NaBH(OAc)_3$. Compound **197** (33.25 mg, 71.48 µmol, 31.84% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt = 0.498 min, m/z = 461.4 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.26 - 1.40 (m, 3 H) 2.57 - 2.78 (m, 6 H) 2.82 (br s, 2 H) 3.10 - 3.30 (m, 2 H) 3.94 - 4.15 (m, 2 H) 6.57 (br d, J=5.75 Hz, 1 H) 6.95 - 7.05 (m, 2 H) 7.07

- 7.16 (m, 2 H) 7.16 - 7.25 (m, 3 H) 7.29 - 7.40 (m, 2 H) 7.66 - 7.81 (m, 1 H) 8.10 (br s, 1 H) 9.43 - 9.62 (m, 1 H) 9.78 (br d, J=5.13 Hz, 1 H).

Synthesis of Compound 198

Compound **198** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **198** (20.24 mg, 39.89 µmol, 15.24% yield, 95.9% purity) was obtained as an off-white solid. **LCMS**: Rt = 0.501 min, m/z=487.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.74 (br s, 1H), 7.96 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.25 - 7.13 (m, 3H), 7.11 (s, 2H), 7.09 - 6.99 (m, 3H), 6.94 (br d, J = 7.6 Hz, 1H), 6.86 (br t, J = 7.9 Hz, 1H), 6.20 (br d, J = 5.4 Hz, 1H), 3.61 (br s, 1H), 2.63 (s, 3H), 2.41 (br d, J = 6.9 Hz, 2H), 2.22 (s, 7H), 0.74 - 0.51 (m, 4H).

Synthesis of Compound 199

Compound **199** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **199** (5.6 mg, 11.59 µmol, 17.36% yield, 97% purity) was obtained as a brown solid. **LCMS**: Rt = 0.487min, m/z=469.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.13 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.53 - 7.44 (m, 3H), 7.42 - 7.32 (m, 5H), 7.24 - 7.16 (m, 2H), 6.35 (br dd, J = 4.9, 9.9 Hz, 1H), 3.89 - 3.80 (m, 1H), 3.37 - 3.28 (m, 1H), 3.07 - 3.00 (m, 1H), 2.86 (s, 9H), 2.79 - 2.54 (m, 2H), 0.86 - 0.60 (m, 4H).

Synthesis of Compounds 200 and 201

Compounds **200** and **201** were prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and separated by SFC. Compound **200** (62.54 mg, 127.23 µmol, 41.44% yield, 99.4% purity) was obtained as a white solid. **LCMS**: Rt = 0.530 min, m/z=489.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.82 (br s, 1H), 8.13 (s, 1H), 7.40 - 7.28 (m, 5H), 7.08 - 7.01 (m, 3H), 6.95 (d, J = 7.2 Hz, 1H), 6.31 (br dd, J = 5.8, 9.2 Hz, 1H), 4.14 - 4.00 (m, 2H), 2.80 (s, 3H), 2.69 (br d, J = 6.8 Hz, 2H), 2.63 (s, 3H), 2.60 - 2.42 (m, 9H), 1.36 (t, J = 6.8 Hz, 3H). Compound **201** was obtained as a white solid (62.54 mg, 127.23 µmol, 41.44% yield, 99.4% purity). **LCMS**: Rt = 0.536 min, m/z=489.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.92 - 11.69 (m, 1H), 8.13 (s, 1H), 7.40 - 7.27 (m, 5H), 7.10 - 6.99 (m, 3H), 6.95 (d, J = 7.2 Hz, 1H), 6.31 (br dd, J = 5.6, 9.2 Hz, 1H), 4.16 - 3.98 (m, 2H), 2.81 (s, 3H), 2.73 (br d, J = 6.2 Hz, 2H), 2.66 - 2.46 (m, 11H), 1.36 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 202 and 203

Compounds **202** and **203** were prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and separated by SFC. Compound **202** (28.5 mg, 56.93 µmol, 25.91% yield) was obtained as a white solid. **LCMS**: Rt = 0.529 min, m/z=501.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.86 (br s, 1H), 8.18 - 8.08 (m, 1H), 7.44 (s, 1H), 7.39 - 7.27 (m, 3H), 7.26 - 7.17 (m, 2H), 7.10 (dd, J = 1.2, 7.8 Hz, 1H), 7.06 - 6.99 (m, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.33 (br dd, J = 5.6, 9.4 Hz, 1H), 3.84 - 3.72 (m, 1H), 2.78 (s, 3H), 2.64 (s, 5H), 2.53 - 2.33 (m, 8H), 0.88 - 0.67 (m, 4H). Compound **203** was obtained as a white solid

(14.39 mg, 28.75 μmol, 13.08% yield). **LCMS**: Rt = 0.520 min, m/z=501.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.99 - 11.71 (m, 1H), 8.13 (s, 1H), 7.44 (s, 1H), 7.39 - 7.27 (m, 3H), 7.24 - 7.16 (m, 2H), 7.10 (br d, J = 6.8 Hz, 1H), 7.02 (dt, J = 2.4, 8.2 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.37 - 6.28 (m, 1H), 3.77 (br d, J = 3.2 Hz, 1H), 2.80 (s, 3H), 2.64 (s, 5H), 2.56 - 2.39 (m, 8H), 0.88 - 0.68 (m, 4H).

Synthesis of Compounds 204 and 205

Compounds **204** and **205** were prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and separated by SFC. Compound **204** (13.66 mg, 29.01 μmol, 27.30% yield, 99.93% purity) was obtained as a white solid. **LCMS**: Rt = 0.525 min, m/z=471.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.95 (br s, 1H), 8.14 (s, 1H), 7.59 - 7.53 (m, 2H), 7.46 - 7.40 (m, 2H), 7.38 - 7.33 (m, 2H), 7.29 (s, 1H), 7.12 - 7.03 (m, 2H), 6.95 (d, J = 7.2 Hz, 1H), 6.34 (br dd, J = 5.8, 9.2 Hz, 1H), 4.18 - 3.96 (m, 2H), 2.78 (s, 3H), 2.65 (s, 3H), 2.59 - 2.48 (m, 2H), 2.47 - 2.28 (m, 7H), 1.37 (t, J = 6.8 Hz, 3H). Compound **205** was obtained as a white solid (25.12 mg, 50.43 μmol, 47.46% yield, 94.47% purity). **LCMS**: Rt = 0.526 min, m/z=471.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.95 (br s, 1H), 8.14 (s, 1H), 7.56 (d, J = 7.2 Hz, 2H), 7.46 - 7.39 (m, 2H), 7.38 - 7.33 (m, 2H), 7.31 (s, 1H), 7.29 (s, 1H), 7.10 - 7.04 (m, 2H), 6.95 (d, J = 7.2 Hz, 1H), 6.34 (br dd, J = 5.8, 9.0 Hz, 1H), 4.17 - 3.98 (m, 2H), 3.94 (s, 1H), 3.88 (s, 1H), 2.78 (s, 3H), 2.65 (s, 3H), 2.58 - 2.48 (m, 2H), 2.47 - 2.31 (m, 8H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 208 and 209

Compounds **208** and **209** were prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and separated by SFC. Compound **208** (7.77 mg, 18.97 μmol, 19.92% yield) was obtained as a white solid. **LCMS**: Rt = 0.430 min, m/z=410.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.58 - 12.39 (m, 1H), 9.09 (s, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.33 (br dd, J = 5.4, 10.6 Hz, 1H), 4.15 - 3.98 (m, 2H), 3.45 - 3.30 (m, 2H), 2.85 - 2.80 (m, 1H), 2.79 (s, 3H), 2.44 (s, 6H), 1.44 (t, J = 6.8 Hz, 3H), 1.21 (d, J = 6.6 Hz, 6H). Compound **209** was obtained as a white solid (8.29 mg, 20.24 μmol, 21.26% yield). **LCMS**: Rt = 0.434 min, m/z=410.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.61 - 12.39 (m, 1H), 9.09 (s, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.33 (br dd, J = 5.4, 10.6 Hz, 1H), 4.15 - 3.98 (m, 2H), 3.46 - 3.28 (m, 2H), 2.86 - 2.80 (m, 1H), 2.79 (s, 3H), 2.44 (s, 6H), 1.44 (t, J = 6.8 Hz, 3H), 1.21 (br d, J = 6.8 Hz, 6H).

Synthesis of Compound 211

Compound **211** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and bis(methyl-d_3)amine. Compound **211** (3251.09 mg, 6.75 mmol, 75.35% yield, 100% purity) was obtained as a white solid. **LCMS**: Rt = 0.502min, m/z=482.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.44 (br s, 1H), 9.18 - 9.03 (m, 1H), 8.45 - 8.43

(m, 1H), 8.41 (br s, 1H), 8.30 - 8.21 (m, 1H), 7.40 - 7.29 (m, 2H), 7.29 - 7.19 (m, 2H), 7.19 - 7.06 (m, 2H), 7.05 - 6.94 (m, 1H), 6.23 (br d, J = 3.3 Hz, 1H), 4.28 - 3.87 (m, 2H), 3.29 - 3.09 (m, 1H), 3.03 - 2.72 (m, 5H), 2.60 (br s, 1H), 1.50 - 1.20 (m, 3H).

Synthesis of Compound 212

Compound **212** was prepared in a similar manner to Compound **040**. Compound **212** (54.03 mg, 115.97 µmol, 42.53% yield, 98% purity) was obtained as a yellow gum. **LCMS**: Rt = 0.480 min, m/z = 457.2 (M+H+).**^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.35 (br t, J=6.88 Hz, 3 H) 2.35 (s, 6 H) 2.37 - 2.49 (m, 2 H) 2.50 - 2.62 (m, 2 H) 2.77 (s, 3 H) 3.95 - 4.15 (m, 2 H) 6.37 (br dd, J=9.01, 5.50 Hz, 1 H) 7.00 - 7.11 (m, 2 H) 7.17 (t, J=7.57 Hz, 1 H) 7.31 - 7.45 (m, 5 H) 7.54 (d, J=7.38 Hz, 2 H) 7.75 (d, J=8.00 Hz, 1 H) 8.12 (s, 1 H) 11.84 - 12.04 (m, 1 H).

Synthesis of Compound 213

Compound **213** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **213** (34.17 mg, 150.45 µmol, 70.92% yield, 99.6% purity) was obtained as a white solid. **LCMS**: Rt = 0.524 min, m/z=491.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.56 (s, 1H), 8.12 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.43 - 7.37 (m, 2H), 7.37 - 7.30 (m, 3H), 7.23 - 7.14 (m, 1H), 7.13 - 7.07 (m, 2H), 6.34 (br dd, J = 5.3, 9.5 Hz, 1H), 4.16 - 3.99 (m, 2H), 2.90 - 2.82 (m, 1H), 2.81 - 2.75 (m, 3H), 2.75 - 2.67 (m, 1H), 2.65 - 2.58 (m, 1H), 2.53 (s, 6H), 2.49 - 2.30 (m, 1H), 1.36 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 206

Compound **206** was prepared by treating Compound **213** with m-CPBA. Compound **206** was isolated as a white solid (13.75 mg, 26.28 µmol, 37.01% yield, 96.9% purity). **LCMS**: Rt = 0.513 min, m/z=507.1[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.40 (s, 1H), 8.11 (s, 1H), 7.76 (br d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.45 (br d, J = 7.0 Hz, 1H), 7.39 (br d, J = 6.1 Hz, 1H), 7.32 - 7.28 (m, 1H), 7.29 - 7.26 (m, 1H), 7.22 - 7.10 (m, 3H), 6.36 (br dd, J = 5.6, 9.1 Hz, 1H), 4.13 - 3.99 (m, 3H), 3.80 - 3.57 (m, 3H), 3.48 (br s, 3H), 3.39 (s, 3H), 3.17 - 3.09 (m, 1H), 2.86 (s, 3H), 2.82 - 2.68 (m, 1H), 1.34 (br t, J = 6.9 Hz, 3H).

Synthesis of Compound 207

Compound **207** was prepared in a similar manner to Compound **206**. Compound **207** was isolated as a yellow gum (94.31 mg, 173.08 µmol, 53.93% yield, 98.2% purity). **LCMS**: Rt = 0.515 min, m/z=535.3 [M+H]+. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.43 (s, 1H), 8.13 (s, 1H), 7.78 (br d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.47 (br d, J = 7.0 Hz, 1H), 7.41 (br d, J = 6.4 Hz, 1H), 7.35 - 7.30 (m, 3H), 7.26 - 7.08 (m, 3H), 6.33 (br dd, J = 4.5, 9.9 Hz, 1H), 4.17 - 4.00 (m, 2H), 3.83 - 3.37 (m, 6H), 3.21 (q, J = 10.5 Hz, 1H), 2.87 (s, 3H), 2.71 - 2.50 (m, 1H), 1.46 - 1.29 (m, 8H)

Synthesis of Compound 214

Compound **214** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and *N*-methylethanamine. Compound **214** (52.67 mg, 103.49 µmol, 46.10% yield, 96% purity) was obtained as a yellow oil. **LCMS**: Rt = 0.483 min, m/z = 489.3 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.14 - 1.29 (m, 3 H) 1.36 (br t, J=6.88 Hz, 3 H) 2.40 - 2.56 (m, 4 H) 2.58 - 2.70 (m, 1 H) 2.72 - 2.84 (m, 6 H) 2.86 - 2.93 (m, 1 H) 3.97 - 4.18 (m, 2 H) 6.33 (br dd, J=9.51, 5.13 Hz, 1 H) 6.98 - 7.07 (m, 1 H) 7.07 - 7.14 (m, 2 H) 7.18 (t, J=7.57 Hz, 1 H) 7.27 - 7.43 (m, 5 H) 7.76 (d, J=8.00 Hz, 1 H) 8.12 (s, 1 H) 8.61 (s, 1 H).

Synthesis of Compound 215

Compound **215** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and diethylamine. Compound **215** (48.19 mg, 91.08 µmol, 40.58% yield, 95% purity) was obtained as a yellow gum. **LCMS**: Rt = 0.502 min, m/z = 503.3 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.18 (t, J=7.13 Hz, 6 H) 1.36 (t, J=6.94 Hz, 3 H) 2.37 - 2.53 (m, 1 H) 2.57 - 2.72 (m, 1 H) 2.74 - 3.03 (m, 9 H) 3.97 - 4.18 (m, 2 H) 6.33 (br dd, J=9.57, 5.19 Hz, 1 H) 6.99 - 7.07 (m, 1 H) 7.07 - 7.13 (m, 2 H) 7.18 (t, J=7.57 Hz, 1 H) 7.28 - 7.45 (m, 5 H) 7.76 (d, J=8.13 Hz, 1 H) 8.12 (s, 1 H) 8.66 (s, 1 H).

Synthesis of Compound 216

Compound **216** was prepared by treating Compound **215** with m-CPBA. Compound **216** (66.36 mg, 125.40 µmol, 52.52% yield, 98% purity) was obtained as a white solid. **LCMS**: Rt = 0.525 min, m/z = 519.2 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.35 (q, J=6.75 Hz, 6 H) 1.42 (br t, J=7.07 Hz, 3 H) 2.58 - 2.73 (m, 1 H) 2.93 (s, 3 H) 3.14 - 3.25 (m, 1 H) 3.43 - 3.65 (m, 4 H) 3.68 - 3.86 (m, 2 H) 4.01 - 4.17 (m, 2 H) 6.36 (br dd, J=10.07, 4.94 Hz, 1 H) 6.97 - 7.06 (m, 1 H) 7.14 - 7.25 (m, 3 H) 7.27 - 7.39 (m, 4 H) 7.47 (br d, J=7.00 Hz, 1 H) 7.77 (d, J=8.13 Hz, 1 H) 8.12 (s, 1 H).

Synthesis of Compound 219

Compound **219** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **219** (240.38 mg, 487.05 µmol, 36.41% yield, 99.8% purity) was obtained as a white solid. **LCMS**: Rt = 0.509 min, m/z=493.4 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.15 - 11.46 (m, 1H), 8.58 - 8.53 (m, 1H), 8.12 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.13 - 7.04 (m, 4H), 6.78 (tt, J = 2.4, 8.8 Hz, 1H), 6.34 (br dd, J = 5.2, 9.2 Hz, 1H), 4.17 - 3.99 (m, 2H), 2.81 (s, 3H), 2.80 - 2.69 (m, 2H), 2.69 - 2.60 (m, 1H), 2.55 (s, 6H), 2.51 (br d, J = 5.6 Hz, 1H), 1.38 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 220 and 221

Compounds **220** and **221** were prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and separated by SFC. Compound **220** (10.89 mg, 21.88 µmol, 8.70% yield, 95.8% purity) was obtained as an off-white solid. **LCMS**: Rt = 0.515 min, m/z = 477.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.19 (br s, 1H), 8.14 (s, 1H), 7.77 (d, J = 8.0 Hz,

1H), 7.56 (s, 1H), 7.47 - 7.42 (m, 1H), 7.37 - 7.30 (m, 4H), 7.19 - 7.13 (m, 3H), 6.47 - 6.37 (m, 1H), 4.15 - 4.02 (m, 2H), 3.44 (t, J = 12.0 Hz, 1H), 2.78 (s, 3H), 2.76 - 2.71 (m, 1H), 2.47 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H). Compound **221** was obtained as a white solid (11.84 mg, 24.53 µmol, 9.75% yield, 98.838% purity). **LCMS**: Rt = 0.510 min, m/z = 477.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.19 (br s, 1H), 8.14 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.44 (br d, J = 7.2 Hz, 1H), 7.37 - 7.29 (m, 4H), 7.20 - 7.13 (m, 3H), 6.42 (dd, J = 5.2, 11.2 Hz, 1H), 4.16 - 4.01 (m, 2H), 3.45 (t, J = 12.0 Hz, 1H), 2.81 - 2.76 (m, 3H), 2.76 - 2.71 (m, 1H), 2.47 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H).

Synthesis of Compound 226

Compound **226** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **226** (5.02 mg, 11.19 µmol, 64.20% yield, 98.9% purity) was obtained as a white solid. **LCMS**: Rt = 0.430 min, m/z = 444.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.82 - 11.85 (m, 1H), 9.58 - 8.81 (m, 1H), 8.29 (s, 2H), 7.55 (br d, J = 7.2 Hz, 2H), 7.44 - 7.33 (m, 4H), 7.26 - 7.18 (m, 2H), 6.53 - 6.38 (m, 1H), 4.19 - 4.00 (m, 2H), 3.78 - 3.62 (m, 1H), 3.06 - 2.96 (m, 1H), 2.91 (br s, 3H), 2.60 (br s, 6H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 228

Compound **228** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **228** (42.5 mg, 88.91 µmol, 20.58% yield, 100% purity) was obtained as a white solid. **LCMS**: Rt = 0.437min, m/z=478.2(M+H+) **^{1}H NMR** (400 MHz, deuterium oxide) δ = 9.19 (br s, 1H), 8.48 (br s, 2H), 7.30 - 6.87 (m, 4H), 6.79 (br d, J = 8.4 Hz, 3H), 6.31 (br s, 1H), 3.68 (br d, J = 2.0 Hz, 2H), 3.25 (br d, J = 4.4 Hz, 3H), 2.77 (s, 4H), 2.70 - 2.60 (m, 1H), 2.48 (br s, 3H), 0.88 (br s, 3H).

Synthesis of Compound 229

Compound **229** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and 2-methoxy-*N*-methylethan-1-amine. Compound **229** (134.75 mg, 246.34 µmol, 57.02% yield, 98% purity) was obtained as a white solid. **LCMS**: Rt = 0.433min, m/z=536.3(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.16 (s, 1H), 8.47 (s, 1H), 8.42 (br s, 1H), 8.30 (s, 1H), 7.55 (s, 1H), 7.43 (br d, J = 6.7 Hz, 1H), 7.38 - 7.30 (m, 3H), 7.23 - 7.03 (m, 2H), 6.26 (br dd, J = 5.0, 9.5 Hz, 1H), 4.23 - 3.92 (m, 2H), 3.70 (br s, 2H), 3.37 (s, 3H), 3.17 (br d, J = 3.1 Hz, 1H), 3.09 (br t, J = 4.6 Hz, 2H), 3.05 - 2.94 (m, 1H), 2.87 (s, 3H), 2.83 - 2.75 (m, 1H), 2.71 (s, 3H), 2.65 - 2.50 (m, 1H).

Synthesis of Compound 230

Compound **230** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and 2-((*tert*-butyldimethylsilyl)oxy)-*N*-methylethan-1-amine. The resulting product was treating with NH_4F to remove the TBS protecting group. Compound **230** (82.18 mg, 157.42 µmol, 40.07% yield, 100% purity) was obtained as a white solid. **LCMS**: Rt =

0.444min, m/z=522.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.08 (s, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 8.23 (s, 1H), 7.49 (s, 1H), 7.40 - 7.27 (m, 3H), 7.27 - 7.22 (m, 1H), 7.07 (br d, J = 3.6 Hz, 2H), 6.30 (br dd, J = 3.9, 9.6 Hz, 1H), 4.15 - 3.93 (m, 2H), 3.80 (q, J = 4.5 Hz, 2H), 3.15 - 3.01 (m, 1H), 2.92 (br d, J = 4.4 Hz, 3H), 2.82 (s, 3H), 2.74 (br d, J = 9.0 Hz, 1H), 2.61 (s, 3H), 2.57 (br d, J = 6.8 Hz, 1H), 1.31 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 231

Compound **231** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and methan-d_3-amine. Compound **231** (27.06 mg, 57.67 µmol, 65.13% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt = 0.427 min, m/z=465.3 [M+H]+ **^{1}H NMR** (400 MHz, deuterium oxide) δ = 99.51 (s, 1H), 8.87 (s, 1H), 8.54 (s, 1H), 7.37 - 7.30 (m, 1H), 7.23 (br dd, J = 7.8, 18.8 Hz, 2H), 7.15 (br d, J = 9.9 Hz, 1H), 7.08 - 6.95 (m, 3H), 6.37 (br dd, J = 4.6, 10.1 Hz, 1H), 3.99 (br dd, J = 4.1, 6.8 Hz, 2H), 3.28 (br t, J = 7.6 Hz, 2H), 2.88 - 2.74 (m, 1H), 2.68 (s, 3H), 2.65 - 2.56 (m, 1H), 1.18 (br t, J = 6.9 Hz, 3H).

Synthesis of Compound 232

Compound **232** was prepared in a similar manner to Compound **040**. Compound **232** (14.8 mg, 30.68 µmol, 13.91% yield, 97.12% purity) was obtained as a white solid. **LCMS**: Rt = 0.430 min, m/z = 444.2 [M+H]+ **^{1}H NMR** (400 MHz, DMSO-d6) δ = 9.76 - 9.62 (m, 1H), 9.23 - 9.09 (m, 2H), 9.05 - 8.82 (m, 1H), 8.67 - 8.54 (m, 1H), 7.97 (br s, 1H), 7.91 - 7.86 (m, 1H), 7.82 (br d, J = 7.6 Hz, 1H), 7.66 - 7.61 (m, 1H), 7.50 - 7.39 (m, 1H), 7.19 (br s, 2H), 6.20 (s, 1H), 4.84 - 4.34 (m, 2H), 4.19 - 4.00 (m, 2H), 3.10 - 2.89 (m, 3H), 2.62 (br s, 5H), 1.27 (br d, J = 1.2 Hz, 3H)

Synthesis of Compound 233

Compound **233** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **233** (27.92 mg, 53.72 µmol, 62.01% yield, 98.8% purity, HCl) was obtained as a yellow solid. **LCMS**: Rt = 0.508 min, m/z=477.2 [M+H]+ **^{1}H NMR** (400 MHz, METHANOL-d4) δ = 8.27 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.61 (br d, J = 7.2 Hz, 1H), 7.53 (br s, 1H), 7.45 - 7.40 (m, 1H), 7.40 - 7.35 (m, 2H), 7.34 - 7.28 (m, 2H), 7.19 - 7.08 (m, 2H), 6.34 (br s, 1H), 4.16 - 3.97 (m, 2H), 3.30 - 3.19 (m, 2H), 2.87 - 2.71 (m, 7H), 2.66 - 2.57 (m, 1H), 1.32 (br t, J = 6.0 Hz, 3H).

Synthesis of Compound 254

Compound **254** was prepared in a similar manner to Compound **206**. Compound **254** was isolated as an off-white gum (23.26 mg, 44.38 µmol, 41.59% yield, 99.6% purity). **LCMS**: Rt = 0.432 min, m/z=522.2, M+H+. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.05 (br s, 1H), 8.41 (br s, 1H), 8.19 (s, 1H), 7.46 (br s, 1H), 7.33 (br s, 1H), 7.24 (br s, 3H), 7.16 - 6.99 (m, 2H), 6.21 (br s, 1H), 4.01 (br dd, J = 7.1, 12.8 Hz, 2H), 3.73 - 3.33 (m, 5H), 3.26 - 3.15 (m, 3H), 3.13 - 2.98 (m, 1H), 2.84 (br d, J = 6.8 Hz, 3H), 1.52 - 1.18 (m, 6H). **13C NMR**: (101 MHz, CHLOROFORM-d) δ = 155.95, 145.54 (br d, J = 6.2 Hz, 1C), 143.20 - 141.27 (m,

1C), 139.22, 135.95 - 132.56 (m, 1C), 130.58 (br s, 1C), 129.36 (br d, J = 35.2 Hz, 1C), 127.49 (br d, J = 21.1 Hz, 1C), 121.12, 119.90 (br d, J = 5.8 Hz, 1C), 115.59 (br s, 1C), 111.96 (br d, J = 5.4 Hz, 1C), 65.58 - 63.30 (m, 1C), 54.78, 50.65 (br d, J = 12.0 Hz, 1C), 33.01 (br s, 1C), 22.60 (br s, 1C), 14.56, 9.55 - 7.98 (m, 1C).

Synthesis of Compound 255

Compound **255** was prepared in a similar manner to Compound **206**. Compound **255** was isolated as a yellow gum (43.97 mg, 75.16 µmol, 70.81% yield, 99.5% purity). **LCMS**: Rt = 0.444 min, m/z=536.3, M+H+ **^{1}H NMR**(400 MHz, CHLOROFORM-d) δ = 9.17 - 9.08 (m, 1H), 8.46 (br d, J = 19.8 Hz, 2H), 8.30 - 8.21 (m, 1H), 7.54 (s, 1H), 7.41 (br d, J = 6.5 Hz, 1H), 7.37 - 7.29 (m, 3H), 7.22 - 7.07 (m, 2H), 6.32 - 6.16 (m, 1H), 4.22 - 3.96 (m, 2H), 3.81 - 3.37 (m, 5H), 3.27 (br d, J = 10.1 Hz, 1H), 2.95 - 2.86 (m, 3H), 2.84 (br d, J = 3.9 Hz, 1H), 2.72 (br d, J = 5.5 Hz, 1H), 1.44 - 1.16 (m, 9H) **^{13}C NMR**: (101 MHz, CHLOROFORM-d) δ = 173.43 (br s, 1C), 167.31, 155.99, 146.40 - 144.80 (m, 1C), 142.53 - 140.65 (m, 1C), 139.28, 135.98 - 134.37 (m, 1C), 133.82, 131.83, 130.65 (br s, 1C), 129.41 (d, J = 35.2 Hz, 1C), 127.53 (br d, J = 22.4 Hz, 1C), 121.06, 120.38 - 119.38 (m, 1C), 112.04 (br s, 1C), 64.56, 61.47 (br s, 1C), 59.94 (br s, 1C), 58.25 (br s, 1C), 50.69 (br s, 1C), 46.53, 33.06, 22.13 (br s, 1C), 14.61, 10.36, 8.63 (br d, J = 41.0 Hz, 1C).

Synthesis of Compounds 256 and 257

Compounds **256** and **257** were prepared in a similar manner to Compound **040** and separated by SFC. Compound **256** (16.55 mg, 35.40 µmol, 34.68% yield, 98.5 % purity) was obtained as a yellow solid. **LCMS**: Rt = 0.472 min, m/z=461.2, M+H+ **^{1}H NMR**(400 MHz, CHLOROFORM-d) δ = 12.35 - 11.83 (m, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.40 - 7.27 (m, 5H), 7.22 - 7.09 (m, 3H), 7.03 (br t, J = 7.8 Hz, 1H), 6.43 (br dd, J = 4.5, 10.9 Hz, 1H), 4.19 - 3.94 (m, 2H), 3.48 (br t, J = 10.9 Hz, 1H), 2.78 (s, 4H), 2.49 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H). **13C NMR** (101 MHz, CHLOROFORM-d) δ = 173.08, 163.64, 161.21, 155.82, 139.88 (br d, J = 8.3 Hz, 1C), 136.45, 134.76 (br s, 1C), 131.27, 130.46, 129.33 (d, J = 8.3 Hz, 1C), 125.09 (d, J = 2.5 Hz, 1C), 123.41, 120.92, 120.01 (br d, J = 47.7 Hz, 1C), 116.48 (d, J = 22.4 Hz, 1C), 114.03 (d, J = 21.1 Hz, 1C), 111.91, 64.32, 57.35, 49.76, 46.22 - 45.16 (m, 1C), 32.10, 14.60. Compound **257** was obtained as a yellow solid (16.36 mg, 35.27 µmol, 34.56% yield, 99.3 % purity). **LCMS**: Rt = 0.473 min, m/z=461.2, M+H+. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.14 (br s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.41 - 7.28 (m, 5H), 7.21 - 7.10 (m, 3H), 7.03 (br t, J = 7.4 Hz, 1H), 6.44 (br dd, J = 3.8, 7.3 Hz, 1H), 4.08 (dt, J = 8.9, 15.9 Hz, 2H), 3.59 - 3.41 (m, 1H), 2.79 (s, 4H), 2.49 (br s, 6H), 1.37 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ = 173.11 (br s, 1C), 163.65, 161.21, 155.83, 139.89 (br d, J = 8.3 Hz, 1C), 136.43 (br s, 1C), 134.76 (br s, 1C), 131.29, 130.47, 129.33 (d, J = 8.3 Hz, 1C), 125.09 (d, J = 2.1 Hz, 1C), 123.78 - 122.96 (m, 1C),

121.18 - 119.07 (m, 1C), 116.48 (d, J = 22.4 Hz, 1C), 114.03 (d, J = 21.1 Hz, 1C), 111.94, 64.34, 57.34 (br s, 1C), 49.76, 45.74 (br s, 1C), 32.13, 14.60.

Synthesis of Compounds 258 and 259

Compounds **258** and **259** were prepared in a similar manner to Compound **040** using N-methylethanamine and separated by SFC. Compound **258** (22.9 mg, 48.25 µmol, 46.12% yield, 100% purity) was obtained as an off-white solid. **LCMS**: Rt = 0.482 min, m/z=475.2, M+H+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.17 (br s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.41 - 7.28 (m, 5H), 7.21 - 7.11 (m, 3H), 7.03 (br t, J = 7.6 Hz, 1H), 6.45 (br dd, J = 4.0, 11.0 Hz, 1H), 4.24 - 3.94 (m, 2H), 3.52 (br s, 1H), 2.77 (s, 5H), 2.62 (br s, 1H), 2.46 (br s, 3H), 1.38 (t, J = 6.9 Hz, 3H), 1.20 (br t, J = 6.9 Hz, 3H). **13C NMR** (101 MHz, CHLOROFORM-d) δ = 173.08 (br s, 1C), 163.64, 161.21, 155.78, 139.90 (br d, J = 7.9 Hz, 1C), 136.55 (br d, J = 1.7 Hz, 1C), 134.72 (br s, 1C), 131.24 (br s, 1C), 130.50, 129.32 (br d, J = 8.3 Hz, 1C), 125.07 (br s, 1C), 123.39, 120.87 (br s, 1C), 120.02 (br d, J = 40.2 Hz, 1C), 116.47 (br d, J = 22.0 Hz, 1C), 114.02 (br d, J = 21.1 Hz, 1C), 111.90, 64.30, 55.17 (br s, 1C), 51.82 (br s, 1C), 49.62, 41.63 (br s, 1C), 32.12 (br s, 1C), 14.61, 12.52 (br s, 1C). Compound **259** was obtained as an off-white solid (23.18 mg, 48.40 µmol, 46.27% yield, 99.1% purity). **LCMS**: Rt = 0.475 min, m/z=475.2, M+H+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.17 (br s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.42 - 7.28 (m, 5H), 7.20 - 7.11 (m, 3H), 7.03 (br t, J = 8.0 Hz, 1H), 6.57 - 6.32 (m, 1H), 4.23 - 3.92 (m, 2H), 3.51 (br s, 1H), 2.77 (br s, 5H), 2.61 (br d, J = 4.5 Hz, 1H), 2.46 (br s, 3H), 1.38 (t, J = 6.9 Hz, 3H), 1.20 (br t, J = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ = 173.09, 163.65, 161.21 (br s, 1C), 155.78, 139.91 (br d, J = 7.5 Hz, 1C), 134.72 (br s, 1C), 131.26, 130.51, 129.32 (br d, J = 8.3 Hz, 1C), 125.08 (br s, 1C), 123.39 (br s, 1C), 120.88 (br s, 1C), 120.02 (br d, J = 40.2 Hz, 1C), 116.48 (br d, J = 22.0 Hz, 1C), 114.02 (br d, J = 21.6 Hz, 1C), 111.91, 64.31, 55.21 (br s, 1C), 51.80 (br s, 1C), 49.63 (br s, 1C), 41.63 (br s, 1C), 32.12 (br s, 1C), 14.61, 12.51 (br d, J = 2.1 Hz, 1C).

Synthesis of Compounds 260 and 261

Compounds **260** and **261** were prepared in a similar manner to Compound **040** using diethylamine and separated by SFC. Compound **260** (12.70 mg, 25.84 µmol, 31.56% yield, 99.4% purity) was obtained as a white solid. **LCMS**: Rt = 0.517 min, MS (ESI) m/z: 489.4, M+H+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.17 (br s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.39 - 7.28 (m, 5H), 7.24 - 7.13 (m, 3H), 7.03 (br t, J = 7.5 Hz, 1H), 6.51 - 6.38 (m, 1H), 4.16 - 4.02 (m, 2H), 3.77 - 3.50 (m, 1H), 3.10 - 2.87 (m, 4H), 2.79 (br s, 3H), 2.74 - 2.66 (m, 1H), 1.38 (t, J = 6.9 Hz, 3H), 1.17 (br t, J = 6.3 Hz, 6H). Compound **261** was obtained as a white solid (11.44 mg, 23.18 µmol, 28.31% yield, 99.0% purity). **LCMS**: Rt = 0.513 min, MS (ESI) m/z: 489.4, M+H+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.63 - 11.40 (m, 1H), 8.04 (s, 1H), 7.68 (br d, J = 8.0 Hz, 1H), 7.32 - 7.19 (m, 5H), 7.13 - 7.03 (m,

3H), 6.94 (br t, J = 7.8 Hz, 1H), 6.37 (br d, J = 8.0 Hz, 1H), 4.08 - 3.91 (m, 2H), 3.57 (br s, 1H), 3.20 - 2.81 (m, 4H), 2.70 (s, 3H), 2.68 - 2.58 (m, 1H), 1.29 (br t, J = 6.9 Hz, 3H), 1.09 (br t, J = 6.8 Hz, 5H).

Synthesis of Compound 262

Compound **262** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$ and 2-((*tert*-butyldimethylsilyl)oxy)-*N*-methylethan-1-amine. The resulting product was treating with NH_4F to remove the TBS protecting group. Compound **262** (28.97 mg, 57.24 µmol, 35.48% yield, 99.9% purity) was obtained as a white solid. **LCMS**: Rt = 0.415 min, m/z=506.3 M+H+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.06 (br s, 1H), 8.48 (br s, 1H), 8.21 (s, 1H), 7.35 - 7.28 (m, 1H), 7.27 - 7.17 (m, 3H), 7.13 - 7.03 (m, 2H), 6.99 (br t, J = 8.2 Hz, 1H), 6.38 (br d, J = 4.6 Hz, 1H), 4.07 - 3.96 (m, 2H), 3.78 (br s, 2H), 3.03 - 2.88 (m, 4H), 2.80 (s, 3H), 2.73 (br d, J = 1.8 Hz, 1H), 2.61 (br s, 4H), 1.31 (br t, J = 6.8 Hz, 3H). **^{13}C NMR**: (101 MHz, CHLOROFORM-d) δ = 173.50, 163.65, 161.22, 156.00, 145.30 (br s, 1C), 142.26, 141.41 (br s, 1C), 139.57 (d, J = 8.3 Hz, 1C), 135.20 (br d, J = 45.2 Hz, 1C), 131.82 (br s, 1C), 130.57, 129.44 (br d, J = 8.3 Hz, 1C), 125.09 (br s, 1C), 120.77, 119.69, 117.21 - 115.93 (m, 1C), 114.25 (br d, J = 21.1 Hz, 1C), 112.02, 64.49, 59.12 (br s, 1C), 57.73, 54.27 (br s, 1C), 49.69 (br s, 1C), 41.62, 32.64 (br s, 1C), 25.20 (br s, 1C), 14.60.

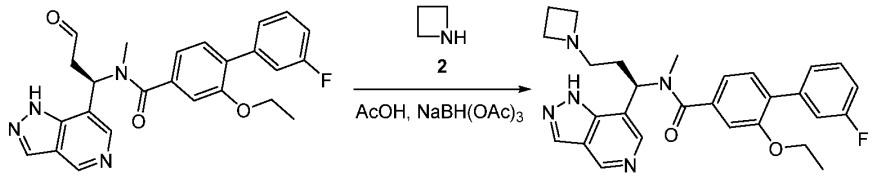
Synthesis of Compound 279

Compound **279** was prepared in a similar manner to Compound **040** using $NaBH(OAc)_3$. Compound **279** (16.94 mg, 32.49 µmol, 10.21% yield, 96% purity) was obtained as a yellow solid. **LCMS**: Rt = 0.420min, m/z=501.3(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.11 (s, 1H), 8.47 (br s, 1H), 8.39 (s, 1H), 7.75 (br s, 1H), 7.66 (br d, J = 8.4 Hz, 1H), 7.54 - 7.51 (m, 1H), 7.45 (br d, J = 8.0 Hz, 1H), 7.19 - 7.05 (m, 2H), 6.34 - 6.22 (m, 1H), 4.23 - 4.02 (m, 2H), 2.99 - 2.75 (m, 3H), 2.43 (br s, 4H), 2.36 (br s, 6H), 1.43 - 1.25 (m, 3H).

Synthesis of Compound 280

Compound **280** was prepared in a similar manner to Compound **040** using methylamine. Compound **280** (11.86 mg, 20.77 µmol, 4.90% yield, 98% purity, 2HCl) was obtained as a yellow solid. **LCMS**: Rt = 0.417min, m/z=478.2(M+H+) **^{1}H NMR** (400 MHz, methanol-d) δ = 9.72 - 9.60 (m, 1H), 9.08 - 8.86 (m, 1H), 8.80 - 8.62 (m, 1H), 7.75 (s, 1H), 7.66 (dd, J = 2.0, 10.0 Hz, 1H), 7.53 (dd, J = 1.2, 8.0 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.29 - 7.16 (m, 2H), 6.40 (br d, J = 4.0 Hz, 1H), 4.23 - 4.06 (m, 2H), 3.32 (br s, 1H), 3.30 (br s, 1H), 2.92 (br s, 3H), 2.84 (s, 3H), 2.81 - 2.61 (m, 2H), 1.40 - 1.31 (m, 3H)Synthesis of Compound 077

Compound **077** was prepared by the following scheme.



1 077

To a solution of compound 1 (200 mg, 447.96 µmol, 1 eq) and compound 2 (51.15 mg, 895.91 µmol, 60.46 µL, 2 eq) in DCE (8 mL) was added AcOH (2.69 mg, 44.80 µmol, 2.56 µL, 0.1 eq) and Molecular sieve 4A (100 mg, 447.96 µmol, 1 eq). The mixture was stirred at 25 °C for 12hr. To the reaction mixture was added $NaBH(OAc)_3$ (284.82 mg, 1.34 mmol, 3 eq) at 0°C and stirred at 0°C for 1hr. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient:8%-38% B over 9 min) and lyophilized to give a product. Compound **077** (22.84 mg, 45.91 µmol, 10.25% yield, 98% purity) was obtained as a white solid. **LCMS**: RT=0.433 min, m/z=488.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.38 - 11.71 (m, 1H), 9.03 (s, 1H), 8.32 (s, 1H), 8.18 (s, 1H), 7.33 - 7.25 (m, 2H), 7.25 - 7.20 (m, 2H), 7.04 - 6.93 (m, 3H), 6.20 (br d, J = 3.4 Hz, 1H), 4.12 - 3.86 (m, 2H), 3.22 (t, J = 6.9 Hz, 4H), 2.73 (s, 3H), 2.65 - 2.51 (m, 2H), 2.37 - 2.25 (m, 1H), 2.22 - 2.13 (m, 1H), 2.06 (quin, J = 7.0 Hz, 2H), 1.29 (br t, J = 6.9 Hz, 3H).

Synthesis of Compounds 123 and 124

Compounds **123** and **124** were prepared in a similar manner to compound **077**. Compound **123** (31.73 mg, 66.34 µmol, 34.90% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt=0.400 min, m/z=474.4[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.53 (br s, 1H), 9.02 (s, 1H), 8.20 - 8.12 (m, 2H), 7.31 - 7.20 (m, 4H), 7.15 - 7.09 (m, 2H), 6.96 (br s, 1H), 6.01 (br dd, J = 5.6, 9.4 Hz, 1H), 4.13 - 3.94 (m, 2H), 3.41 - 3.29 (m, 5H), 3.02 - 2.95 (m, 1H), 2.74 (s, 3H), 2.14 - 2.07 (m, 2H), 1.31 (t, J = 6.9 Hz, 3H)

Compound **124** (30.08 mg, 62.89 µmol, 33.09% yield, 99% purity) was obtained as a white solid. **LCMS**: Rt=0.400 min, m/z=474.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.53 (br s, 1H), 9.02 (s, 1H), 8.21 - 8.17 (m, 2H), 7.32 - 7.21 (m, 4H), 7.15 - 7.08 (m, 2H), 6.99 - 6.94 (m, 1H), 6.01 (br dd, J = 5.6, 9.6 Hz, 1H), 4.09 - 3.97 (m, 2H), 3.41 - 3.29 (m, 5H), 2.97 (br dd, J = 5.6, 12.0 Hz, 1H), 2.74 (s, 3H), 2.14 - 2.07 (m, 2H), 1.31 (t, J = 6.9 Hz, 3H).

Synthesis of Compounds 129 and 130

Compounds **129** and **130** were prepared in a similar manner to compound **077**.

Compound **129** (31.45 mg, 64.10 µmol, 44.65% yield, 99.369% purity) was obtained as a white solid. **LCMS**: Rt = 0.434 min, m/z = 488.2 [M+H]+ **^{1}H NMR**: (400 MHz,

CHLOROFORM-d) δ = 12.51 (br s, 1H), 9.10 (s, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 7.40 - 7.27 (m, 4H), 7.18 - 7.11 (m, 2H), 7.03 (br t, J = 7.6 Hz, 1H), 6.32 (br dd, J = 4.8, 10.8 Hz, 1H), 4.08 (br dd, J = 7.2, 15.2 Hz, 2H), 3.73 (br t, J = 11.6 Hz, 1H), 2.94 (br dd, J = 5.2, 12.4 Hz, 1H), 2.82 (s, 5H), 2.67 (br d, J = 5.6 Hz, 2H), 1.87 (br s, 4H), 1.37 (br t, J = 6.8 Hz, 3H).

Compound **130** (35.19 mg, 72.17 µmol, 50.27% yield) was obtained as a white solid. **LCMS**: Rt = 0.438 min, m/z = 488.2 [M+H]+ **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 12.51 (br s, 1H), 9.11 (s, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 7.42 - 7.27 (m, 4H), 7.19 - 7.10 (m, 2H), 7.06 - 6.99 (m, 1H), 6.32 (br dd, J = 5.2, 10.8 Hz, 1H), 4.16 - 3.99 (m, 2H), 3.74 (br t, J = 11.6 Hz, 1H), 2.94 (dd, J = 5.2, 12.4 Hz, 1H), 2.82 (s, 5H), 2.67 (br d, J = 7.6 Hz, 2H), 1.87 (br s, 4H), 1.38 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 187

Compound **187** was prepared in a similar manner to Compound **077** using *N,N*-dimethylazetidin-3-amine instead of azetidine. Compound **187** (26.64 mg, 49.30 µmol, 79.72% yield, 95.6% purity) was obtained as a white gum. **LCMS**: Rt=0.429 min, m/z = 517.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.11 (s, 1H), 8.36 (br s, 1H), 8.31 - 8.21 (m, 2H), 7.40 - 7.32 (m, 2H), 7.32 - 7.27 (m, 2H), 7.21 - 7.10 (m, 2H), 7.06 - 7.00 (m, 1H), 6.17 (br dd, J = 5.1, 9.9 Hz, 1H), 4.09 (br dd, J = 7.0, 11.1 Hz, 2H), 3.82 - 3.68 (m, 2H), 3.63 (br s, 1H), 3.38 (br t, J = 6.8 Hz, 1H), 3.29 (br t, J = 6.9 Hz, 1H), 3.23 - 3.12 (m, 2H), 2.82 (s, 3H), 2.28 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 217

Compound **217** was prepared in a similar manner to compound **077**. Compound **217** (18.52 mg, 36.31 µmol, 5.39% yield, 95.4% purity) was obtained as an off-white solid. **LCMS**: Rt=0.492 min, m/z=487.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.87 (br s, 1H), 8.12 (br s, 1H), 7.76 (br d, J = 7.5 Hz, 1H), 7.44 (br s, 1H), 7.40 - 7.31 (m, 1H), 7.19 (br s, 1H), 7.12 - 6.95 (m, 3H), 6.34 (br s, 1H), 4.55 - 4.38 (m, 2H), 4.12 - 3.99 (m, 2H), 3.89 (br s, 2H), 3.32 (br s, 2H), 2.93 - 2.81 (m, 3H), 2.80 - 2.74 (m, 1H), 2.60 (br s, 1H), 2.42 (br s, 1H), 1.34 (br s, 3H).

Synthesis of Compound 218

Compound **218** was prepared in a similar manner to compound **077**. Compound **218** (13.21 mg, 25.13 µmol, 11.85% yield, 95.7% purity) was obtained as an off-white solid. **LCMS**: Rt=0.528 min, m/z=503.1[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.79 (br s, 1H), 8.59 (s, 1H), 8.04 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.46 (s, 1H), 7.33 (br d, J = 6.8 Hz, 1H), 7.29 - 7.21 (m, 4H), 7.09 (t, J = 7.6 Hz, 1H), 7.02 - 6.95 (m, 2H), 6.25 (br dd, J = 5.7, 9.4 Hz, 1H), 4.07 - 3.89 (m, 2H), 3.36 (br t, J = 7.1 Hz, 4H), 2.79 (br s, 1H), 2.71 - 2.66 (m, 4H), 2.62 (br s, 1H), 2.37 - 2.24 (m, 1H), 2.22 - 2.10 (m, 3H), 1.28 (br t, J = 6.9 Hz, 3H).

Synthesis of Compounds 222 and 223

Compounds **222** and **223** were prepared in a similar manner to Compound **077** using pyrrolidine and separated by SFC. Compound **222** (21.48 mg, 42.38 µmol, 37.49% yield, 96% purity) was obtained as a white solid. **LCMS**: Rt = 0.490 min, m/z = 487.2 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.38 (t, J=6.88 Hz, 3 H) 1.59 - 1.75 (m, 1 H) 1.88 (br s, 5 H) 2.64 (br d, J=10.38 Hz, 2 H) 2.79 (br s, 5 H) 3.66 - 3.89 (m, 1 H) 4.09 (br dd, J=17.01, 7.13 Hz, 2 H) 6.40 (br d, J=1.25 Hz, 1 H) 7.03 (br t, J=7.32 Hz, 1 H) 7.09 - 7.23 (m, 3 H) 7.28 - 7.39 (m, 5 H) 7.76 (br d, J=7.88 Hz, 1 H) 8.13 (s, 1 H) 12.22 (br d, J=0.88 Hz, 1 H). Compound **223** was obtained as a white solid (20.30 mg, 41.30 µmol, 36.54% yield, 99% purity). **LCMS**: Rt = 0.490 min, m/z = 487.2 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.38 (t, J=6.82 Hz, 3 H) 1.68 (br s, 1 H) 1.87 (br s, 4 H) 2.65 (br d, J=2.38 Hz, 2 H) 2.75 - 2.87 (m, 5 H) 3.77 (br t, J=11.69 Hz, 1 H) 3.98 - 4.16 (m, 2 H) 6.38 (br d, J=7.63 Hz, 1 H) 7.03 (br t, J=8.19 Hz, 1 H) 7.11 - 7.19 (m, 3 H) 7.28 - 7.40 (m, 5 H) 7.76 (br d, J=8.00 Hz, 1 H) 8.13 (s, 1 H) 12.24 (br s, 1 H).

Synthesis of Compound 225

Compound **225** was prepared in a similar manner to compound **077** using $NaBH_4$. Compound **225** (18.52 mg, 36.31 µmol, 5.39% yield, 95.4% purity) was obtained as an off-white solid. **LCMS**: Rt=0.417 min, m/z=500.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.06 (s, 1H), 8.45 (br s, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 7.39 (s, 1H), 7.32 - 7.23 (m, 2H), 7.16 - 7.04 (m, 3H), 6.95 (dt, J = 2.1, 8.3 Hz, 1H), 6.16 (br dd, J = 5.3, 9.6 Hz, 1H), 4.11 - 3.64 (m, 5H), 3.21 - 3.02 (m, 1H), 2.92 (dt, J = 5.0, 11.3 Hz, 1H), 2.87 - 2.69 (m, 3H), 2.62 (br d, J = 10.3 Hz, 1H), 2.68 - 2.50 (m, 1H), 2.47 - 2.23 (m, 3H), 0.82 - 0.57 (m, 4H).

Synthesis of Compound 226

Compound **226** was prepared in a similar manner to compound **077** using $NaBH_4$. Compound **226** (5.47 mg, 10.37 µmol, 6.15% yield, 97.8% purity) was obtained as an off-white solid. **LCMS**: Rt=0.430min, m/z=516.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.43 - 11.72 (m, 1H), 9.13 (s, 1H), 8.42 (s, 1H), 8.26 (s, 1H), 7.45 (br d, J = 7.7 Hz, 2H), 7.35 - 7.30 (m, 4H), 7.15 (br d, J = 7.7 Hz, 1H), 6.26 (br dd, J = 4.6, 9.4 Hz, 1H), 3.80 (br s, 1H), 3.70 (br s, 3H), 3.09 - 2.96 (m, 1H), 2.88 (s, 3H), 2.63 (br dd, J = 2.8, 5.0 Hz, 1H), 2.46 - 2.29 (m, 3H), 1.36 - 1.20 (m, 2H), 0.86 - 0.71 (m, 4H).

Synthesis of Compound 246

Compound **246** was prepared following the procedure provided for **077** using 3-azetidin-3-ol instead of azetidine. Compound **246** (14.80 mg, 29.91 µmol, 98.94% yield, 98.94% purity) was obtained as a white solid. **LCMS**: RT= 0.408 min, m/z=490.3 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.12 (s, 1H), 8.28 (d, J = 4.4 Hz, 2H), 7.41 - 7.28 (m, 4H), 7.21 - 7.14 (m, 2H), 7.08 - 7.01 (m, 1H), 6.14 (br dd, J = 4.8, 9.8 Hz, 1H), 4.61 - 4.52 (m, 1H), 4.18 - 4.01 (m, 2H), 3.89 (td, J = 6.8, 13.6 Hz, 2H), 3.68 (br t, J = 11.2 Hz, 1H), 3.34 - 3.19 (m, 2H), 3.13 (br dd, J = 5.2, 12.1 Hz, 1H), 2.83 (s, 3H), 1.39 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 247

Compound **247** was prepared following the procedure provided for **077** using 3-pyrrolidin-3-ol instead of azetidine. Compound **247** (5.75 mg, 11.41 µmol, 100.00% yield, 99.95% purity) was obtained as a white solid. **LCMS**: RT= 0.408 min, m/z=504.2 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.14 (s, 1H), 8.35 (d, J = 2.0 Hz, 1H), 8.29 (s, 1H), 7.41 - 7.28 (m, 4H), 7.17 (br d, J = 7.2 Hz, 2H), 7.04 (br t, J = 7.8 Hz, 1H), 6.37 (br t, J = 11.8 Hz, 1H), 4.49 (br d, J = 0.8 Hz, 1H), 4.18 - 4.01 (m, 2H), 3.84 (dt, J = 6.3, 11.6 Hz, 1H), 3.31 - 3.14 (m, 2H), 3.11 - 3.00 (m, 2H), 3.00 - 2.91 (m, 2H), 2.87 (s, 3H), 2.82 - 2.48 (m, 2H), 2.29 (td, J = 6.4, 13.0 Hz, 1H), 2.00 - 1.83 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 264

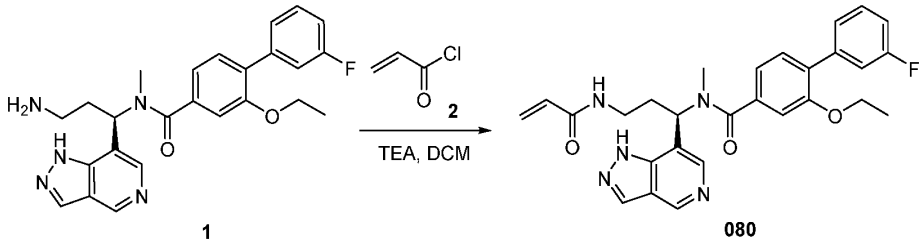
Compound **264** was prepared following the procedure provided for **077**. Compound **264** (12.8 mg, 24.92 µmol, 27.31% yield, 92% purity) was obtained as a white solid. **LCMS**: RT= 0.503 min, m/z = 473.2.4 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 1.38 (t, J=6.94 Hz, 3 H) 2.13 - 2.27 (m, 2 H) 2.78 (s, 3 H) 2.93 - 3.04 (m, 1 H) 3.29 (br d, J=1.25 Hz, 1 H) 3.41 - 3.61 (m, 4 H) 4.00 - 4.20 (m, 2 H) 6.19 (br dd, J=10.38, 4.63 Hz, 1 H) 7.03 (br t, J=7.88 Hz, 1 H) 7.10 - 7.17 (m, 1 H) 7.18 - 7.26 (m, 3 H) 7.28 - 7.41 (m, 4 H) 7.75 (d, J=8.00 Hz, 1 H) 8.12 (s, 1 H).

Synthesis of Compound 281

Compound **281** was prepared following the procedure provided for **077**. Compound **281** (5.47 mg, 10.37 µmol, 6.15% yield, 97.8% purity) was obtained as a white solid. **LCMS**: RT= 0.430min, m/z=516.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.43 - 11.72 (m, 1H), 9.13 (s, 1H), 8.42 (s, 1H), 8.26 (s, 1H), 7.45 (br d, J = 7.7 Hz, 2H), 7.35 - 7.30 (m, 4H), 7.15 (br d, J = 7.7 Hz, 1H), 6.26 (br dd, J = 4.6, 9.4 Hz, 1H), 3.80 (br s, 1H), 3.70 (br s, 3H), 3.09 - 2.96 (m, 1H), 2.88 (s, 3H), 2.63 (br dd, J = 2.8, 5.0 Hz, 1H), 2.46 - 2.29 (m, 3H), 1.36 - 1.20 (m, 2H), 0.86 - 0.71 (m, 4H).

Synthesis of Compound 080

Compound **080** was prepared according to the following scheme:



1 **080**

To a solution of compound 1 (120 mg, 268.15 µmol, 1 eq) in DCM (3 mL) was added TEA (54.27 mg, 536.31 µmol, 74.65 µL, 2 eq) and compound 2 (24.27 mg, 268.15 µmol, 21.79 µL, 1 eq) at 0°C. The reaction mixture was stirred at 0°C for 2h. The reaction mixture was added into water (10mL) and extracted with DCM (10ML*3), then the organic phase was

dried with Na2SO4 and concentrated under reduce pressure to give the residue. The crude product was purified by Prep-TLC (DCM: MeOH=10:1) to give the product (Rf =0.55). The crude product was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 5%-35% B over 15 min) to give the product Compound **080** (19.88 mg, 38.25 µmol, 14.26% yield, 96.5% purity) as white solid. **LCMS**: Rt =0.453min, m/z=502.2(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.30 - 11.88 (m, 1H), 9.31 - 9.00 (m, 1H), 8.62 - 8.37 (m, 1H), 8.32 (s, 1H), 7.43 - 7.36 (m, 2H), 7.35 - 7.30 (m, 2H), 7.19 - 7.15 (m, 2H), 7.07 (dt, J = 1.6, 8.3 Hz, 1H), 6.41 - 6.30 (m, 2H), 6.27 - 6.14 (m, 2H), 5.76 - 5.70 (m, 1H), 4.20 - 4.05 (m, 2H), 4.00 - 3.87 (m, 1H), 3.43 - 3.30 (m, 1H), 2.90 (s, 3H), 2.81 - 2.69 (m, 1H), 2.51 - 2.38 (m, 1H), 1.40 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 083

Compound **083** was prepared in a similar manner to Compound **076** and was isolated as a brown solid (13.64 mg, 24.25 µmol, 12.40% yield, 96.1% purity). **LCMS**: Rt =0.478min, m/z=540.2(M+H+) **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 8.44 (br s, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 7.43 (d, J = 2.0 Hz, 2H), 7.35 - 7.31 (m, 2H), 7.17 - 7.09 (m, 2H), 6.21 (br dd, J = 5.2, 8.8 Hz, 1H), 4.15 - 4.05 (m, 2H), 3.05 - 2.95 (m, 1H), 2.86 (s, 3H), 2.83 (s, 3H), 2.75 - 2.49 (m, 9H), 1.38 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 085 and 087

Compounds **085** and **087** were prepared by the steps of **GP1-3** and **GP5-8**, where the product of **GP6** was Boc-protected and the product on **GP8** was deprotected under acidic conditions and then purified by SFC column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: [CO2-EtOH (0.1%NH3H2O)]; B%:62.5%, isocratic elution mode to give two peaks.

Peak 1: Compound **087** (100 mg, 210.12 µmol, 55.28% yield, 99.5% purity) was obtained as a white solid. **LCMS**: Rt =0.435 min, m/z=474.2(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.34 - 11.91 (m, 1H), 9.13 (s, 1H), 8.44 (s, 1H), 8.28 (s, 1H), 7.43 - 7.29 (m, 4H), 7.06 (s, 3H), 6.08 - 6.01 (m, 1H), 4.20 - 3.97 (m, 2H), 3.32 - 3.30 (m, 2H), 3.24 - 3.03 (m, 2H), 2.87 (s, 3H), 2.64 - 2.63 (m, 1H), 2.33 - 2.21 (m, 1H), 1.82 - 1.81 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H).

Peak 2 was re-purified by prep-HPLC column: Unisil 3-100 C18 Ultra 150*50mm*3 um;mobile phase: [water(FA)-ACN];gradient:8%-38% B over 10 min to give Compound **085** (9.94 mg, 18.94 µmol, 4.98% yield, 99% purity, FA) was obtained as a white solid. **LCMS**: Rt =0.429min, m/z=474.2(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (br s, 1H), 8.44 (s, 1H), 8.28 (s, 1H), 7.43 - 7.29 (m, 4H), 7.06 (s, 3H), 6.08 - 6.01 (m, 1H), 4.20 - 3.97 (m, 2H), 3.32 - 3.30 (m, 2H), 3.24 - 3.03 (m, 2H), 2.87 (s, 3H), 2.64 - 2.63 (m, 1H), 2.33 - 2.21 (m, 1H), 1.82 - 1.81 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H).

Synthesis of Compounds 088 and 089

Compounds **088** and **089** were prepared by the steps of Scheme 3, **GP1-3** and **GP5-8**, where the product of **GP6** was Boc-protected and the product on **GP8** was deprotected under acidic conditions and then purified by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: [CO2-ACN/i-PrOH(0.1% NH3H2O)];B%:55%, isocratic elution mode) and concentrated and lyophilized to get the peak 1. Compound **089** (90 mg, 187.78 µmol, 55.58% yield, 98.8% purity) as an off-white solid.

Peak 2 was re-purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:5%-35% B over 9 min) and lyophilized to get the crude, the crude was re-purified by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [CO2-ACN/i-PrOH(0.1% NH3H2O)];B%:55%, isocratic elution mode) and concentrated and lyophilized to give Compohnd **088** (9.77 mg, 20.20 µmol, 5.98% yield, 97.89% purity) as a brown gum.

Compound **088**: **LCMS**: Rt=0.425 min, m/z=474.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.11 (s, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 7.40 - 7.31 (m, 2H), 7.31 - 7.28 (m, 1H), 7.27 - 7.23 (m, 1H), 7.08 - 6.98 (m, 3H), 6.17 - 5.85 (m, 1H), 4.18 – 3.95 (m, 2H), 3.43 - 3.36 (m, 1H), 3.35 - 3.22 (m, 1H), 3.17 (br t, J = 7.2 Hz, 2H), 3.02 - 2.95, 2.85 (s, 3H), 2.27 - 2.16 (m, 1H), 1.47 - 1.39 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H)

Compound **089**: **LCMS**: Rt=0.425 min, m/z=474.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ =9.11 (s, 1H), 8.45 (s, 1H), 8.26 (s, 1H), 7.40 - 7.31 (m, 2H), 7.27 (s, 2H), 7.06 – 7.00 (m, 3H), 6.17 - 5.85 (m, 1H), 4.18 - 3.95 (m, 2H), 3.43 - 3.36 (m, 1H), 3.35 - 3.22 (m, 1H), 3.08 (br t, J = 67.2 Hz, 2H), 3.02 - 2.95 (m, 1H), 2.82 (s, 3H), 2.22 - 2.10 (m, 1H), 1.47 - 1.39 (m, 1H), 1.36 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 081

Compound **081** was prepared using Compound **088** as starting material. To a solution of compound **088** in DMA (1 mL) was added formaldehyde (30.85 mg, 380.12 µmol, 28.30 µL, 37% purity, 3 eq) and NaBH(OAc)3 (80.56 mg, 380.12 µmol, 3 eq) at 0°C, the mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with water (3 mL) and extracted with DCM (3 mL * 3). The combined organic layers dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*7um; mobile phase: [water (FA)-ACN]; gradient: 5%-35% B over 10 min) to give the Compound **081** (38.57 mg, 71.76 µmol, 87.47% yield, 99.28% purity, FA) was obtained as a white solid. **LCMS**: RT=0.428 min, m/z=488.2 [M+H]+ **^{1}H NMR** (400 MHz, D_2O) δ = 9.04 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 7.27 - 7.26 (m, 2H), 7.25- 7.15 (m, 2H), 6.89 - 6.78 (m, 3H), 6.20 - 5.80 (m, 1H), 4.00 - 3.94 (m, 2H), 3.70 - 3.55 (m, 1H), 3.31 - 3.01 (m, 2H), 2.95 - 2.85 (m, 1H), 2.78 (s, 3H), 2.45 (s, 3H), 2.38 - 2.32 (m, 2H), 2.00 - 1.96 (m, 1H), 1.28 (br t, J = 7.2 Hz, 3H).

Synthesis of Compound 082

Compound **082** was according to Compound **081** using Comound **089** as starting material. Compound **082** (22.96 mg, 46.84 µmol, 44.36% yield, 99.46% purity) was obtained as an off-white solid. **LCMS**: Rt=0.435 min, m/z=488.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.33 (br s, 1H), 9.33 (s, 1H), 8.61 (s, 1H), 8.48 (s, 1H), 7.62 - 7.55 (m, 2H), 7.53 - 7.48 (m, 2H), 7.27 (s, 3H), 6.33 (br s, 1H), 4.36 - 4.21 (m, 2H), 3.77 - 3.57 (m, 1H), 3.32 (br t, J = 8.0 Hz, 1H), 3.04 (s, 4H), 2.72 - 2.63 (m, 5H), 2.60 - 2.30 (m, 1H), 1.76 - 1.63 (m, 1H), 1.59 (t, J = 7.2 Hz, 3H).

Synthesis of Compound 090

Compound **090** was prepared following the steps of **GP4-8**. The resulting product was then oxidized and N-methylated using the same procedure described for Compound **074**. Compound **090** (8.78 mg, 16.56 µmol, 13.73% yield, 99.32% purity) was obtained as white solid. **LCMS**: Rt =0.457min, m/z=526.3(M+H+) **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.48 (br s, 1H), 8.44 (s, 1H), 8.27 (s, 1H), 7.43 (d, J = 2.0 Hz, 2H), 7.36 - 7.30 (m, 2H), 7.19 - 7.01 (m, 2H), 6.28 (br d, J = 8.8 Hz, 1H), 4.16 - 4.03 (m, 2H), 2.83 (s, 3H), 2.73 - 2.62 (m, 2H), 2.51 (s, 6H), 2.01 (s, 2H), 1.38 (t, J = 7.2 Hz, 3H).

Synthesis of Compound 091

Compound **091** was prepared following the steps of **GP4-8**. The resulting product was then oxidized and N-methylated using the same procedure described for Compound **074.** Compound **091** (111.31 mg, 231.52 µmol, 32.02% yield, 98.09% purity) was obtained as white solid. **LCMS**: Rt =0.428min, m/z=472.3(M+H+) **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.30 - 9.19 (m, 1H), 8.58 - 8.49 (m, 1H), 8.37 (s, 1H), 7.48 - 7.42 (m, 2H), 7.39 (br d, J = 6.4 Hz, 2H), 7.27 - 7.21 (m, 2H), 7.16 - 7.08 (m, 1H), 6.34 (br d, J = 8.1 Hz, 1H), 4.25 - 4.10 (m, 2H), 3.29 - 3.20 (m, 1H), 2.96 (s, 3H), 2.95 - 2.85 (m, 2H), 2.77 (s, 6H), 2.74 - 2.57 (m, 1H), 1.46 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 092 and 097:

Compounds **092** and **097** were synthesized following the steps of **GP1-3** and **GP5-9**, then **GP11-13**. The crude compounds **092** and **097** was purified by SFC (column: DAICEL CHIRALPAK AD (250mm x 50mm, 10um); mobile phase: [CO_2:*i*-PrOH (0.1%NH_3H_2O)]; B%: 30%, isocratic elution mode). The eluent was concentrated to remove organic solvents and the residual aqueous solution was lyophilized to afford the desired products.

Compound **092** (80 mg, 174.10 µmol, 33.33% yield) was obtained as an off-white solid. **LCMS**: t_R = 0.418 min, m/z = 460.2 $[M+H]^+$ **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.06 (s, 1H), 8.20 - 8.10 (m, 2H), 7.31 - 7.26 (m, 1H), 7.30 - 7.10 (m, 3H), 7.00 - 6.89 (m, 3H), 6.43 (br d, J = 10.0 Hz, 1H), 4.05 - 3.93 (m, 2H), 3.87 (s, 2H), 3.82 (br d, J = 7.6 Hz, 1H), 3.80 - 3.75 (m, 1H), 3.36 (br s, 1H), 2.68 (s, 3H), 1.28 (t, J = 6.8 Hz, 3H).

Compound **097** (60 mg, 118.69 µmol, 22.72% yield) was obtained as an off-white solid. **LCMS**: t_R = 0.418 min, m/z = 460.2 $[M+H]^+$ **NMR**: ^{1}H NMR (400 MHz, CHLOROFORM-

d) δ = 9.06 (s, 1H), 8.52 (br s, 1H), 8.30 - 8.19 (m, 2H), 7.35 - 7.29 (m, 1H), 7.21 - 7.16 (m, 3H), 7.00 (br s, 2H), 6.93 (br d, J = 8.0 Hz, 1H), 6.58 (br d, J = 11.2 Hz, 1H), 4.42 - 4.32 (m, 1H), 4.30 - 4.24 (m, 1H), 4.22 - 4.08 (m, 2H), 4.00 - 3.90 (m, 2H), 3.80 - 3.70 (m, 1H), 2.69 (s, 3H), 1.27 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 095

Compound **095** was prepared following the steps of **GP4-8**. The resulting product was then oxidized and N-methylated using the same procedure described for Compound **074.** Compound **095** (1851.73 mg, 3.64 mmol, 46.49% yield, 99.9% purity) was isolated as light-yellow gum. **LCMS**: Rt =0.432min, m/z=508.3(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.10 (s, 1H), 8.39 (s, 1H), 8.25 (s, 1H), 8.21 (s, 2H), 7.28 (td, J = 3.0, 7.8 Hz, 2H), 7.25 - 7.19 (m, 2H), 7.07 - 7.01 (m, 2H), 6.99 - 6.93 (m, 1H), 6.23 (br dd, J = 4.5, 10.3 Hz, 1H), 4.75 - 4.68 (m, 1H), 4.63 - 4.56 (m, 1H), 4.08 - 3.92 (m, 2H), 3.09 - 3.01 (m, 1H), 3.01 - 2.91 (m, 2H), 2.84 (td, J = 6.2, 9.4 Hz, 1H), 2.78 (s, 3H), 2.72 - 2.58 (m, 1H), 2.54 (s, 3H), 2.49 - 2.36 (m, 1H), 1.29 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 079:

Compound **079** was prepared using Compound **097** as starting material. To a solution of **097** (40 mg, 79.12 µmol, 1 eq) and formaldehyde (19.27 mg, 237.37 µmol, 17.67 µL, 37% purity, 3 eq) in DMA (0.5 mL) was added AcOH (475.14 µg, 7.91 µmol, 0.1 eq). The mixture was stirred at 25°C for 0.5 h, then $NaBH(OAc)_3$ (50.31 mg, 237.37 µmol, 3 eq) was added at 0°C. The mixture was stirred at 25°C for 0.5 h and filtered to isolate the filtrate. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-CAN]; gradient: 5%-35% B over 15 min) and lyophilized to get the crude product. The crude product was repurified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 5%-35% B over 15 min) and lyophilized. Compound **079** (15.55 mg, 29.85 µmol, 37.72% yield, 99.73% purity) was obtained as a white solid. **LCMS**: Rt=0.431 min, m/z=474.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.81 - 11.30 (m, 1H), 9.12 (s, 1H), 8.54 (br s, 1H), 8.34 - 8.21 (m, 2H), 7.41 - 7.32 (m, 2H), 7.31 - 7.26 (m, 2H), 7.09 - 6.99 (m, 3H), 6.34 (br d, J = 10.8 Hz, 1H), 4.13 - 4.00 (m, 2H), 3.95 - 3.79 (m, 3H), 3.43 (t, J = 5.6 Hz, 1H), 3.14 (br s, 1H), 2.80 (s, 3H), 2.51 (s, 3H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 210

Compound **210** was prepared in a similar manner to Compound **157** and was then treated with m-CPBA in DCM. Compound **210** (1736.51 mg, 3.38 mmol, 55.50% yield, 99% purity) was obtained as an off-white solid. **LCMS**: RT=0.449min, m/z=508.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.08 (s, 1H), 8.46 (s, 1H), 8.35 (s, 1H), 8.22 (s, 1H), 7.49 (s, 1H), 7.36 (br d, J = 6.3 Hz, 1H), 7.28 (br d, J = 6.8 Hz, 2H), 7.25 (s, 1H), 7.14 - 7.04 (m,

2H), 6.26 (br dd, J = 6.0, 8.6 Hz, 1H), 4.15 - 3.85 (m, 2H), 3.82 - 3.53 (m, 2H), 3.44 (s, 3H), 3.36 (s, 3H), 3.19 (br d, J = 9.5 Hz, 1H), 2.96 - 2.66 (m, 4H), 1.32 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 105

Compound **105** was prepared according to the steps of **GP16**, **GP5**, **GP8**, and **GP9** and was isolated as a white solid (41.43 mg, 87.97 µmol, 10.03% yield, 98% purity). **LCMS**: Rt=0.383 min, m/z=462.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.05 (s, 1H), 8.48 (s, 1H), 8.24 - 8.19 (m, 1H), 7.39 - 7.30 (m, 2H), 7.25 (br s, 2H), 7.10 - 6.99 (m, 3H), 5.07 (br s, 2H), 4.07 - 3.72 (m, 4H), 3.33 - 2.77 (m, 4H), 1.38 - 1.17 (m, 6H).

Synthesis of Compound 106

Compound **106** was prepared in a similar manner to Compound **067** using (3S,5R)-3,5-difluoropiperidine and was isolated as a white solid. (44.36 mg, 81.69 µmol, 38.42% yield, 99% purity). **LCMS**: RT= 0.433 min, m/z= 538.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.04 (br s, 1H), 8.31 (br s, 1H), 8.19 (s, 1H), 7.31 - 7.23 (m, 2H), 7.23 - 7.18 (m, 2H), 6.97 - 6.87 (m, 3H), 5.03 (s, 2H), 4.50 (br s, 1H), 4.38 (br s, 1H), 3.94 (br d, J = 4.3 Hz, 2H), 3.39 (br s, 2H), 2.61 - 2.33 (m, 6H), 2.14 - 1.86 (m, 2H), 1.26 (br t, J = 6.2 Hz, 3H).

Synthesis of Compound 107

Compound **107** was prepared in a similar manner to Compound **067** using (3R,4R)-3,4-difluoropyrrolidine and isolated as a white solid (60.40 mg, 114.21 µmol, 46.67% yield, 99% purity). **LCMS**: Rt=0.423 min, m/z=524.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 0.83 (br t, J=6.88 Hz, 3 H) 1.99 - 2.44 (m, 6 H) 2.96 (br s, 2 H) 3.51 (br s, 2 H) 4.39 - 4.66 (m, 4 H) 6.38 - 6.60 (m, 3 H) 6.74 - 6.88 (m, 4 H) 7.69 - 7.91 (m, 2 H) 8.60 (s, 1 H) 11.40 - 11.81 (m, 1 H).

Synthesis of Compound 108

Compound **108** was prepared in a similar manner to Compound **067** using (3R,4S)-3,4-difluoropyrrolidine and was isolated as a white solid. **LCMS**: Rt=0.417 min, m/z= 524.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.35 (br t, J=6.75 Hz, 3 H) 2.54 - 2.92 (m, 6 H) 3.46 (br s, 2 H) 4.03 (br s, 2 H) 4.85 (br s, 1 H) 4.99 (br s, 1 H) 5.04 (br s, 2 H) 6.91 - 7.09 (m, 3 H) 7.29 (br d, J=7.00 Hz, 2 H) 7.32 - 7.42 (m, 2 H) 8.23 - 8.39 (m, 2 H) 9.12 (br s, 1 H) 11.87 - 12.24 (m, 1 H).

Synthesis of Compound 109

Compound **109** was prepared in a similar manner to Compound **067** using 3-fluoropiperidine and was isolated as a white solid (27.36 mg, 54.06 µmol, 24.91% yield, 99.9% purity). **LCMS**: Rt =0.419min, m/z=506.2(M+H+). **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 12.34 - 11.77 (m, 1H), 9.03 (br s, 1H), 8.30 - 8.10 (m, 2H), 7.33 - 7.21 (m, 3H), 7.18 (br s, 1H), 7.01 - 6.80 (m, 3H), 5.18 - 4.93 (m, 3H), 4.04 - 3.83 (m, 2H), 3.56 - 3.33 (m, 2H), 2.77 - 2.61 (m, 4H), 2.39 - 1.76 (m, 4H), 1.27 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 110

Compound **110** was prepared in a similar manner to Compound **067** using 4-fluoropiperidine and was isolated as a light yellow oil (117 mg, 180.04 µmol, 50.66% yield). **LCMS**: Rt =0.502 min, m/z=650.2[M+H]+

Synthesis of Compound 111

Compound **111** was prepared in a similar manner to Compound **067** using (3S,5S)-3,5-difluoropiperidine and was isolated as a white solid (67.67 mg, 123.36 µmol, 49.63% yield, 98% purity). **LCMS**: RT= 0.442 min, m/z= 538.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.49 - 11.64 (m, 1H), 9.15 (s, 1H), 8.38 (br s, 1H), 8.29 (s, 1H), 7.36 (td, J = 5.2, 7.9 Hz, 2H), 7.31 (br d, J = 7.3 Hz, 2H), 7.09 - 6.93 (m, 3H), 5.28 - 5.14 (m, 1H), 5.11 - 4.98 (m, 1H), 4.96 - 4.68 (m, 2H), 4.05 (br d, J = 6.6 Hz, 2H), 3.47 (br s, 2H), 2.76 - 2.60 (m, 2H), 2.59 - 2.51 (m, 2H), 2.49 (br s, 2H), 2.11 - 1.99 (m, 2H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 112

Compound **112** was prepared in a similar manner to Compound **117**. Compound **112** was isolated as a white solid (40.16 mg, 82.21 µmol, 20.19% yield, 99% purity). **LCMS**: Rt=0.420 min, m/z=484.5[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 13.03 - 11.91 (m, 1H), 9.09 (br s, 1H), 8.26 (s, 2H), 7.53 (br d, J = 7.6 Hz, 2H), 7.46 - 7.38 (m, 2H), 7.37 - 7.29 (m, 2H), 7.00 (br d, J = 5.3 Hz, 2H), 5.06 (br s, 2H), 3.98 (br s, 2H), 3.52 (br s, 2H), 2.58 (br s, 2H), 2.33 (br s, 4H), 1.61 (br s, 4H), 1.46 (br s, 2H), 1.34 (br t, J = 6.9 Hz, 3H).

Synthesis of Compound 113

Compound **113** was prepared in a similar manner to Compound **067** using 3,3-difluoropiperidine and was isolated as a white solid (58.1 mg, 107.65 µmol, 52.86% yield, 99.6% purity). **LCMS**: Rt =0.447 min, m/z=538.2[M+H]+ **HPLC**: Rt =1.220 min. **1HNMR**:(400 MHz, CHLOROFORM-d) δ = 12.31 - 11.89 (m, 1H), 9.13 (s, 1H), 8.35 (br s, 1H), 8.27 (s, 1H), 7.40 - 7.32 (m, 2H), 7.29 (br d, J = 7.8 Hz, 2H), 7.09 - 6.93 (m, 3H), 5.10 (s, 2H), 4.04 (br d, J = 6.8 Hz, 2H), 3.46 (br s, 2H), 2.69 - 2.44 (m, 4H), 2.29 (br s, 2H), 1.93 - 1.78 (m, 4H), 1.36 (t, J = 6.8 Hz, 3H).

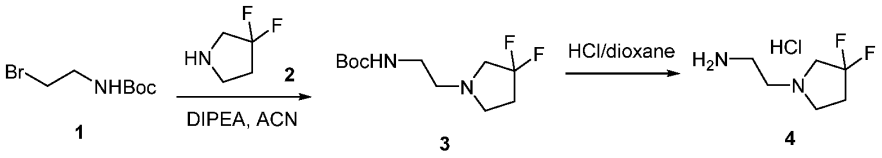
Synthesis of Compound 114

Compound **114** was prepared according to the steps of **GP16**, **GP5**, **GP8**, **GP9**, followed by oxidation IBX in DMSO. The oxidized product was then coupled with 3-fluoropiperidine following the procedure for Compound 067, then deprotected with TFA in DCM (**GP9**). Compound **114** was isolated as a white solid (53.39 mg, 92.88 µmol, 32.42% yield, 98.4% purity). **LCMS**: Rt =0.429min, m/z=520.2(M+H+) **^{1}H NMR**: (400 MHz, chloroform-d) δ = 9.07 (s, 1H), 8.30 (br s, 1H), 8.24 (s, 1H), 8.19 (s, 1H), 7.32 - 7.20 (m, 3H), 7.17 (br s, 1H), 7.03 - 6.78 (m, 3H), 5.09 - 4.94 (m, 2H), 4.68 - 4.39 (m, 1H), 3.93 (br s, 2H),

3.43 (br s, 2H), 2.74 - 2.34 (m, 4H), 2.25 (br d, J = 1.3 Hz, 2H), 1.84 - 1.54 (m, 3H), 1.43 (br s, 1H), 1.27 (br t, J = 6.9 Hz, 3H).

Synthesis of Compound 115

Compound **115** was prepared in a similar manner to Compound **117**. The amine starting material was prepared according to the following scheme:



Compound **115** was isolated as a white solid (84.22 mg, 159.26 µmol, 18.49% yield, 99% purity). **LCMS**: Rt=0.443 min, m/z=524.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.36 (t, J=6.94 Hz, 3 H) 2.19 (br s, 2 H) 2.52 (br s, 2 H) 2.66 (br s, 4 H) 3.43 - 3.55 (m, 2 H) 4.03 (br s, 2 H) 5.05 (s, 2 H) 6.88 - 7.10 (m, 3 H) 7.29 (br d, J=7.38 Hz, 2 H) 7.31 - 7.41 (m, 2 H) 8.22 - 8.41 (m, 2 H) 9.12 (s, 1 H) 11.94 - 12.26 (m, 1 H).

Synthesis of Compound 116

Compound **116** was prepared in a similar manner to Compound **117**. Compound **116** was isolated as a white solid (61.75 mg, 131.09 µmol, 22.22% yield, 95% purity). **LCMS**: Rt =0.410min, m/z=448.2(M+H+) **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 12.56 - 12.10 (m, 1H), 9.23 - 8.95 (m, 1H), 8.45 - 8.06 (m, 2H), 7.41 - 7.31 (m, 2H), 7.26 - 7.13 (m, 2H), 7.03 (br t, J = 7.3 Hz, 3H), 5.02 (br s, 2H), 4.15 - 3.88 (m, 2H), 3.68 - 3.37 (m, 2H), 3.01 - 2.74 (m, 2H), 2.61 - 2.24 (m, 3H), 1.40 - 1.29 (m, 3H).

Synthesis of Compound 117

Compound **117** was prepared according to the steps of **GP16**, **GP5**, **GP8**, and **GP9**. Compound **117** was isolated as a white solid (148.3 mg, 292.70 µmol, 41.10% yield, 99% purity). **LCMS**: Rt=0.413 min, m/z=502.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 10.59 - 9.39 (m, 3H), 9.11 (br s, 1H), 8.47 - 8.22 (m, 3H), 7.40 - 7.28 (m, 3H), 7.25 (br s, 1H), 7.17 - 6.88 (m, 3H), 5.08 (s, 2H), 3.98 (br s, 2H), 3.91 - 3.54 (m, 2H), 3.50 - 2.19 (m, 6H), 1.98 - 1.62 (m, 4H), 1.55 (br s, 2H), 1.33 (br t, J = 6.4 Hz, 3H).

Synthesis of Compound 118

Compound **118** was prepared in a similar manner to Compound **117**. Compound **118** was isolated as a white solid (99.03 mg, 194.69 µmol, 27.42% yield, 99% purity). **LCMS**: Rt=0.408 min, m/z=504.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.12 (br s, 1H), 8.54 - 7.88 (m, 3H), 7.40 - 7.27 (m, 2H), 7.26 - 7.23 (m, 1H), 7.08 - 6.79 (m, 3H), 5.06 (br s, 2H), 3.99 (br s, 2H), 3.79 - 3.28 (m, 6H), 2.78 - 2.49 (m, 2H), 2.47 - 1.78 (m, 4H), 1.35 (br t, J = 6.6 Hz, 3H).

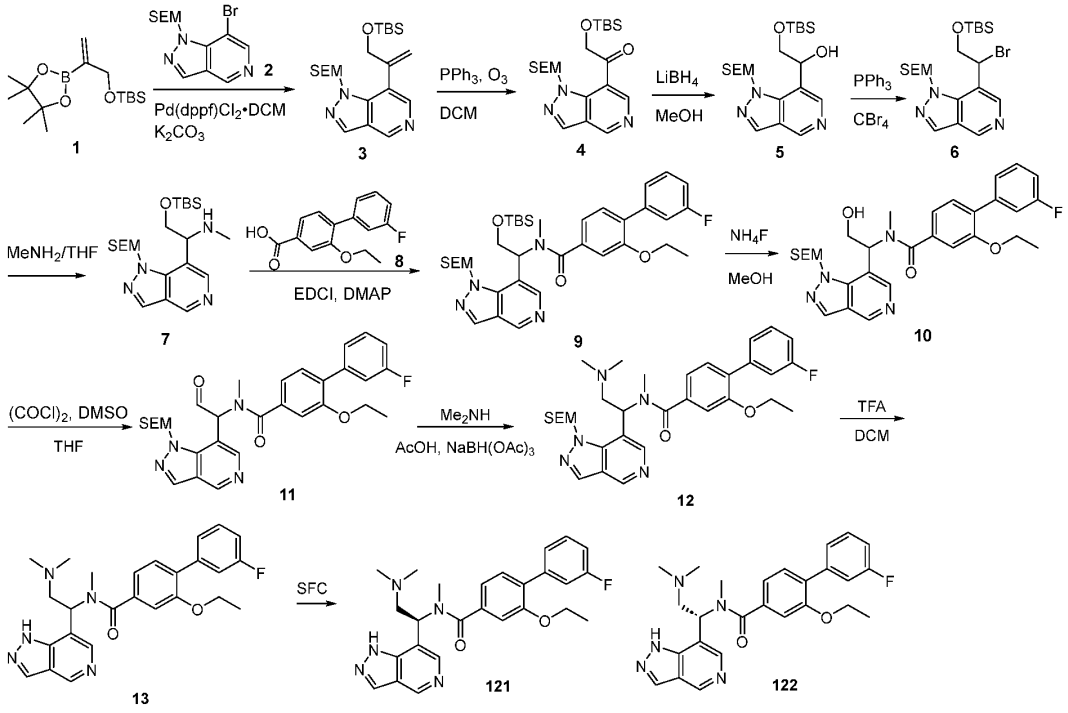
Synthesis of Compound 119

Compound **119** was prepared in a similar manner to Compound **117**. Compound **119** was isolated as a white solid (52.61 mg, 106.82 μmol, 15.62% yield, 99% purity). **LCMS**: Rt=0.420 min, m/z=488.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.33 (br t, J=6.50 Hz, 3 H) 1.79 - 2.17 (m, 4 H) 2.40 - 3.17 (m, 4 H) 3.25 - 3.51 (m, 2 H) 3.58 - 3.90 (m, 2 H) 3.98 (br s, 2 H) 5.08 (br s, 2 H) 6.92 - 7.12 (m, 3 H) 7.27 (s, 2 H) 7.30 - 7.40 (m, 2 H) 8.07 - 8.58 (m, 3 H) 9.09 (br s, 1 H) 10.68 - 11.21 (m, 3 H).

Synthesis of Compound 120

Compound **120** was prepared in a similar manner to Compound **117**. Compound **119** was isolated as a white solid (95.96 mg, 194.04 μmol, 27.60% yield, 99% purity). **LCMS**: Rt=0.421 min, m/z=490.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 0.84 - 1.34 (m, 6 H) 1.37 (br t, J=6.75 Hz, 3 H) 2.43 - 3.02 (m, 4 H) 3.10 - 3.51 (m, 2 H) 3.57 - 3.94 (m, 2 H) 4.04 (br d, J=5.00 Hz, 2 H) 5.14 (br s, 2 H) 6.97 - 7.15 (m, 3 H) 7.28 - 7.33 (m, 2 H) 7.35 - 7.44 (m, 2 H) 8.06 - 8.61 (m, 3 H) 9.14 (br s, 1 H) 10.22 - 11.01 (m, 3 H).

Synthesis of Compounds 121 and 122



To a solution of compound **1** (10 g, 33.52 mmol, 1 eq) and compound **2** (11.01 g, 33.52 mmol, 1 eq) in dioxane (100 mL) and H_2O (10 mL) was added K_2CO_3 (9.27 g, 67.05 mmol, 2 eq) and $Pd(dppf)Cl_2•CH_2Cl_2$ (1.37 g, 1.68 mmol, 0.05 eq). The mixture was stirred at 100°C for 12h under N_2 atmosphere. The reaction mixture was poured into H_2O (300 mL) under N_2 and extracted by EtOAc (200 mL x 3), the organic phase was combined and washed with brine (200 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated to

give a residue. The resulting residue was purified by silica gel column chromatography (PE: EA = 1: 0 to 3:1) to give the product (Rf = 0.5). Compound **3** (11.5 g, 27.40 mmol, 81.73% yield) was obtained as a brown oil. **^{1}H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.05 (br s, 1H), 8.21 (br d, *J* = 10.0 Hz, 1H), 8.19 (s, 1H), 5.78 (s, 3H), 5.30 (d, *J* = 1.2 Hz, 1H), 4.47 (s, 2H), 3.62 - 3.50 (m, 2H), 0.89 (s, 9H), 0.85 (d, *J* = 8.4 Hz, 2H), 0.02 (s, 6H), -0.04 (s, 9H)

To a solution of compound **3** (5.5 g, 13.10 mmol, 1 eq) in DCM (60 mL) and MeOH (60 mL) was added ozone (628.99 mg, 13.10 mmol, 1 eq) at -70°C for 0.5h, then added PPh_3 (6.87 g, 26.21 mmol, 2 eq) in DCM (5 mL) at -70 °C, the mixture was stirred at 20°C for 1hr. The reaction was concentrated to give a crude product. The resulting residue was purified by silica gel column chromatography (PE: EA = 1:0 to 3:1) to give the product (Rf = 0.35). Compound **4** (5.1 g, 12.09 mmol, 92.29% yield) was obtained as a yellow oil. **^{1}H NMR:** (400 MHz, METHANOL-d_4) δ = 9.26 (s, 1H), 8.81 (s, 1H), 8.42 (s, 1H), 5.90 (s, 2H), 4.93 (s, 2H), 3.30 - 3.25 (m, 2H), 0.89 (s, 9H), 0.74 (dd, *J* = 7.6, 8.8 Hz, 2H), 0.15 (s, 6H), -0.11 (s, 9H)

To a solution of compound **4** (5 g, 11.86 mmol, 1 eq) in MeOH (55 mL) was added $LiBH_4$ (2 M, 17.79 mL, 3 eq) at 0°C under N_2 atmosphere, the mixture was stirred at 20°C for 2hr under N_2 atmosphere. The combined mixture was poured into sat. NH_4Cl. aq (50 mL) at 0 °C, and the aqueous phase was extracted with EA (80 mL x 3). The combined organic phase was dried with Na_2SO_4 and concentrated to give the crude product. The resulting residue was purified by silica gel column chromatography (PE: EA = 1: 0 to 1: 1) to give the product (Rf = 0.4). Compound **5** (5.7 g, crude) was obtained as a yellow oil. **^{1}H NMR:** (400 MHz, METHANOL-d_4) δ = 9.02 (s, 1H), 8.54 (s, 1H), 8.31 (s, 1H), 6.15 (d, *J* = 11.6 Hz, 1H), 5.85 (d, *J* = 11.6 Hz, 1H), 5.51 (dd, *J* = 5.6, 7.6 Hz, 1H), 4.16 - 4.12 (m, 1H), 3.87 (dd, *J* = 8.0, 9.6 Hz, 1H), 3.62 - 3.53 (m, 2H), 0.89 - 0.78 (m, 2H), 0.71 (s, 9H), -0.06 (s, 9H), -0.10 (s, 3H), -0.24 (s, 3H)

To a solution of compound **5** (5.7 g, 13.45 mmol, 1 eq) in DCM (60 mL) was added CBr_4 (8.92 g, 26.91 mmol, 2 eq) and PPh_3 (5.29 g, 20.18 mmol, 1.5 eq) in DCM (20 mL) at 0°C, the mixture was stirred at 20°C for 2h. The mixture was concentrated to give a crude product. The resulting residue was purified by silica gel column chromatography (PE: EA = 1:0 to 3:1) to give the product (Rf = 0.5). Compound **6** (2.31 g, 4.75 mmol, 35.29% yield) was obtained as a yellow oil. **^{1}H NMR:** (400 MHz, METHANOL-d_4) δ = 9.06 (s, 1H), 8.67 (s, 1H), 8.35 (s, 1H), 6.09 - 6.03 (m, 1H), 6.02 - 5.95 (m, 2H), 4.43 - 4.29 (m, 2H), 3.63 - 3.51 (m, 2H), 0.93 - 0.82 (m, 2H), 0.75 (s, 9H), 0.03 (s, 3H), -0.04 - -0.08 (m, 12H)

To a solution of compound **6** (2.31 g, 4.75 mmol, 1 eq) in DMF (25 mL) was added K_2CO_3 (1.31 g, 9.49 mmol, 2 eq) and $MeNH_2$ (2 M, 11.87 mL, 5 eq), the mixture was stirred at 30°C for 12h. The reaction mixture was poured in water (30 mL), and extracted with EA (50 mL x 3). The combined organic layers were washed by brine (50 mL x 3) and dried over

Na_2SO_4 and concentrated under reduced pressure to give a residue. Compound **7** (2.2 g, crude) was obtained as a yellow oil. **LCMS:** Rt = 0.509 min, m/z = 437.3 $[M+H]^+$

To a solution of compound **7** (2.2 g, 3.78 mmol, 1 eq) and compound **8** (1.08 g, 4.16 mmol, 1.1 eq) in DCM (20 mL) was added EDCI (1.09 g, 5.67 mmol, 1.5 eq) and DMAP (46.15 mg, 377.80 µmol, 0.1 eq), the mixture was stirred at 25°C for 1hr. The mixture was concentrated to give a crude product. The resulting residue was purified by silica gel column chromatography (PE: EA = 1:1) to give the product (Rf = 0.4). Compound **9** (2.4 g, 3.53 mmol, 93.56% yield) was obtained as a yellow oil. **LCMS:** Rt = 0.646 min, m/z = 679.4 $[M+H]^+$

To a solution of compound **9** (2.1 g, 3.09 mmol, 1 eq) in MeOH (30 mL) was added NH_4F (1.15 g, 30.93 mmol, 10 eq), the mixture was stirred at 60 °C for 5 hr. The reaction mixture was poured in water (50 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed by brine (50 mL x 3) and dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The resulting residue was purified by silica gel column chromatography (PE: EA = 1: 0 to 0:1) to give the product. (Rf = 0.3). Compound **10** (1.37 g, 2.43 mmol, 78.51% yield) was obtained as a yellow solid. **LCMS:** Rt = 0.603 min, m/z = 565.2 $[M+H]^+$ **^{1}H NMR:** (400 MHz, METHANOL-*d*$_4$) δ = 9.06 (s, 1H), 8.67 (s, 1H), 8.35 (s, 1H), 6.09 - 6.03 (m, 1H), 6.02 - 5.95 (m, 2H), 4.43 - 4.29 (m, 2H), 3.63 - 3.51 (m, 2H), 0.93 - 0.82 (m, 2H), 0.75 (s, 9H), 0.03 (s, 3H), -0.04 - -0.08 (m, 12H)

To a solution of $(COCl)_2$ (289.94 mg, 2.28 mmol, 199.96 µL, 3 eq) in DCM (10 mL) at -70 °C was added a solution of DMSO (178.48 mg, 2.28 mmol, 178.48 µL, 3 eq) in DCM (2 mL). The mixture was stirred for 30 min at -70 °C, and a solution of compound **10** (430 mg, 761.44 µmol, 1 eq) in DCM (5 mL) was added to the mixture and stirred at -70 °C for 0.5 h. The mixture was treated with TEA (462.29 mg, 4.57 mmol, 635.89 µL, 6 eq) and allowed to warm to 20 °C slowly, then the mixture was stirred at 20 °C for 0.5 h. The reaction mixture was poured in water (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed by brine (30 mL x 3) and dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Compound **11** (400 mg, crude) was obtained as a yellow solid. **^{1}H NMR:** (400 MHz, METHANOL-*d*$_4$) δ = 9.94 (s, 1H), 9.19 (s, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 7.38 - 7.35 (m, 2H), 7.34 - 7.31 (m, 2H), 7.20 (s, 1H), 7.17 (br d, *J* = 7.6 Hz, 1H), 7.05 (br s, 1H), 6.73 (s, 1H), 5.83 (br d, *J* = 6.4 Hz, 1H), 5.79 - 5.74 (m, 1H), 4.12 - 4.08 (m, 2H), 3.57 - 3.50 (m, 2H), 2.97 (s, 3H), 1.39 (s, 3H), 0.89 - 0.83 (m, 2H), -0.06 (s, 9H)

To a mixture of compound **11** (300 mg, 533.14 µmol, 1 eq) and N-methylmethanamine (2 M, 2.67 mL, 10 eq) in DCE (10 mL) was added AcOH (32.02 mg, 533.14 µmol, 30.52 µL, 1 eq) and 4A MS (60 mg) at 20 °C. The mixture was stirred at 30 °C for 12 h. Then $NaBH(OAc)_3$ (1.13 g, 5.33 mmol, 10 eq) was added and the mixture was stirred at 30 °C for 3 h. $NaBH_3CN$ (167.52 mg, 2.67 mmol, 5 eq) was added to the reaction

mixture, then the mixture was stirred at 30°C for 1h. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed by brine (50 mL) and dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% FA condition) and lyophilized to give the product. Compound **12** (73 mg, 123.35 µmol, 23.14% yield) was obtained as a yellow oil. **LCMS:** Rt = 0.522 min, m/z = 592.3 $[M+H]^+$

To a mixture of compound **12** (90 mg, 152.08 µmol, 1 eq) in DCM (1 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 88.52 eq) at 0 °C, then the mixture was stirred at 25 °C for 3 h. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed by brine (50 mL) and dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25mmx5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 35%-65% B over 15 min), the purified solution was lyophilized to give a white solid. Compound **13** (45 mg, 97.50 µmol, 64.11% yield) was obtained as a white solid. **LCMS:** Rt = 0.423 min, m/z = 462.2 $[M+H]^+$

The residue was purified by SFC (column: DAICEL CHIRALCEL OD (250mmx30mm, 10um); mobile phase: [CO_2-i-PrOH (0.1%NH_3•H_2O)]; B%: 23%, isocratic elution mode), the purified solution was concentrated to give a white solid.

Compound 121 (19.18 mg, 41.21 µmol, 42.27% yield, 99.163% purity) was obtained as a white solid. **LCMS:** Rt = 0.426 min, m/z = 462.1 $[M+H]^+$ **^{1}H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 12.44 (br s, 1H), 9.11 (s, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 7.41 - 7.27 (m, 4H), 7.19 - 7.11 (m, 2H), 7.07 - 7.00 (m, 1H), 6.35 (br dd, *J* = 5.6, 10.4 Hz, 1H), 4.18 - 3.99 (m, 2H), 3.43 (t, *J* = 11.6 Hz, 1H), 2.82 (s, 4H), 2.46 (s, 6H), 1.38 (t, *J* = 6.8 Hz, 3H)

Compound 122 (20.70 mg, 44.41 µmol, 45.55% yield, 99.019% purity) was obtained as a white solid. **LCMS:** Rt = 0.424 min, m/z = 462.2 $[M+H]^+$ **^{1}H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 12.44 (br s, 1H), 9.11 (s, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 7.41 - 7.27 (m, 4H), 7.20 - 7.10 (m, 2H), 7.07 - 6.99 (m, 1H), 6.35 (br dd, *J* = 5.6, 10.4 Hz, 1H), 4.19 - 3.99 (m, 2H), 3.43 (br t, *J* = 11.6 Hz, 1H), 2.89 - 2.75 (m, 4H), 2.46 (s, 6H), 1.37 (t, *J* = 6.8 Hz, 3H)

Synthesis of Compounds 125 and 126

Compounds 125 and 126 were prepared in a similar manner to compounds 121 and 122.

Compound **125** (14.05 mg, 29.36 µmol, 35.09% yield, 99.9% purity) was obtained as a white solid. **LCMS**: Rt = 0.821 min, m/z = 478.2 [M+H]+ **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 12.36 (br s, 1H), 9.03 (s, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 7.47 (s, 1H), 7.35 (br d, J = 6.8 Hz, 1H), 7.28 - 7.22 (m, 3H), 7.11 - 7.03 (m, 2H), 6.28 (br dd, J = 5.2, 10.4

Hz, 1H), 4.10 - 3.92 (m, 2H), 3.36 (t, J = 11.6 Hz, 1H), 2.82 - 2.70 (m, 4H), 2.39 (s, 6H), 1.30 (t, J = 6.8 Hz, 3H)

Compound **126** (14.2 mg, 29.62 µmol, 35.39% yield, 99.7% purity) was obtained as a white solid. **LCMS**: Rt = 0.820 min, m/z = 478.2 [M+H]+ **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 9.41 (br s, 1H), 8.72 (br s, 1H), 8.54 (br s, 1H), 7.45 (s, 1H), 7.42 - 7.19 (m, 7H), 6.71 (br s, 1H), 4.55 (br d, J = 2.4 Hz, 1H), 4.16 - 3.97 (m, 2H), 3.97 - 3.77 (m, 1H), 3.03 (br s, 9H), 1.31 - 1.25 (m, 3H).

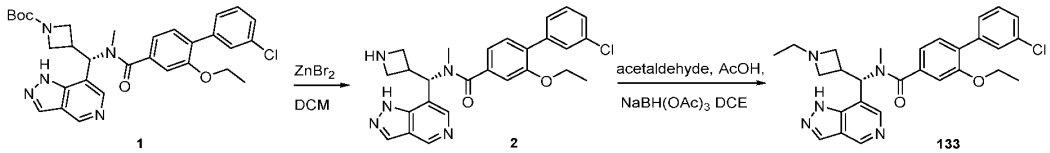
Synthesis of Compounds 127 and 128

Compounds 127 and 128 were prepared in a similar manner to compounds 121 and 122.

Compound **127** (29.79 mg, 59.99 µmol, 41.96% yield, 98.598% purity) was obtained as a white solid. **LCMS**: Rt = 0.439 min, m/z = 490.2 [M+H]+ **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 12.44 (br s, 1H), 9.11 (s, 1H), 8.34 (s, 1H), 8.25 (s, 1H), 7.41 - 7.27 (m, 4H), 7.19 - 7.12 (m, 2H), 7.06 - 6.99 (m, 1H), 6.36 (br dd, J = 4.8, 11.2 Hz, 1H), 4.08 (br dd, J = 6.8, 13.2 Hz, 2H), 3.50 (br t, J = 12.0 Hz, 1H), 3.04 (dd, J = 4.8, 12.8 Hz, 1H), 2.90 - 2.78 (m, 5H), 2.73 - 2.65 (m, 2H), 1.38 (t, J = 6.8 Hz, 3H), 1.13 (t, J = 7.2 Hz, 6H)

Compound **128** (31.17 mg, 63.08 µmol, 44.12% yield, 99.08% purity) was obtained as a white solid. **LCMS**: Rt = 0.441 min, m/z = 490.3 [M+H]+ **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 12.44 (br s, 1H), 9.11 (s, 1H), 8.34 (s, 1H), 8.25 (s, 1H), 7.41 - 7.27 (m, 4H), 7.20 - 7.11 (m, 2H), 7.07 - 6.99 (m, 1H), 6.36 (br dd, J = 4.8, 11.2 Hz, 1H), 4.08 (br dd, J = 6.8, 13.2 Hz, 2H), 3.50 (t, J = 12.0 Hz, 1H), 3.04 (dd, J = 4.8, 12.8 Hz, 1H), 2.92 - 2.76 (m, 5H), 2.68 (qd, J = 6.8, 13.6 Hz, 2H), 1.38 (t, J = 6.8 Hz, 3H), 1.13 (t, J = 7.2 Hz, 6H).

Synthesis of Compound 131



To a solution of compound 1 (500.00 mg, 867.93 µmol, 1 eq) in DCM (10 mL) was added ZnBr2 (977.29 mg, 4.34 mmol, 217.17 µL, 5 eq). The mixture was stirred at 25 °C for 3hr. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by reversed-phase HPLC (0.1% FA condition) and lyophilized to give compound 2 (360 mg, 733.66 µmol, 84.53% yield, 97% purity) as white solid. **LCMS**: RT=0.441 min, m/z=476.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.54 (s, 1H), 8.26 (d, J = 10.1 Hz, 2H), 7.48 (s, 1H), 7.37 - 7.33 (m, 1H), 7.30 (br d, J = 4.5 Hz, 2H), 7.26 - 7.22 (m, 1H), 7.06 (s, 1H), 6.97 (br d, J = 7.7 Hz, 1H), 6.63 - 6.54 (m, 1H), 4.37 (br t, J = 8.7 Hz, 1H), 4.26 (br t, J = 8.8 Hz, 1H), 4.20 - 4.11 (m, 2H), 4.06 - 3.98 (m, 2H), 3.80 - 3.73 (m, 1H), 2.82 - 2.72 (m, 3H), 1.33 (t, J = 6.8 Hz, 3H).

To a solution of compound 2 (200 mg, 420.20 μmol, 1 eq) in DCE (4 mL) was added one drop of AcOH and acetaldehyde (55.53 mg, 1.26 mmol, 70.74 μL, 3 eq) and stirred at 25 °C for 5 min. Then NaBH(OAc)3 (267.17 mg, 1.26 mmol, 3 eq) was added to the mixture and the mixture was stirred at 25 °C for 0.5hr. The reaction mixture was partitioned between ethyl acetate (30 mL x2) and water (30 mL). The combined organic layers were dried over sodium sulfate anhydrous, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient:8%-38% B over 15 min) and lyophilized to give Compound **133** (12.06 mg, 22.82 μmol, 21.72% yield, 95.363% purity) as white solid. **LCMS**: RT=0.452 min, m/z=504.2 [M+H] + **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.58 (s, 1H), 8.35 (s, 1H), 8.28 (s, 1H), 7.53 (s, 1H), 7.43 - 7.37 (m, 1H), 7.32 (dd, J = 3.1, 6.5 Hz, 3H), 7.07 - 7.00 (m, 2H), 6.31 (br d, J = 10.9 Hz, 1H), 4.18 - 4.08 (m, 2H), 4.08 - 3.95 (m, 3H), 3.68 (br s, 1H), 3.37 (br d, J = 6.6 Hz, 1H), 2.95 - 2.89 (m, 2H), 2.87 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H).

Synthesis of Compounds 132 and 133

Compounds **132** and **133** were prepared in a similar manner to Compound **131**.

Compound **132** (50.12 mg, 91.33 μmol, 67.21% yield, 96.51% purity, FA) was isolated as colorless gum. **LCMS**: RT=0.436 min, m/z= 484.4 [M+H]+ **^{1}H NMR** (400 MHz, DMSO-d6) δ = 11.16 - 10.75 (m, 1H), 9.33 (br s, 1H), 8.72 - 8.57 (m, 1H), 8.45 (br s, 1H), 8.13 (s, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (br d, J = 7.2 Hz, 2H), 7.11 (br s, 2H), 6.58 - 6.26 (m, 1H), 4.51 - 4.31 (m, 1H), 4.28 - 4.15 (m, 1H), 4.13 - 3.92 (m, 5H), 3.77 - 3.63 (m, 1H), 2.80 (br s, 3H), 1.29 - 1.23 (m, 3H), 1.19 (br d, J = 6.2 Hz, 6H).

Compound **133** (19.64 mg, 38.13 μmol, 30.61% yield, 97.372% purity, FA) was isolated as a white solid. **LCMS**: RT=0.451 min, m/z = 456.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.15 (s, 1H), 8.47 - 8.44 (m, 1H), 8.36 (s, 1H), 8.29 (s, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.45 - 7.38 (m, 2H), 7.35 (m, 2H), 7.09 - 7.00 (m, 2H), 6.36 - 6.26 (m, 1H), 4.37 - 4.27 (m, 1H), 4.17 (m, 2H), 4.10 - 4.00 (m, 2H), 3.97 - 3.88 (m, 1H), 3.64 - 3.54 (m, 1H), 2.91 (s, 3H), 2.79 (s, 3H), 1.36 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 134

Compound **134** was prepared in a similar manner to Compound **131**. Compound **134** (7.40 mg, 13.86 μmol, 15.30% yield, 96.578% purity, FA) was obtained as a white solid. **LCMS**: RT=0.469 min, m/z=470.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.58 (s, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 7.57 - 7.49 (m, 2H), 7.45 - 7.38 (m, 2H), 7.37 - 7.31 (m, 2H), 7.05 (br d, J = 2.2 Hz, 2H), 6.29 (br d, J = 11.2 Hz, 1H), 4.10 - 3.97 (m, 4H), 3.88 (br s, 1H), 3.48 (br s, 1H), 3.19 (br s, 1H), 2.84 (s, 3H), 2.81 - 2.74 (m, 2H), 1.35 (t, J = 6.8 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H).

Synthesis of Compounds 141-144

Compounds **141-144** were prepared in a similar manner to Compounds **008** and **131**.

Compound **141** (19.01 mg, 39.12 µmol, 9.12% yield, 96% purity) was obtained as white solid. **LCMS**: RT=0.404 min, m/z = 467.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.61 - 8.52 (m, 1H), 8.28 (s, 1H), 8.24 (br s, 1H), 7.80 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.55 - 7.47 (m, 1H), 7.25 (s, 1H), 7.04 (br s, 1H), 6.99 (br d, J = 8.0 Hz, 1H), 6.58 - 6.44 (m, 1H), 4.30 (br s, 1H), 4.22 - 3.97 (m, 6H), 3.73 - 3.65 (m, 1H), 2.84 - 2.73 (m, 3H), 1.38 - 1.30 (m, 3H).

Compound **142** (21.92 mg, 45.11 µmol, 10.52% yield, 96% purity) was obtained as white solid. **LCMS**: RT=0.412 min, m/z = 467.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.17 - 9.12 (m, 1H), 8.49 - 8.42 (m, 1H), 8.32 - 8.28 (m, 1H), 8.25 (s, 1H), 7.81 (s, 1H), 7.73 (br d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.29 - 7.28 (m, 1H), 7.08 - 6.97 (m, 2H), 6.54 - 6.45 (m, 1H), 4.37 - 4.31 (m, 1H), 4.21 - 4.02 (m, 6H), 3.73 (br d, J = 2.4 Hz, 1H), 2.84 - 2.78 (m, 3H), 1.34 (t, J = 6.8 Hz, 3H).

Compound **143** (14.29 mg, 28.86 µmol, 19.24% yield, 97.064% purity) was isolated as yellow gum. **LCMS**: RT=0.416min, m/z=481.2 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.14 (s, 1H), 8.54 - 8.48 (m, 1H), 8.34 - 8.26 (m, 2H), 7.84 (s, 1H), 7.75 (br d, J = 7.8 Hz, 1H), 7.66 - 7.60 (m, 1H), 7.56 - 7.48 (m, 1H), 7.34 - 7.29 (m, 1H), 7.08 - 7.01 (m, 2H), 6.34 - 6.26 (m, 1H), 4.05 (br s, 3H), 3.95 (br d, J = 7.8 Hz, 2H), 3.67 - 3.58 (m, 1H), 3.31 (br s, 1H), 2.83 (s, 3H), 2.61 (s, 3H), 1.36 (br t, J = 6.8 Hz, 3H).

Compound **144** (25.19 mg, 47.94 µmol, 31.95% yield, 91.462% purity) was isolated as yellow gum. **LCMS**: RT=0.410 min, m/z=481.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.14 (s, 1H), 8.51 (br s, 1H), 8.34 - 8.26 (m, 2H), 7.84 (s, 1H), 7.79 - 7.72 (m, 1H), 7.63 (br d, J = 7.8 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.35 - 7.29 (m, 1H), 7.09 - 7.02 (m, 2H), 6.34 - 6.23 (m, 1H), 4.08 (br d, J = 6.6 Hz, 3H), 3.96 (br d, J = 8.4 Hz, 2H), 3.63 (br s, 1H), 3.36 - 3.27 (m, 1H), 2.83 (s, 3H), 2.62 (s, 3H), 1.37 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 148

Compound **148** was prepared in a similar manner as Compound **131**. Compound **148** (16.70 mg, 30.63 µmol, 24.30% yield, 93% purity) was isolated as a white solid. **LCMS**: RT =0.450 min, m/z=490.3 (M+H)+ **^{1}H NMR** (400 MHz, DMSO-d6) δ = 9.10 (s, 1H), 8.40 (s, 1H), 8.37 - 8.29 (m, 2H), 7.57 (s, 1H), 7.49 - 7.35 (m, 4H), 7.11 - 6.97 (m, 2H), 6.28 (br d, J = 2.4 Hz, 1H), 4.03 (br s, 2H), 3.74 - 3.71 (m, 2H), 3.32 (br s, 2H), 3.02 (br s, 1H), 2.77 (br s, 3H), 2.37 (br s, 3H), 1.23 (br t, J = 6.6 Hz, 3H).

Synthesis of Compounds 150 and 151

Compounds **150** and **151** were prepared in a similar manner to Compound **131** using TFA instead of zinc bromide.

Compound **150** (19.12 mg, 85.28 µmol, 28.87% yield, 99% purity, FA salt) as was obtained as a white solid. **LCMS**: Rt =0.426min, m/z=448.2(M+H+). **^{1}H NMR** (400 MHz,

DMSO-d6) δ = 9.13 (s, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.35 - 7.30 (m, 2H), 7.13 - 6.94 (m, 2H), 6.52 - 6.26 (m, 1H), 4.25 - 4.14 (m, 1H), 4.01 (br d, J = 2.4 Hz, 4H), 3.91 (br d, J = 3.6 Hz, 2H), 2.80 - 2.64 (m, 3H), 1.22 (br t, J = 6.4 Hz, 3H).

Compound **151** (47 mg, 104.80 µmol, 47.30% yield, 98.45% purity) was a white gum. **LCMS**: RT=0.421 min, m/z=442.2 [M+H]+ **^{1}H NMR** (400 MHz, DMSO-d6) δ = 9.12 (s, 1H), 8.41 (d, J = 3.0 Hz, 2H), 8.35 (s, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.36 - 7.27 (m, 2H), 7.15 - 6.93 (m, 2H), 6.53 - 6.31 (m, 1H), 4.19 - 4.10 (m, 2H), 4.00 - 3.74 (m, 4H), 3.59 - 3.52 (m, 1H), 2.78 (s, 3H), 1.23 (t, J = 6.0 Hz, 3H).

Synthesis of Compounds 154-156

Compounds **152-154** were prepared in a similar manner to Compounds **008** and **131**.

Compound **152** (300 mg, crude) was obtained as a white solid. **LCMS**: Rt=0.423 min, m/z=456.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.60 (br s, 1H), 8.47 (s, 1H), 8.28 (s, 1H), 7.50 - 7.44 (m, 2H), 7.40 - 7.34 (m, 2H), 7.34 - 7.27 (m, 2H), 7.03 - 6.97 (m, 2H), 6.06 (br s, 1H), 4.09 - 3.91 (m, 2H), 3.82 - 3.60 (m, 2H), 3.51 - 3.22 (m, 3H), 2.88 (s, 3H), 2.36 - 2.16 (m, 1H), 1.82 - 1.63 (m, 1H), 1.30 (t, J = 6.8 Hz, 3H).

Compound **153** (18.01 mg, 37.76 µmol, 27.98% yield, 95.52% purity) as a white solid. **LCMS**: Rt=0.421 min, m/z=456.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.12 (s, 1H), 8.60 (br s, 1H), 8.46 (s, 1H), 8.28 (s, 1H), 7.51 - 7.44 (m, 2H), 7.40 - 7.34 (m, 2H), 7.34 - 7.27 (m, 2H), 7.04 - 6.97 (m, 2H), 6.06 (br s, 1H), 4.07 - 3.91 (m, 2H), 3.80 – 3.61 (m, 2H), 3.50 - 3.23 (m, 3H), 2.87 (s, 3H), 2.34 - 2.17 (m, 1H), 1.77 - 1.63 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H).

Compound **154** (82.53 mg, 175.26 µmol, 53.23% yield, 99.72% purity) was prepared using Compound **152** as starting material and was isolated as a white solid. **LCMS**: Rt=0.431 min, m/z=470.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.49 (br s, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 7.56 - 7.51 (m, 2H), 7.44 - 7.38 (m, 2H), 7.37 - 7.31 (m, 2H), 7.09 - 7.04 (m, 2H), 6.10 - 5.91 (m, 1H), 4.14 - 3.96 (m, 2H), 3.91 - 3.75 (m, 1H), 3.74 - 3.58 (m, 1H), 3.32 (br s, 1H), 3.01 - 2.79 (m, 5H), 2.71 (s, 3H), 2.31 (br s, 1H), 1.78 - 1.62 (m, 1H), 1.35 (t, J = 6.8 Hz, 3H).

Synthesis of Compounds 159 and 160

Compounds **159** and **160** were prepared in a similar manner to Compounds **152** and **154**.

Compound **159** (106.39 mg, 231.21 µmol, 64.24% yield, 99% purity) was obtained as white solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.26 - 1.36 (m, 3 H) 2.08 (br dd, J=12.32, 7.82 Hz, 1 H) 2.40 (br d, J=6.25 Hz, 1 H) 2.84 (s, 3 H) 2.88 - 2.95 (m, 1 H) 3.33 - 3.59 (m, 3 H) 3.69 (br d, J=6.88 Hz, 1 H) 3.92 - 4.09 (m, 2 H) 6.12 (br d, J=1.13 Hz, 1 H) 6.95 - 7.02 (m, 2 H) 7.28 - 7.42 (m, 4 H) 7.50 (br d, J=7.25 Hz, 2 H) 8.21 - 8.25 (m, 1 H) 8.44 (s, 1 H) 8.47 (br s, 1 H) 9.05 (s, 1 H). **LCMS**: Rt =0.426min, m/z=456.2(M+H+).

Compound **160** (74.66 mg, 157.40 µmol, 47.80% yield, 99% purity) was obtained as off-white solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.34 (t, J=6.94 Hz, 3 H) 2.07 - 2.20 (m, 1 H) 2.43 - 2.55 (m, 1 H) 2.58 - 2.65 (m, 1 H) 2.66 (s, 3 H) 2.87 (s, 3 H) 3.17 (br s, 1 H) 3.30 - 3.55 (m, 2 H) 3.85 (br s, 1 H) 3.94 - 4.11 (m, 2 H) 6.04 (br d, J=1.63 Hz, 1 H) 6.99 - 7.05 (m, 2 H) 7.30 - 7.36 (m, 2 H) 7.37 - 7.43 (m, 2 H) 7.52 (d, J=7.75 Hz, 2 H) 8.28 (s, 1 H) 8.43 (s, 1 H) 8.51 (s, 1 H) 9.13 (s, 1 H). **LCMS**: Rt =0.437min, m/z=470.2(M+H+).

Synthesis of Compounds 168-171

Compounds **168-171** were prepared in a similar manner to Compound **131**.

Compound **168** (34.35 mg, 69.37 µmol, 8.76% yield, 92% purity) was obtained as white solid. **LCMS**: RT=0.433 min, m/z=456.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.52 (s, 1H), 8.28 (s, 1H), 8.23 (s, 1H), 7.35 - 7.28 (m, 4H), 7.16 (br d, J = 6.8 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.46 (br d, J = 10.8 Hz, 1H), 4.33 - 4.23 (m, 1H), 4.22 - 4.11 (m, 2H), 4.09 - 3.97 (m, 3H), 3.73 - 3.65 (m, 1H), 2.81 (s, 3H), 2.39 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H).

Compound **169** (6.92 mg, 13.59 µmol, 22.73% yield, 95% purity) was prepared using Compound **168** as starting material and was isolated as an off-white solid. **LCMS**: RT=0.470min, m/z=484.3 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.12 (s, 1H), 8.59 (br s, 1H), 8.29 (s, 1H), 8.27 (s, 1H), 7.37 - 7.33 (m, 3H), 7.32 - 7.28 (m, 1H), 7.16 (br d, J = 7.2 Hz, 1H), 7.07 - 6.99 (m, 2H), 6.34 (br d, J = 10.4 Hz, 1H), 4.14 - 3.99 (m, 2H), 3.91 - 3.78 (m, 2H), 3.76 (br d, J = 7.2 Hz, 1H), 3.30 (br s, 1H), 3.04 - 2.98 (m, 1H), 2.81 (s, 3H), 2.68 - 2.63 (m, 2H), 2.40 (s, 3H), 1.36 (t, J = 6.8 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H).

Compound **170** (17.86 mg, 37.64 µmol, 5.50% yield, 96% purity) was obtained as an off-white solid. **LCMS**: RT=0.465 min, m/z=456.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.55 (s, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 7.35 - 7.28 (m, 4H), 7.16 (br d, J = 7.2 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.47 (br d, J = 11.2 Hz, 1H), 4.27 (br t, J = 8.4 Hz, 1H), 4.19 - 4.11 (m, 2H), 4.06 - 3.98 (m, 3H), 3.71 - 3.66 (m, 1H), 2.81 (s, 3H), 2.39 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H).

Compound **171** (8.77 mg, 17.59 µmol, 22.06% yield, 97% purity) was prepared using Compound **170** as starting material and was isolated as as a white solid. **LCMS**: RT=0.476min, m/z=484.3(M+H)+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.12 (s, 1H), 8.60 (br s, 1H), 8.29 (s, 1H), 8.27 (s, 1H), 7.37 - 7.33 (m, 3H), 7.32 - 7.28 (m, 1H), 7.17 (br d, J = 7.2 Hz, 1H), 7.07 - 7.01 (m, 2H), 6.34 (br d, J = 10.5 Hz, 1H), 4.12 - 4.00 (m, 2H), 3.89 - 3.80 (m, 2H), 3.77 (br d, J = 7.2 Hz, 1H), 3.31 (br s, 1H), 3.07 - 3.00 (m, 1H), 2.81 (s, 3H), 2.67 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H).

Synthesis of Compound 172

Compound **172** was prepared in a similar manner to Compound **133**. Compound **172** (8.36 mg, 18.45 µmol, 7.32% yield, 93% purity) was isolated as a white solid. **LCMS**: RT

=0.461 min, m/z=504.2 (M+H)+ **^{1}H NMR** (400 MHz, DMSO-d6) δ = 9.10 (s, 1H), 8.43 - 8.33 (m, 2H), 8.27 (br s, 1H), 7.57 (s, 1H), 7.49 - 7.36 (m, 4H), 7.10 - 6.95 (m, 2H), 6.37 - 6.15 (m, 1H), 4.04 (br s, 2H), 3.68 (br s, 2H), 3.26 (br s, 2H), 2.95 (br d, J = 2.9 Hz, 1H), 2.77 (br s, 3H), 2.56 (br s, 2H), 1.24 (br t, J = 6.8 Hz, 3H), 0.90 (br t, J = 6.8 Hz, 3H).

Synthesis of Compounds 176 and 177

Compounds **173** and **174** were prepared in a similar manner to Compound **131**.

Compound **173** (26.82 mg, 52.60 µmol, 32.06% yield, 95.62% purity) was obtained as a brown solid. **LCMS**: Rt=0.433 min, m/z=488.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.14 (br d, J = 1.6 Hz, 1H), 9.11 (s, 1H), 8.26 (s, 2H), 7.41 - 7.27 (m, 4H), 7.10 - 6.97 (m, 3H), 6.38 (br d, J = 10.8 Hz, 1H), 4.17 - 3.98 (m, 2H), 3.76 - 3.59 (m, 3H), 3.22 - 3.10 (m, 1H), 2.87 (br t, J = 6.0 Hz, 1H), 2.78 (s, 3H), 2.62 - 2.44 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H)

Compound **174** (20.01 mg, 39.10 µmol, 23.83% yield, 95.26% purity) was isolated as a brown solid. **LCMS**: Rt=0.430 min, m/z=488.1[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.14 (br s, 1H), 9.11 (s, 1H), 8.26 (s, 2H), 7.41 - 7.27 (m, 4H), 7.12 - 6.95 (m, 3H), 6.38 (br d, J = 10.8 Hz, 1H), 4.16 - 3.96 (m, 2H), 3.75 - 3.58 (m, 3H), 3.18 - 3.10 (m, 1H), 2.86 (br t, J = 5.6 Hz, 1H), 2.78 (s, 3H), 2.59 - 2.47 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H).

Synthesis of Compounds 175 and 176

Compounds **175** and **176** were prepared in a similar manner to Compound **131**.

Compound **175** (71.06 mg, 141.67 µmol, 39.48% yield, 100% purity) was isolated as a solid. **LCMS**: Rt=0.443 min, m/z=502.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.32 - 11.95 (m, 1H), 9.11 (s, 1H), 8.36 - 8.21 (m, 2H), 7.41 - 7.32 (m, 2H), 7.31 - 7.28 (m, 1H), 7.27 (s, 1H), 7.09 - 7.00 (m, 3H), 6.33 (br d, J = 10.4 Hz, 1H), 4.20 - 3.94 (m, 2H), 3.79 - 3.59 (m, 3H), 3.14 (br s, 1H), 2.94 - 2.84 (m, 1H), 2.79 (s, 3H), 2.47 - 2.37 (m, 1H), 1.37 (t, J = 6.8 Hz, 3H), 1.01 - 0.91 (m, 6H).

Compound **176** (42.23 mg, 84.19 µmol, 23.46% yield, 100% purity) was isolated as a solid. **LCMS**: Rt=0.437 min, m/z=502.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.13 (br s, 1H), 9.11 (s, 1H), 8.34 - 8.19 (m, 2H), 7.41 - 7.32 (m, 2H), 7.32 - 7.27 (m, 2H), 7.09 - 7.00 (m, 3H), 6.35 (br d, J = 10.4 Hz, 1H), 4.16 - 4.00 (m, 2H), 3.72 - 3.58 (m, 3H), 3.11 (br t, J = 4.8 Hz, 1H), 2.88 - 2.82 (m, 1H), 2.79 (s, 3H), 2.45 - 2.34 (m, 1H), 1.37 (t, J = 6.8 Hz, 3H), 1.00 - 0.91 (m, 6H).

Synthesis of Compound 177

Compound **177** was prepared in a similar manner to Compound **131**. Compound **177** (12.24 mg, 25.40 µmol, 26.08% yield, 97.46% purity) was obtained as a white solid. **LCMS**: RT=0.429 min, m/z=470.4 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.57 (br s, 1H), 8.33 (s, 1H), 8.28 (s, 1H), 7.59 - 7.49 (m, 2H), 7.44 - 7.38 (m, 2H), 7.35 (d, J

= 7.6 Hz, 2H), 7.08 - 7.00 (m, 2H), 6.28 (br d, J = 11.2 Hz, 1H), 4.15 - 3.99 (m, 4H), 3.95 (br d, J = 7.6 Hz, 1H), 3.62 - 3.50 (m, 1H), 3.27 (t, J = 7.2 Hz, 1H), 2.92 - 2.78 (m, 5H), 1.35 (t, J = 6.8 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).

Synthesis of Compounds 178 and 179

Compound **178** was prepared in a similar manner to Compound **131** using Compound **151** as starting material.

Compound **178** (15.66 mg, 34.08 µmol, 23.15% yield, 99.13% purity) was obtained as a white solid. **LCMS**: RT=0.453 min, m/z=456.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.15 (s, 1H), 8.52 (s, 1H), 8.38 - 8.23 (m, 2H), 7.58 - 7.52 (m, 2H), 7.47 - 7.40 (m, 2H), 7.39 - 7.34 (m, 2H), 7.09 - 7.02 (m, 2H), 6.40 - 6.24 (m, 1H), 4.15 - 4.01 (m, 3H), 3.93 (m, 2H), 3.55 (br t, J = 6.8 Hz, 1H), 3.31 - 3.20 (m, 1H), 2.85 (s, 3H), 2.59 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H).

Compound **179** (29.06 mg, 60.09 µmol, 44.22% yield, 100% purity) was obtained as an off-white gum. **LCMS**: RT=0.499 min, m/z=484.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.57 - 11.71 (m, 1H), 9.13 (s, 1H), 8.59 (s, 1H), 8.33 (s, 1H), 8.28 (s, 1H), 7.57 - 7.50 (m, 2H), 7.45 - 7.39 (m, 2H), 7.36 (d, J = 7.4 Hz, 2H), 7.09 - 7.02 (m, 2H), 6.27 (br d, J = 10.8 Hz, 1H), 4.13 - 4.02 (m, 2H), 4.00 - 3.80 (m, 3H), 3.41 (br t, J = 6.8 Hz, 1H), 3.13 (br t, J = 7.2 Hz, 1H), 2.84 (s, 3H), 2.71 - 2.67 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 6.8 Hz, 6H).

Synthesis of Compounds 181 and 182

Compounds **181** and **182** were prepared in a similar manner to the first step shown for Compound **131**.

Compound **181** (22 mg, 43.45 µmol, 4.32% yield, 94% purity FA) as white solid. **LCMS**: Rt =0.437 min, m/z=476.1 (M+H+) **1H NMR** (400 MHz, DMSO-d6) δ = 9.13 (s, 1H), 8.44 (s, 1H), 8.40 - 8.37 (m, 1H), 8.30 (s, 1H), 7.56 (s, 1H), 7.48 - 7.36 (m, 4H), 7.05 (br s, 2H), 6.42 (br d, J = 3.2 Hz, 1H), 4.19 (br t, J = 8.0 Hz, 1H), 4.03 (br d, J = 2.8 Hz, 4H), 3.91 (br s, 2H), 2.71 (br s, 3H), 1.27 - 1.20 (m, 3H).

Compound **182** (23 mg, 45.42 µmol, 5.84% yield, 94% purity) as a white solid. **LCMS**: Rt =0.436 min, m/z=476.2(M+H)+ **^{1}H NMR**: (400 MHz, DMSO-d6) δ = 9.12 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 7.55 (s, 1H), 7.50 - 7.34 (m, 4H), 7.18 - 6.95 (m, 2H), 6.41 (br d, J = 5.6 Hz, 1H), 4.21 (br d, J = 8.8 Hz, 1H), 4.04 (br s, 4H), 3.93 (br d, J = 2.4 Hz, 2H), 2.72 (br s, 3H), 1.23 (br t, J = 6.0 Hz, 3H).

Synthesis of Compound 183

Compound **183** was prepared in a similar manner to Compound **131** using Compound **181** as starting material. Compound **183** (16.14 mg, 30.63 µmol, 24.30% yield, 93% purity) was isolated as a white solid. **LCMS**: Rt =0.437 min, m/z=476.1 (M+H+) **^{1}H NMR**: (400 MHz, DMSO-d6) δ = 9.09 (s, 1H), 8.39 (s, 1H), 8.37 - 8.33 (m, 1H), 7.57 (s, 1H),

7.49 - 7.35 (m, 4H), 7.08 - 6.94 (m, 2H), 6.25 (br s, 1H), 4.03 (br s, 2H), 3.62 (br d, J = 4.8 Hz, 1H), 3.55 - 3.48 (m, 2H), 3.26 (br s, 1H), 3.07 (br s, 1H), 2.75 (br d, J = 12.4 Hz, 3H), 2.22 (s, 3H), 1.27 - 1.20 (m, 3H).

Synthesis of Compounds 065 and 071

Compounds **065** and **071** were prepared in a similar manner to Compound **131**.

Compound **065** (26.07 mg, 46.38 µmol, 22.61% yield, 94.92% purity, FA) was isolated as a white solid. **LCMS**: Rt=0.443 min, m/z=488.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.50 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 7.40 - 7.32 (m, 2H), 7.29 (br s, 1H), 7.27 - 7.23 (m, 1H), 7.06 - 6.99 (m, 3H), 6.25 (br d, J = 10.4 Hz, 1H), 4.14 - 3.94 (m, 5H), 3.63 (br s, 1H), 3.32 (br s, 1H), 2.84 (s, 3H), 2.81 (s, 3H), 2.63 (s, 3H), 1.36 (t, J = 6.8 Hz, 3H).

Compound **071** (7.98 mg, 14.71 µmol, 7.17% yield, 98.38% purity, FA) was isolated as a white solid. **LCMS**: Rt=0.429 min, m/z=488.3[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.50 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 7.41 - 7.32 (m, 2H), 7.31 - 7.27 (m, 2H), 7.09 - 6.97 (m, 3H), 6.26 (br d, J = 10.8 Hz, 1H), 4.13 - 4.01 (m, 3H), 4.00 - 3.88 (m, 2H), 3.61 - 3.54 (m, 1H), 3.26 (br s, 1H), 2.85 (s, 3H), 2.81 (s, 3H), 2.60 (s, 3H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 190

Compound **190** was prepared in a similar manner to Compound **131**. Compound **190** (8.36 mg, 18.45 µmol, 7.32% yield, 93% purity) was obtained as a white solid. **LCMS**: RT=0.461 min, m/z=504.2 (M+H)+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.10 (s, 1H), 8.43 - 8.33 (m, 2H), 8.27 (br s, 1H), 7.57 (s, 1H), 7.49 - 7.36 (m, 4H), 7.10 - 6.95 (m, 2H), 6.37 - 6.15 (m, 1H), 4.04 (br s, 2H), 3.68 (br s, 2H), 3.26 (br s, 2H), 2.95 (br d, J = 2.9 Hz, 1H), 2.77 (br s, 3H), 2.56 (br s, 2H), 1.24 (br t, J = 6.8 Hz, 3H), 0.90 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 241

Compound **241** was prepared in a similar manner to Compound **131** using formaldehyde instead of acetaldehyde and TFA instead of zinc bromide. Compound **241** (18.07 mg, 35.84 µmol, 7.01% yield, 97% purity) was obtained as a brown gum. **LCMS**: RT=0.748 min, m/z = 489.2[M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.92 (br s, 1H), 8.13 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.54 (s, 1H), 7.43 - 7.39 (m, 1H), 7.34 - 7.29 (m, 3H), 7.22 - 7.18 (m, 1H), 7.15 (d, J = 7.7 Hz, 1H), 7.04 (s, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.45 (br d, J = 10.8 Hz, 1H), 4.12 - 3.99 (m, 2H), 3.77 - 3.68 (m, 1H), 3.66 - 3.58 (m, 2H), 3.17 (br t, J = 6.2 Hz, 1H), 2.86 (s, 1H), 2.71 (s, 3H), 2.42 - 2.36 (m, 3H), 1.37 (t, J = 7.0 Hz, 3H).Synthesis of Compounds 282 and 283

Compounds **282** and **283** were isolated by chiral separation of Compound **241** via SFC. Compound **282** (216.06 mg, 441.39 µmol, 47.97% yield, 99.9% purity) was obtained as an off-white gum. **LCMS**: RT=0.560 min, m/z = 489.2 [M+H]+ **^{1}H NMR** (400 MHz,

CHLOROFORM-d) δ = 11.87 (br s, 1H), 8.12 - 8.07 (m, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.51 (s, 1H), 7.41 - 7.37 (m, 1H), 7.29 (s, 2H), 7.25 - 7.23 (m, 1H), 7.19 - 7.16 (m, 1H), 7.14 - 7.09 (m, 1H), 7.01 (s, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.42 (br d, J = 10.9 Hz, 1H), 4.09 - 3.98 (m, 2H), 3.78 - 3.73 (m, 1H), 3.66 (br d, J = 3.5 Hz, 2H), 3.19 (br t, J = 6.4 Hz, 1H), 2.91 - 2.85 (m, 1H), 2.69 (s, 3H), 2.39 (s, 3H), 1.36 - 1.31 (m, 3H). Compound **283** (148.12 mg, 302.90 µmol, 32.92% yield, 100% purity) was obtained as an off-white gum. **LCMS**: RT=0.568 min, m/z = 489.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.91 (br s, 1H), 8.12 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.54 (s, 1H), 7.43 - 7.39 (m, 1H), 7.36 - 7.29 (m, 3H), 7.22 - 7.17 (m, 1H), 7.16 - 7.12 (m, 1H), 7.04 (s, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.45 (br d, J = 10.9 Hz, 1H), 4.12 - 3.98 (m, 2H), 3.75 - 3.68 (m, 1H), 3.66 - 3.56 (m, 2H), 3.16 (br t, J = 6.1 Hz, 1H), 2.90 - 2.82 (m, 1H), 2.71 (s, 3H), 2.38 (s, 3H), 1.40 - 1.33 (m, 3H).

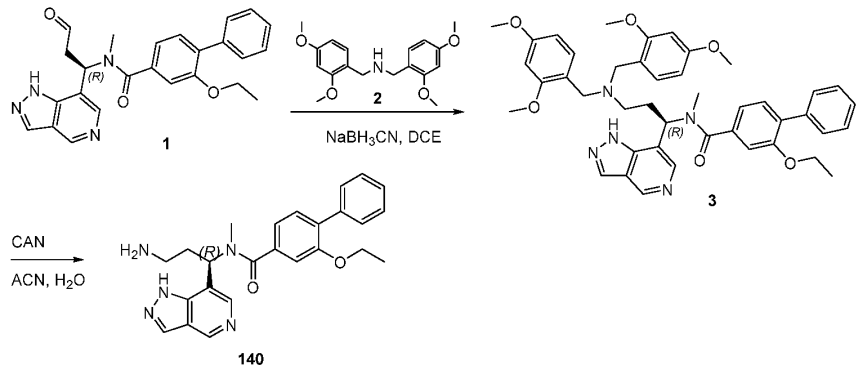
Synthesis of Compound 296

Compound **296** was prepared in a similar manner to Compound **131** using formaldehyde instead of acetaldehyde and $NaBH_2CN$ instead of zinc bromide. Compound **296** (200 mg, 415.62 µmol, 27.22% yield, 98.2% purity) was obtained as a white solid. **LCMS**: RT=0.542 min, m/z = 473.1 [M+H]+.

Synthesis of Compounds 297 and 298

Compounds **297** and **298** were isolated by chiral separation of Compound **296** via SFC. Compound **297** (95.3 mg, 198.44 µmol, 46.89% yield, 98.4% purity) was obtained as a white solid. **LCMS**: RT=0.549 min, m/z = 473.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 11.92 (br s, 1H), 8.12 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.40 - 7.27 (m, 4H), 7.22 - 7.17 (m, 1H), 7.17 - 7.12 (m, 1H), 7.07 - 6.98 (m, 3H), 6.45 (br d, J = 10.8 Hz, 1H), 4.13 - 3.98 (m, 2H), 3.75 - 3.67 (m, 1H), 3.67 - 3.56 (m, 2H), 3.16 (br t, J = 6.1 Hz, 1H), 2.89 - 2.81 (m, 1H), 2.71 (s, 3H), 2.38 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H). Compound **298** (68.17 mg, 141.52 µmol, 33.44% yield, 98.1% purity) was obtained as a white solid. **LCMS**: RT=0.540 min, m/z = 473.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.12 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.40 - 7.28 (m, 4H), 7.22 - 7.17 (m, 1H), 7.17 - 7.11 (m, 1H), 7.07 - 6.98 (m, 3H), 6.45 (br d, J = 10.8 Hz, 1H), 4.13 - 3.99 (m, 2H), 3.76 - 3.67 (m, 1H), 3.62 (br s, 2H), 3.16 (br t, J = 6.2 Hz, 1H), 2.86 (s, 1H), 2.71 (s, 3H), 2.38 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 140



To a solution of compound 2 (333.32 mg, 1.05 mmol, 1.5 eq) in DCE (8 mL) was added compound 1 (300 mg, 700.15 µmol, 1 eq) ,HOAc (21.02 mg, 350.07 µmol, 20.04 µL, 0.5 eq) and Molecular sieve 4A (150 mg, 700.15 µmol, 1 eq) stirred at 25°C for 12hr, then added NaBH(OAc)3 (148.39 mg, 700.15 µmol, 1 eq) at 0°C and stirred at 25°C for 2hr. The reaction mixture was added into water (50mL) and extracted with EtOAc (50ML*3), then the organic phase was dried with Na2SO4 and concentrated under reduce pressure to give the residue. The crude product was purified by prep-TLC (PE: EA= 0:1) and concentrated under reduced pressure to give the product (Rf =0.4). Compound 3 (400 mg, 438.44 µmol, 62.62% yield, 80% purity) was obtained as light-yellow oil. **LCMS**: Rt =0.507 min, m/z=730.5(M+H+)

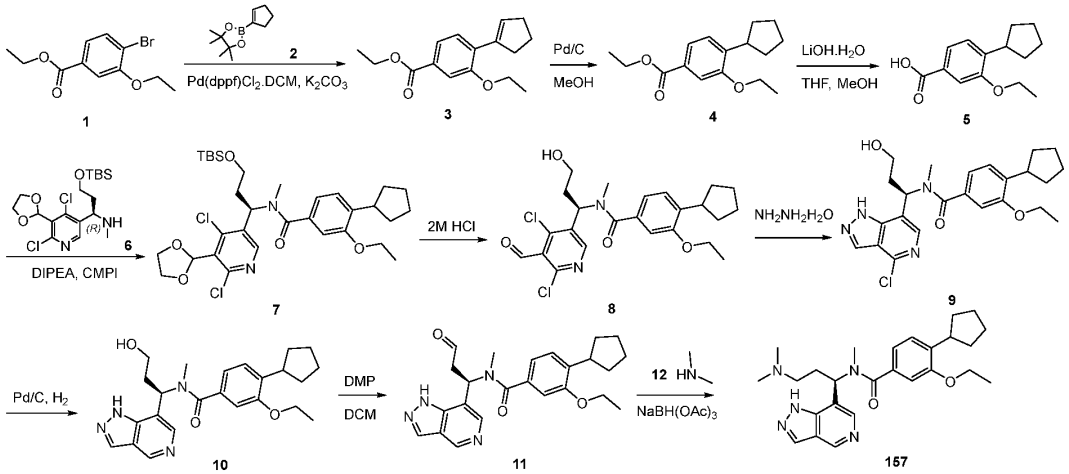
To a solution of compound 3 (270 mg, 369.93 µmol, 1 eq) in ACN (2.8 mL) and H2O (1.2 mL) was added CAN (608.41 mg, 1.11 mmol, 553.10 µL, 3 eq) at 0°C. The reaction mixture was stirred at 50°C for 12 h. The reaction mixture was purified directly. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 2%-32% B over 15 min) and lyophilized to afford product. Compound **140** (38.32 mg, 88.33 µmol, 23.88% yield, 99% purity) was obtained as white solid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.20 (br t, J=6.63 Hz, 3 H) 2.51 - 2.82 (m, 5 H) 3.09 - 3.32 (m, 2 H) 3.81 - 3.96 (m, 2 H) 6.27 (br s, 1 H) 6.94 - 7.00 (m, 2 H) 7.13 (br d, J=7.63 Hz, 1 H) 7.26 - 7.32 (m, 4 H) 7.37 (br d, J=6.88 Hz, 2 H) 8.14 (s, 1 H) 8.44 (br s, 2 H) 8.96 (br s, 1 H). **LCMS**: Rt =0.416min, m/z=430.2(M+H+).

Synthesis of Compound 147

Compound **147** was prepared in a similar manner to compound **140** with an additional coupling step using propionic acid with EDCI and DMAP in DCM. To a solution of starting material (26 mg, 58.10 µmol, 1 eq) and propionic acid (4.30 mg, 58.10 µmol, 4.33 µL, 1 eq) in DCM (1 mL) was added EDCI (16.71 mg, 87.15 µmol, 1.5 eq) and DMAP (709.79 µg, 5.81 µmol, 0.1 eq), the mixture was stirred at 25 °C for 12hr. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 18%-48% B over 9 min), and the product was concentrated and freeze-dried to give the product. The product was purified by prep-HPLC

(column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 18%-48% B over 9 min), and the product was concentrated and freeze-dried to give the product. Compound **147** (7.41 mg, 14.57 μmol, 28.22% yield, 99% purity) was obtained as brown gum. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.19 (t, J=7.57 Hz, 3 H) 1.37 (t, J=6.94 Hz, 3 H) 2.28 (q, J=7.50 Hz, 2 H) 2.34 - 2.41 (m, 1 H) 2.66 (dddd, J=13.98, 10.69, 7.29, 3.56 Hz, 1 H) 2.85 (s, 3 H) 3.20 - 3.33 (m, 1 H) 3.73 - 3.86 (m, 1 H) 4.02 - 4.15 (m, 2 H) 6.04 (br t, J=5.75 Hz, 1 H) 6.29 (br dd, J=11.26, 4.25 Hz, 1 H) 7.00 - 7.07 (m, 1 H) 7.10 - 7.16 (m, 2 H) 7.27 - 7.32 (m, 2 H) 7.32 - 7.39 (m, 2 H) 8.27 (s, 1 H) 8.40 (br s, 1 H) 9.12 (br s, 1 H). **LCMS**: Rt =0.458min, m/z=504.2(M+H+).

Synthesis of Compound 157



To a solution of the compound **1** (13.51 g, 49.46 mmol, 1 eq) and compound **2** (9.6 g, 49.46 mmol, 1 eq) in the dioxane (130 mL) and H_2O (13 mL) was added K_2CO_3 (13.67 g, 98.93 mmol, 2 eq) and $Pd(dppf)Cl_2•CH_2Cl_2$ (4.04 g, 4.95 mmol, 0.1 eq) under N_2, then the mixture was stirred at 100 °C for 12 h. The mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 2), then the organic phase was washed by brine (100 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/EtOAc=1/0 to 10/1), the spot (PE/EtOAc=10/1, Rf=0.6) was collected. Compound **3** (11.6 g, 44.56 mmol, 90.08% yield) was obtained as yellow liquid. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 7.61 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.55 (s, 1H), 7.34 - 7.30 (m, 1H), 6.67 (br s, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.79 (dt, *J* = 2.0, 7.6 Hz, 2H), 2.58 (dt, *J* = 2.4, 7.2 Hz, 2H), 1.97 (quin, *J* = 7.6 Hz, 2H), 1.51 (t, *J* = 6.8 Hz, 3H), 1.42 - 1.38 (m, 3H)

To a solution of the Pd/C (4.74 g, 4.46 mmol, 10% purity, 0.1 eq) in the MeOH (130 mL) was added compound **3** (11.6 g, 44.56 mmol, 1 eq) under N_2, the suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 30 °C for 12 h. The mixture filtered and the filtrate was collected to concentrated.

Compound **4** (10.6 g, crude) was obtained as yellow oil which was used directly for the next step. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 7.59 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.49 (d, *J* = 1.2 Hz, 1H), 7.25 (s, 1H), 4.40 - 4.34 (m, 2H), 4.11 (q, *J* = 6.8 Hz, 2H), 3.43 - 3.31 (m, 1H), 2.09 - 1.97 (m, 2H), 1.85 - 1.76 (m, 2H), 1.74 - 1.67 (m, 2H), 1.64 - 1.59 (m, 2H), 1.47 - 1.43 (m, 3H), 1.41 - 1.37 (m, 3H)

To a solution of compound **4** (10.6 g, 40.41 mmol, 1 eq) in the THF (35 mL), MeOH (35 mL) and H_2O (35 mL) was added $LiOH•H_2O$ (5.09 g, 121.22 mmol, 3 eq), then the mixture was stirred at 25 °C for 12 h. The mixture was adjusted to pH=2 with 1N HCl solution. The reaction mixture was poured into H_2O (200 mL) and extracted by EtOAc (200 mL x 3), the organic phase was combined and washed with brine (200 mL), dried over Na_2SO_4 and concentrated to give a crude product. Compound **5** (9.6 g, crude) was obtained as white solid which was used directly for the next step. **LCMS**: Rt =0.352 min, m/z=233.3 ($M+H^+$)

To a solution of compound **5** (3 g, 12.80 mmol, 1 eq) and compound **6** (5.40 g, 12.80 mmol, 1 eq) in the DMF (50 mL) was added CMPI (4.91 g, 19.21 mmol, 1.5 eq) and DIEA (4.96 g, 38.41 mmol, 6.69 mL, 3 eq), then the mixture was stirred at 50 °C for 12 h. The reaction mixture was poured into H_2O (100 mL) and extracted by EtOAC (100 mL x 3), the organic phase was combined and washed with brine (100 mL), dried with Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/EtOAc=1/0 to 3/1), the spot (PE/EtOAc=3/1, Rf=0.5) was collected. Compound **7** (3.5 g, 5.49 mmol, 42.86% yield) was obtained as yellow oil. **LCMS**: Rt =0.736 min, m/z=637.2 ($M+H^+$) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.62 - 8.45 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.88 - 6.78 (m, 2H), 6.49 (br s, 1H), 6.10 - 5.77 (m, 1H), 4.33 (br s, 2H), 4.12 - 4.08 (m, 2H), 4.07 - 3.96 (m, 2H), 3.87 - 3.68 (m, 2H), 3.38 - 3.25 (m, 1H), 2.94 - 2.65 (m, 3H), 2.51 - 2.36 (m, 1H), 2.33 (br d, *J* = 6.8 Hz, 1H), 2.04 - 1.97 (m, 2H), 1.82 - 1.72 (m, 2H), 1.71 - 1.64 (m, 2H), 1.53 (br s, 2H), 1.41 (br t, *J* = 6.8 Hz, 3H), 0.92 - 0.84 (m, 9H), 0.10 - -0.02 (m, 6H)

To a solution of the compound **7** (3.50 g, 5.49 mmol, 1 eq) in the THF (20 mL) was added HCl (2 M, 19.94 mL, 7.27 eq), then the mixture was stirred at 40 °C for 12 h. The mixture was adjusted pH to 9~10 by $NaHCO_3$ and extracted by EtOAc (50 mL x 2), then the organic phase was washed by brine (50 mL), dried over Na_2SO_4 and concentrated to give a residue. Compound **8** (3.3 g, crude) was obtained as yellow oil. The crude product was used directly for the next step. **LCMS**: Rt =0.599 min, m/z=479.2 ($M+H^+$)

To a solution of the compound **8** (3.3 g, 6.88 mmol, 1 eq) in the dioxane (30 mL) was added $N_2H_4•H_2O$ (834.29 mg, 15.83 mmol, 808.42 µL, 95% purity, 2.3 eq), then the mixture was stirred at 70 °C for 2 h. The mixture was poured into ice water (40 mL) and extracted with EtOAc (40 mL x 2), then the organic phase was washed by brine (40 mL), dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by column

chromatography (SiO_2, PE/EtOAc=1/0 to 0/1), the spot (PE/EtOAc=0/1, Rf=0.6) was collected. Compound **8** (1 g, 2.19 mmol, 31.79% yield) was obtained as yellow oil. **LCMS**: Rt =0.590 min, m/z=457.3 ($M+H^+$) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.57 - 12.07 (m, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.97 - 6.91 (m, 2H), 6.39 (br dd, *J* = 4.4, 10.4 Hz, 1H), 4.08 - 3.98 (m, 2H), 3.95 - 3.84 (m, 2H), 3.39 - 3.27 (m, 1H), 2.77 (s, 3H), 2.63 - 2.53 (m, 1H), 2.45 - 2.35 (m, 1H), 2.22 - 2.12 (m, 1H), 2.04 - 1.96 (m, 2H), 1.84 - 1.75 (m, 2H), 1.74 - 1.62 (m, 4H), 1.43 (t, *J* = 6.8 Hz, 3H)

To a solution of the Pd/C (100 mg, 93.97 µmol, 10% purity, 4.29e-2 eq) in the MeOH (10 mL) was added compound **9** (1 g, 2.19 mmol, 1 eq) and DIEA (282.83 mg, 2.19 mmol, 381.17 µL, 1 eq) under N_2, the suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (20 psi) at 30°C for 12 h. The mixture filtered and the filtrate was collected to concentrated. The residue was used to next step without purification. Compound **10** (1.2 g, crude) was obtained as yellow oil which was used directly for the next step. **LCMS**: RT=0.464 min, m/z=423.3 (M+H+)

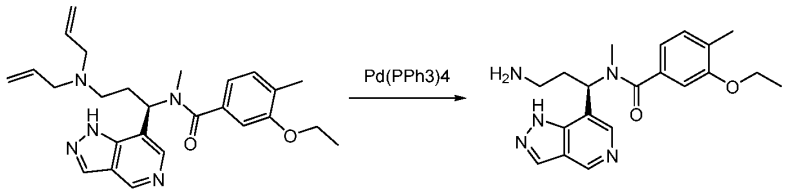
To a solution of compound **10** (1.2 g, 2.84 mmol, 1 eq) in the DCM (12 mL) was added Dess-Martin (2.41 g, 5.68 mmol, 1.76 mL, 2 eq) at 0 °C and stirred for 1 h. The reaction mixture was poured into H_2O (20 mL) and extracted by DCM (20 mL x 2), the organic phase was combined and washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated to give a crude product. The residue was purified by reversed-phase HPLC (0.1% FA condition). Compound **11** (740 mg, 1.76 mmol, 61.96% yield) was obtained as brown oil. **LCMS**: Rt=0.448 min, m/z=421.2 (M+H+)

To a solution of compound **11** (400 mg, 951.24 µmol, 1 eq) and compound **12** (2 M, 1.43 mL, 3 eq) in the DCE (8 mL) was added 4A MS (0.4 g) and AcOH (5.71 mg, 95.12 µmol, 5.45 µL, 0.1 eq) and stirred at 25 °C for 12 h. Then the mixture was added $NaBH(OAc)_3$ (604.82 mg, 2.85 mmol, 3 eq) at 0 °C and stirred at 25 °C for 3 h. The reaction mixture was filtered. The filter liquor was poured into H_2O (20 mL) under N_2 and extracted by DCM (20 mL x 3), the organic phase was combined and washed with brine (20 mL x 3), dried over Na2SO4, filtered and concentrated to give a crude product in vacuum. The residue was purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 10%-40% B over 10 min). Compound **157** (77 mg, 171.27 µmol, 18.00% yield, 96.3% purity) was obtained as white solid. **LCMS:** Rt =0.473min, m/z=450.2 (M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.10 (s, 1H), 8.49 (s, 1H), 8.41 (s, 1H), 8.24 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.03 - 6.90 (m, 2H), 6.25 (br d, *J* = 8.4 Hz, 1H), 4.11 - 3.99 (m, 2H), 3.38 - 3.29 (m, 1H), 2.80 (s, 3H), 2.77 - 2.70 (m, 1H), 2.69 - 2.58 (m, 2H), 2.46 (d, *J* = 1.2 Hz, 6H), 2.45 - 2.38 (m, 1H), 2.08 - 1.93 (m, 2H), 1.82 - 1.72 (m, 2H), 1.72 - 1.63 (m, 2H), 1.61 - 1.50 (m, 2H), 1.42 (br t, *J* = 6.8 Hz, 3H).

Synthesis of Compound 210

Compound **210** was prepared in a similar manner to Compound **079** and was then treated with m-CPBA in DCM. Compound **210** (8.99 mg, 18.11 µmol, 6.12% yield, 98.6% purity) was obtained as an off-white gum. **LCMS**: RT=0.441min, m/z=490.2[M+H]+ **^{1}H NMR** (400 MHz, METHANOL-d4) δ = 9.24 (br s, 1H), 8.61 - 8.47 (m, 1H), 8.43 - 8.28 (m, 1H), 7.49 - 7.21 (m, 6H), 7.11 - 7.01 (m, 1H), 6.36 - 5.29 (m, 1H), 5.08 - 4.95 (m, 1H), 4.49 - 4.15 (m, 2H), 4.12 - 3.91 (m, 1H), 3.27 - 3.07 (m, 1H), 3.03 (s, 3H), 3.00 - 2.80 (m, 2H), 2.76 - 2.65 (m, 3H), 1.41 - 1.26 (m, 3H).

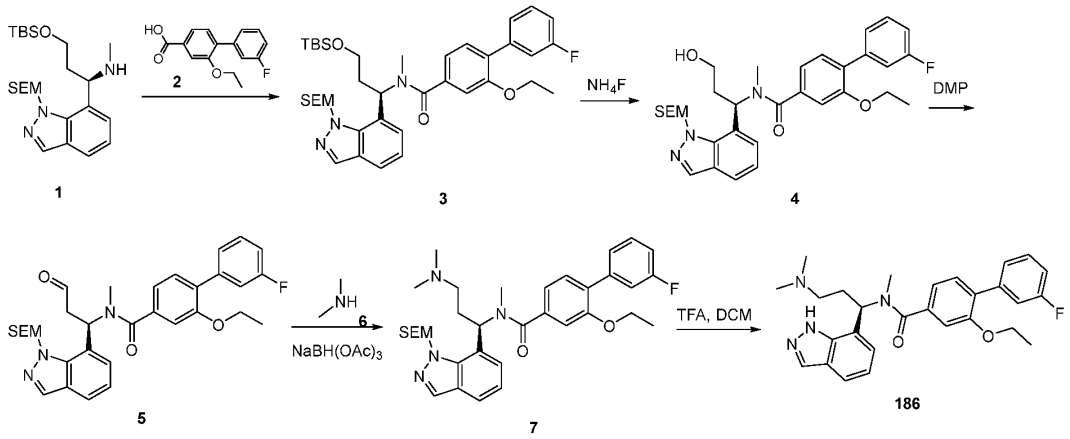
Synthesis of Compound 185



1 185

To a solution of compound 1 (200 mg, 446.86 µmol, 1 eq) in EtOH (8 mL) was added 4-methylbenzenesulfinic acid (418.80 mg, 2.68 mmol, 6 eq) and Pd(PPh3)4 (129.09 mg, 111.71 µmol, 0.25 eq). The mixture was stirred at 40 °C for 12 h under N2. The reaction mixture was added into saturated NaHCO3 (30 mL) and extracted with DCM (30 mL x 3), then the organic phase was dried with Na2SO4 and concentrated under reduce pressure to give the residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150x25mmx5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 10%-40% B over 15 min), the purified solution was lyophilized to give a white solid. Then the residue was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150x50mmx3um; mobile phase: [water (FA)-ACN]; gradient: 1%-28% B over 10 min), the purified solution was lyophilized to give a white solid. Compound **185** (95.46 mg, 226.79 µmol, 50.75% yield, 98.229% purity, FA) was obtained as a white solid. **LCMS**: Rt = 0.411 min, m/z = 368.1 [M+H]+ **^{1}H NMR**: (400 MHz, CHLOROFORM-d) δ = 8.95 (s, 1H), 8.51 (br s, 1H), 8.35 (br s, 1H), 8.12 (s, 1H), 6.92 (br d, J = 7.6 Hz, 1H), 6.78 (br d, J = 3.6 Hz, 2H), 6.19 (br s, 1H), 3.95 - 3.75 (m, 2H), 3.23 - 2.96 (m, 2H), 2.57 (br s, 5H), 2.07 (s, 3H), 1.28 (br t, J = 6.4 Hz, 3H).

Synthesis of Compound 186



To a solution of compound **1** (150 mg, 333.50 μmol, 1 eq) and compound **2** (86.80 mg, 333.50 μmol, 1 eq) in DMF (3 mL) was added CMPI (127.80 mg, 500.25 μmol, 1.5 eq) and DIPEA (4.60 g, 35.59 mmol, 6.20 mL, 3 eq) at 25°C. The mixture was stirred at 50°C for 12hr. The reaction mixture was poured into H_2O (30 mL) and extracted by EtOAc (30 mLx3), the organic phase was combined and washed with brine (30 mLX3), dried with anhydrous Na_2SO_4, filtered and concentrated to give a crude product in vacuum. The crude product was purified by prep-TLC (PE: EA=2:1) and concentrated under reduced pressure to give the product (Rf =0.6) compound **3** (90 mg, 126.15 μmol, 37.83% yield, 97% purity) as a light-yellow oil. **LCMS**: RT=0.776 min, m/z=692.5 [M+H]+

To a solution of compound **3** (90 mg, 130.05 μmol, 1 eq) in MeOH (1 mL) was added NH4F (48.17 mg, 1.30 mmol, 10 eq), the mixture was stirred at 60°C for 2h. The mixture was stirred at 40°C for 5 h. The reaction mixture was poured into H2O (10 mL), and extracted with EA (10mLx3). The combined organic phase was dried with Na_2SO_4 and concentrated to give the crude product. Compound **4** (76 mg, crude) as a light yellow oil. The crude product was used directly for the next step. **LCMS**: RT=0.638 min, m/z=578.4 [M+H]+

To a solution of compound **4** (100 mg, 173.08 μmol, 1 eq) in DMSO (2 mL) was added IBX (96.93 mg, 346.16 μmol, 2 eq). The reaction mixture was stirred at 25°C for 3h. The reaction mixture was poured into H_2O (10 mL) under N_2 and extracted by DCM (10 mLx3), the organic phase was combined and washed with brine (10 mLX3), dried with anhydrous Na_2SO_4, filtered and concentrated to give a crude product in vacuum. The crude product was purified by prep-TLC (PE: EA=0:1) and concentracted to give the product (Rf =0.8) compound **7** (84 mg, 81.70 μmol, 47.20% yield, 56% purity) was obtained as light-yellow oil. **LCMS**: RT=0.676 min, m/z=576.3 [M+H]+

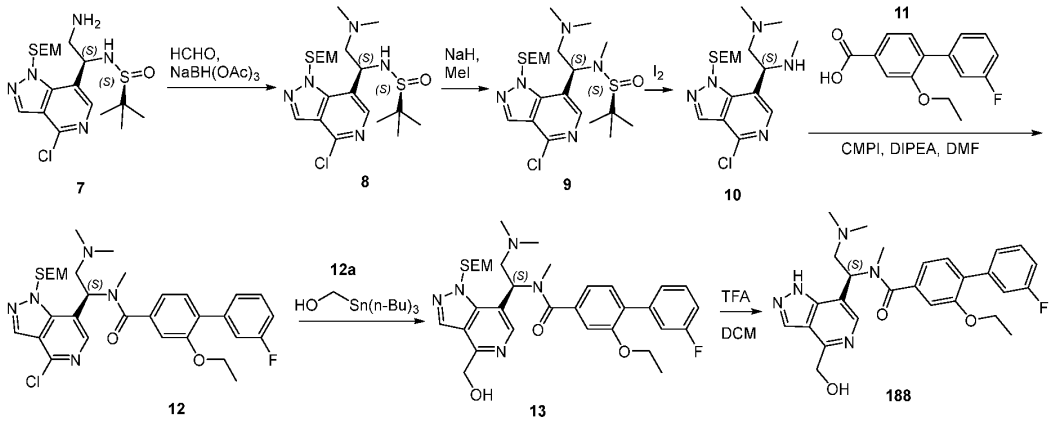
To a solution of compound **7** (152 mg, 385.33 μmol, 1 eq), Me_2NH (2 M, 963.33 μL, 5 eq) in DCE (3 mL) was added AcOH (3.86 mg, 64.26 μmol, 3.68 μL, 0.5 eq) and Molecular sieve 4A (20 mg, 128.53 μmol, 1 eq). Then the reaction mixture was stirred at 25°C for 11h.

Then $NaBH(OAc)_3$ (81.72 mg, 385.59 μmol, 3 eq) was added to the solution at 0°C. The reaction mixture was stirred at 25°C for 1h. The reaction mixture was added into water (20mL) and extracted with EA (20ML*3), then the organic phase was dried with Na_2SO_4 and concentrated under reduce pressure to give the residue. The crude product was purified by prep-TLC (PE: EA=0:1) and concentrated under reduced pressure to give the product (Rf =0.1). Compound **7** (54.55 mg, 127.50 μmol, 33.09% yield, 99% purity) was obtained as light-yellow oil. **LCMS**: RT=0.506 min, m/z=475.4 [M+2+H]+

To a solution of compound **7** (30 mg, 49.60 μmol, 1 eq) in DCM (0.3 mL) was added TFA (2.30 g, 20.19 mmol, 1.50 mL, 407.13 eq), The reaction mixture was stirred at 25°C for 1hr. The reaction mixture was adjusted PH=8. The filter liquor was added into H_2O (20 mL) at 25°c under N_2 and extracted by DCM (20 mLx3), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated to give a crude product in vacuum. The crude product was purified by prep-HPLC (column: Waters Xbridge C18 150*25mm*5um; mobile phase: [H_2O (0.05% NH_3H_2O)-ACN]; gradient: 50%-80% B over 11.0 min), and concentrated under reduced pressure to give the product. Compound **186** (16.02 mg, 33.42 μmol, 67.38% yield, 99% purity) was obtained as brown gum. **LCMS:** Rt = 0.483 min, m/z = 475.3 (M+H+). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 1.31 - 1.45 (m, 3 H) 2.31 - 2.55 (m, 8 H) 2.57 (br d, J=6.88 Hz, 2 H) 2.71 - 2.96 (m, 3 H) 3.94 - 4.22 (m, 2 H) 6.36 (br dd, J=8.69, 5.44 Hz, 1 H) 6.99 - 7.11 (m, 3 H) 7.18 (t, J=7.63 Hz, 1 H) 7.28 - 7.42 (m, 5 H) 7.76 (d, J=8.13 Hz, 1 H) 8.12 (s, 1 H) 11.83 - 11.95 (m, 1 H).

Synthesis of Compound 188

Compound **188** was prepared following Scheme 4, GP1, GP5, GP13, and G16 using nitromethane and reducing with iron and ammonium chloride. The remaining of the synthesis is shown below.



To a solution of compound **7** (1.45 g, 3.25 mmol, 1 eq) in the MeOH (25 mL) was added HCHO (1.32 g, 16.25 mmol, 1.21 mL, 37% purity, 5 eq) and $NaBH_3CN$ (817.08 mg, 13.00 mmol, 4 eq), then the mixture was stirred at 20 °C for 1 h under N_2. The reaction

mixture was quenched with aq.sat.NH_4Cl (50 mL) at 0 °C under nitrogen protect and then extracted with EA (50 mL * 3), the combined organic were washed with brine (50 mL), then the organic phase was dried with Na_2SO_4 and concentrated under reduce pressure to give the residue. The residue was purified by column chromatography (SiO_2, Commercial hexanes: Ethyl acetate=0/1 to 1/0). Compound **8** (1.4 g, 2.95 mmol, 90.84% yield, N/A purity) as yellow oil. **LCMS:** Rt =0.497 min, m/z=474.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.40 (br s, 1H), 8.19 (s, 1H), 6.29 - 5.99 (m, 1H), 5.88 - 5.60 (m, 1H), 5.49 - 5.08 (m, 1H), 3.72 - 3.47 (m, 2H), 2.63 - 2.29 (m, 5H), 1.37 - 1.15 (m, 10H), 1.11 - 0.77 (m, 2H), 0.00 (s, 9H)

To a 100 mL vial was added compound **8** (1.30 g, 2.74 mmol, 1 eq) and THF (20 mL), the flask was evacuated and back filled with nitrogen for three times. Then cooled to 0 °C, NaH (164.51 mg, 4.11 mmol, 60% purity, 1.5 eq) was added at 0 °C in portions under nitrogen protected, the mixture was stirred at 0 °C for 1 h, then MeI (377.00 mg, 2.66 mmol, 165.35 µL, 9.69e-1 eq) was added to the mixture at 0-10 °C, the mixture was allow warm up to 25 °C and stirred at 25 °C for 1 hr. The reaction mixture was added NH_4Cl(300 ML) in N_2, then extracted with EA(300 x 2) then extracted with brine (300 mL x 3), then the organic phase was dried with Na_2SO_4 and concentrated under reduce pressure to give the residue. The residue was purified by column chromatography (SiO_2, Commercial hexanes: Ethyl acetate=1/0 to 0/1). Compound **9** (700 mg, 1.43 mmol, 52.30% yield, N/A purity) as yellow solid. **LCMS**: RT=0.472 min, m/z=488.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.27 (s, 1H), 8.15 (s, 1H), 6.00 (d, J = 11.8 Hz, 1H), 5.76 (d, J = 11.8 Hz, 1H), 5.36 (t, J = 7.7 Hz, 1H), 3.60 - 3.40 (m, 2H), 3.13 - 2.86 (m, 2H), 2.70 (s, 3H), 2.42 - 2.23 (m, 6H), 1.26 - 1.10 (m, 9H), 1.00 - 0.72 (m, 2H), -0.03 (s, 9H)

To a solution of compound **9** (700.00 mg, 1.43 mmol, 1 eq) in THF (5 mL) was added HCl (2 M, 5 mL, 6.97 eq). The reaction mixture was stirred at 20 °C for 1 hr. The reaction mixture was added $NaHCO_3$(10 ML) in N_2, then extracted with EA(10 x 2) then extracted with brine (10 mL x 3), then the organic phase was dried with Na_2SO_4 and concentrated under reduce pressure to give the residue. The crude was used into next step without farther purification. Compound **10** (520 mg, 947.94 µmol, 66.11% yield, 70% purity) as yellow solid. **LCMS**: RT=0.454 min, m/z=384.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.43 (s, 1H), 8.19 - 8.13 (m, 1H), 3.62 - 3.58 (m, 3H), 2.35 - 2.32 (m, 6H), 1.94 - 1.84 (m, 3H), 1.78 - 1.66 (m, 3H), 1.02 - 0.77 (m, 3H), -0.02 - -0.04 (m, 9H)

To a solution of Compound **10** (480 mg, 1.25 mmol, 1 eq) and Compound **11** (325.33 mg, 1.25 mmol, 1 eq) in DMF (5 mL) was added CMPI (638.72 mg, 2.50 mmol, 2 eq) and DIEA (484.67 mg, 3.75 mmol, 653.20 µL, 3 eq), the mixture was stirred at 50 °C for 2 hr. The reaction mixture was added NH_4Cl(30 ML) in N_2, then extracted with EA (30 x 2) then extracted with brine (30 mL x 3), then the organic phase was dried with Na_2SO_4 and

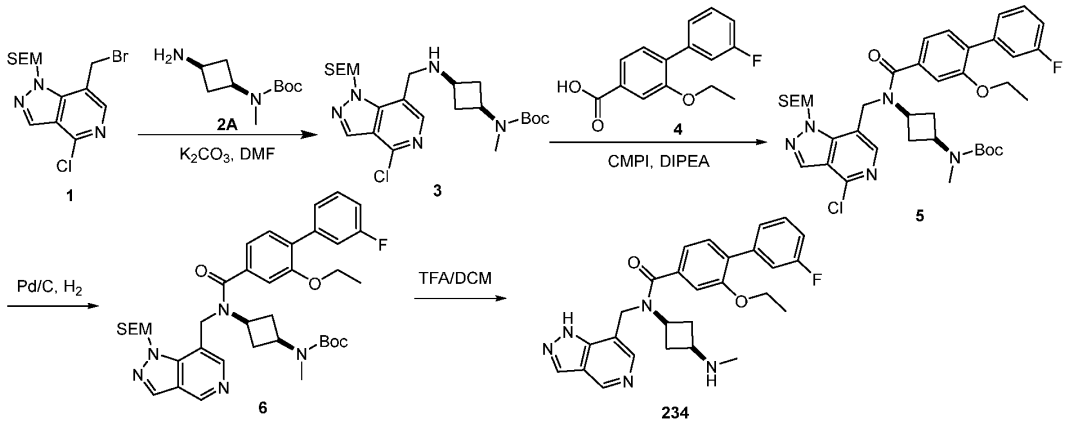
concentrated under reduce pressure to give the residue. The residue was purified by column chromatography (SiO_2, Commercial hexanes: Ethyl acetate=1/0 to 0/1). Compound **12** (350 mg, 463.88 µmol, 37.11% yield, 83% purity) as yellow solid. **LCMS**: RT=0.614 min, m/z=626.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.32 (s, 1H), 8.20 (s, 1H), 7.40 - 7.31 (m, 2H), 7.30 (br s, 1H), 7.07 - 6.92 (m, 4H), 6.72 - 6.29 (m, 2H), 5.83 - 5.63 (m, 1H), 4.08 - 3.97 (m, 2H), 3.62 - 3.39 (m, 2H), 2.94 - 2.83 (m, 3H), 2.41 (s, 6H), 1.38 - 1.32 (m, 3H), 1.00 - 0.74 (m, 3H), -0.04 (s, 9H)

To a solution of Compound **12** and compound **12a** (384.54 mg, 1.20 mmol, 3 eq) in dioxane (3 mL) was added Xphos Pd G_4 (34.35 mg, 39.92 µmol, 0.1 eq). The reaction mixture was stirred at 80 °C for 16 hr. After the reaction was cooled into 20 °C and being filtered at 20 °C under N_2, the filtrate was extracted with ethyl acetate (20 mL × 2). The combined organic phase was evaporated under reduced pressure. The combined filter cake was quenched with 1 N HCl aqueous at 0 °C under N_2. The residue was purified by column chromatography (SiO_2, Commercial hexanes : Ethyl acetate=10/1 to 0/1) and by prep-TLC (SiO_2, DCM: MeOH = 10:1). Compound **13** (80 mg, 128.66 µmol, 32.23% yield, N/A purity) as yellow solid. **LCMS**: RT=0.853 min, m/z=622.4 [M+H]+

To a solution of Compound **13** (75 mg, 120.61 µmol, 1 eq) in HFIP (1 mL) was added MsOH (23.18 mg, 241.23 µmol, 17.24 µL, 2 eq). The reaction mixture was stirred at 30 °C for 2 hr. The reaction was concentrated under reduce pressure to give the residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [H_2O (0.225% FA)-ACN]; gradient: 1%-30% B over 15.0 min) and lyophilizated to give product. Compound **188** (5.89 mg, 11.77 µmol, 9.75% yield, 98.19% purity) as white solid. **LCMS:** RT =0.423 min, m/z=492.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.28 (br dd, J = 4.8, 11.8 Hz, 2H), 7.39 - 7.34 (m, 2H), 7.35 - 7.28 (m, 4H), 7.17 (br d, J = 4.4 Hz, 1H), 7.10 - 6.97 (m, 1H), 6.45 - 6.35 (m, 1H), 5.19 - 5.04 (m, 2H), 4.16 - 4.02 (m, 2H), 3.63 - 3.43 (m, 1H), 2.91 (br d, J = 10.0 Hz, 2H), 2.86 (br d, J = 4.4 Hz, 3H), 2.53 (br s, 6H), 1.46 - 1.32 (m, 3H).

Compound 234

Compound **234** was prepared in accordance with the following scheme



To a solution of compound **1** (282.17 mg, 748.96 µmol, 1 eq) and compound **2A** (450 mg, 2.25 mmol, 3 eq) in DMF (4 mL) was added K_2CO_3 (310.54 mg, 2.25 mmol, 3 eq). Then the reaction was stirred at 25°C for 12h. The reaction mixture was added water (15 mL) and extracted by EA (15 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under vacuo to give a residue. The crude product was purified by RP-HPLC (spherical C18 20-45 mm 100A 80g; mobile phase: [water (0.1%FA)-ACN]; B%: 40%-55% (DP collected)) and lyophilized, compound **3** (280 mg, 564.38 µmol, 75.36% yield) was obtained as a white oil, **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.20 (s, 1H), 8.15 (s, 1H), 6.09 (s, 2H), 4.17 (s, 2H), 3.65 - 3.56 (m, 2H), 3.16 - 3.06 (m, 1H), 2.84 (s, 3H), 2.53 (br d, J = 6.6 Hz, 3H), 1.96 (br dd, J = 2.3, 4.7 Hz, 2H), 1.51 (s, 9H), 0.96 - 0.86 (m, 2H), 0.00 (s, 9H)

To a solution of compound **3** (260 mg, 524.07 µmol, 1 eq) and compound **4** (163.67 mg, 628.88 µmol, 1.2 eq) in DMF (4 mL) was added CMPI (200.83 mg, 786.11 µmol, 1.5 eq) and DIEA (203.19 mg, 1.57 mmol, 273.84 µL, 3 eq). The mixture was stirred at 50 °C for 12hr. The reaction mixture was poured into H_2O (10 mL) under N_2 and extracted by EtOAC (10 mLx3), the organic phase was combined and washed with brine (10 mL X 3), dried with anhydrous Na_2SO_4, filtered and concentrated to give a crude product in vacuum. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [H_2O (0.225% FA)-ACN]; gradient:80%-100% B over 9.0 min) and lyophilized. Compound **5** (193 mg, 261.39 µmol, 49.88% yield) was obtained as a white gum. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.18 (s, 1H), 8.03 (s, 1H), 7.39 - 7.33 (m, 4H), 7.08 (br s, 3H), 5.92 (br s, 2H), 5.43 - 5.30 (m, 2H), 4.38 - 4.24 (m, 1H), 4.11 - 3.99 (m, 2H), 3.97 - 3.79 (m, 1H), 3.63 - 3.47 (m, 2H), 2.73 (s, 3H), 2.44 (br dd, J = 2.5, 11.2 Hz, 4H), 1.41 (s, 9H), 1.39 (br s, 3H), 0.90 (br d, J = 1.8 Hz, 2H), 0.00 (s, 9H)

To a 35 ml hydrogenation flask with a magnetic stir bar was added Pd/C (34.59 mg, 32.50 µmol, 10% purity, 0.15 eq) and followed by the addition of MeOH (4 mL) under argon, then added compound **5** (160 mg, 216.70 µmol, 1 eq) in MeOH (4 mL) and DIEA (28.01 mg,

216.70 µmol, 37.74 µL, 1 eq) under N_2. The reaction mixture was stirred at 25°C for 3h under H_2 (15psi). The reaction mixture was filtered under N_2 with diatomite and the filter cake was recycling, filter liquor was concentrated to give the crude. Compound **6** was obtained as a colorless oil. **LCMS**: RT=0.617min, m/z=704.4 [M+H]+

A mixture of compound **6** (150 mg, 213.09 µmol, 1 eq) in DCM (2 mL) and TFA (2 mL) was at stirred at 25 °C for 1hr. The solvent was removed under reduced pressure. The crude product was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [H_2O (0.225% FA)-ACN]; gradient:5%-35% B over 11.0 min) and lyophilized. Compound **234** (24.92 mg, 51.57 µmol, 24.20% yield, 98% purity) was obtained as a white solid. **LCMS**: RT=0.451 min, m/z=474.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.95 (br s, 1H), 8.68 - 8.39 (m, 2H), 8.13 (s, 1H), 7.35 - 7.25 (m, 2H), 7.25 - 7.20 (m, 2H), 7.01 - 6.88 (m, 3H), 5.20 (br s, 2H), 4.42 - 4.11 (m, 1H), 3.96 (br d, J = 4.0 Hz, 2H), 3.05 (br s, 1H), 2.70 (br d, J = 0.8 Hz, 2H), 2.42 (s, 5H), 1.29 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 244

Compound **244** was prepared by reacting Compound **234** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **244** (9.47 mg, 18.82 µmol, 8.65% yield, 96.9% purity) was obtained as an off-white gum. **LCMS**: RT=0.425 min, m/z=488.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.13 (br s, 1H), 9.03 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 7.32 - 7.20 (m, 4H), 7.01 - 6.93 (m, 1H), 6.90 - 6.84 (m, 2H), 5.06 (br s, 2H), 3.98 (q, J = 6.8 Hz, 3H), 2.13 (br d, J = 7.9 Hz, 5H), 2.03 (s, 6H), 1.30 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 235

Compound **235** was prepared following the protocol above for Compound **234** starting with a different diastereomer of compound 2A. Compound **235** (23.00 mg, 48.33 µmol, 17.01% yield, 99.5% purity) was obtained as a white solid. **LCMS**: RT=0.401 min, m/z=474.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.10 (s, 1H), 8.38 (br s, 1H), 8.25 (s, 1H), 8.17 (br s, 1H), 7.39 - 7.33 (m, 1H), 7.33 - 7.28 (m, 3H), 7.06 - 6.99 (m, 1H), 6.97 (s, 1H), 6.93 (br d, J = 6.8 Hz, 1H), 5.08 (br s, 2H), 4.92 (br s, 1H), 4.02 (br d, J = 6.4 Hz, 2H), 3.41 (br s, 1H), 2.81 - 2.50 (m, 2H), 2.31 (br s, 3H), 2.24 (br d, J = 1.2 Hz, 2H), 1.34 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 240

Compound **240** was prepared by reacting Compound **235** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **240** (21.06 mg, 42.11 µmol, 52.48% yield, 97.5% purity) was obtained as a white solid. **LCMS**: RT=0.412 min, m/z=488.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.45 (br s, 1H), 8.28 (s, 1H), 8.17 (br s, 1H), 7.41 - 7.34 (m, 2H), 7.34 - 7.28 (m, 2H), 7.07 - 7.01 (m, 1H), 6.97 (s, 1H), 6.94 (br d, J = 7.3 Hz, 1H), 5.13 (br s, 2H), 4.81 (br t, J = 8.3 Hz, 1H), 4.06 (q, J = 6.9 Hz, 2H), 3.10 - 2.87 (m, 1H), 2.53 (br s, 2H), 2.42 - 2.31 (m, 2H), 2.26 (br s, 6H), 1.38 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 236

Compound **236** was prepared in a similar manner to Compound **234** starting with a different diastereomer of compound 2A. Compound **236** (22.42 mg, 45.07 µmol, 32.47% yield, 98.5% purity) was obtained as a white solid. **LCMS**: RT=0.425 min, m/z=490.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.14 (br s, 1H), 9.12 (s, 1H), 8.45 (s, 1H), 8.26 (s, 1H), 7.56 (s, 1H), 7.46 - 7.42 (m, 1H), 7.38 - 7.34 (m, 1H), 7.33 (s, 1H), 7.31 (s, 1H), 6.99 - 6.92 (m, 2H), 5.13 (br s, 2H), 4.72 (t, J = 8.4 Hz, 1H), 4.06 (q, J = 6.8 Hz, 2H), 3.24 (br t, J = 7.6 Hz, 1H), 2.54 - 2.43 (m, 2H), 2.26 (s, 3H), 1.96 - 1.87 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 242

Compound **242** was prepared by reacting Compound **236** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **242** was obtained as a white solid. **LCMS**: RT=0.412 min, m/z=488.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.30 - 12.04 (m, 1H), 9.12 (s, 1H), 8.47 (s, 1H), 8.27 (s, 1H), 7.55 (s, 1H), 7.46 - 7.41 (m, 1H), 7.37 - 7.30 (m, 3H), 6.97 - 6.90 (m, 2H), 5.15 (br s, 2H), 4.66 (quin, J = 8.4 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 2.70 (dt, J = 3.6, 7.6 Hz, 1H), 2.50 - 2.40 (m, 2H), 2.15 - 2.08 (m, 2H), 2.06 (s, 6H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 237

Compound **237** was prepared in a similar manner to Compound **234** starting with a different diastereomer of compound 2A. Compound **237** (45.17 mg, 98.16 µmol, 70.71% yield, 99% purity) was obtained as a white solid. **LCMS**: RT=0.400 min, m/z=456.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.07 (br s, 1H), 8.45 - 8.30 (m, 1H), 8.30 - 8.12 (m, 2H), 7.52 (br d, J = 7.2 Hz, 2H), 7.41 - 7.35 (m, 2H), 7.34 - 7.29 (m, 2H), 6.98 (s, 1H), 6.94 (br d, J = 6.4 Hz, 1H), 5.07 (br s, 2H), 4.91 (br s, 1H), 3.99 (br d, J = 5.2 Hz, 2H), 3.45 (br s, 1H), 2.85 - 2.52 (m, 2H), 2.32 (br s, 5H), 1.31 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 243

Compound **243** was prepared by reacting Compound **237** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **243** (44.59 mg, 94.01 µmol, 13.84% yield, 99% purity) was obtained as a white solid. **LCMS**: RT=0.397 min, m/z=470.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.21 (br s, 1H), 9.12 (s, 1H), 8.47 (s, 1H), 8.26 (s, 1H), 7.56 (d, J = 7.2 Hz, 2H), 7.46 - 7.39 (m, 2H), 7.38 - 7.31 (m, 2H), 6.97 - 6.90 (m, 2H), 5.15 (br s, 2H), 4.68 (quin, J = 8.4 Hz, 1H), 4.04 (q, J = 7.2 Hz, 2H), 2.70 (dt, J = 3.6, 7.6 Hz, 1H), 2.51 - 2.38 (m, 2H), 2.16 - 2.08 (m, 2H), 2.06 (s, 6H), 1.36 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 238

Compound **238** was prepared in a similar manner to Compound **234**. Compound **238** (24.59 mg, 45.17 µmol, 27.11% yield, 90% purity) was obtained as a yellow gum. **LCMS**: RT=0.434 min, m/z=490.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.13 (s, 1H), 9.12 (s, 1H), 8.50 (s, 1H), 8.27 (s, 1H), 7.57 (s, 1H), 7.47 - 7.43 (m, 1H), 7.40 - 7.32 (m, 4H),

7.01 - 6.94 (m, 2H), 5.16 (br s, 2H), 4.07 (q, J = 6.8 Hz, 3H), 2.84 - 2.73 (m, 1H), 2.38 - 2.30 (m, 5H), 2.14 - 2.01 (m, 2H), 1.39 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 239

Compound **239** was prepared in a similar manner to Compound **234**. Compound **239** (24.59 mg, 45.17 µmol, 27.11% yield, 90% purity) was obtained as an off-white gum. **LCMS**: RT=0.417 min, m/z=456.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.30 - 11.98 (m, 1H), 9.12 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.48 - 7.40 (m, 2H), 7.39 - 7.34 (m, 2H), 7.00 - 6.95 (m, 2H), 5.15 (br s, 2H), 4.15 - 3.98 (m, 3H), 2.77 (br t, J = 7.1 Hz, 1H), 2.34 (s, 5H), 2.11 - 1.99 (m, 2H), 1.38 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 245

Compound **245** was prepared by reacting Compound **239** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **244** (30.22 mg, 63.71 µmol, 43.32% yield, 99% purity) was obtained as a white solid. **LCMS**: RT=0.405 min, m/z=470.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.22 (br d, J = 3.0 Hz, 1H), 9.10 (s, 1H), 8.52 (s, 1H), 8.25 (s, 1H), 7.56 (d, J = 7.3 Hz, 2H), 7.45 - 7.39 (m, 2H), 7.38 - 7.32 (m, 2H), 6.98 - 6.93 (m, 2H), 5.14 (br s, 2H), 4.05 (q, J = 6.9 Hz, 3H), 2.25 - 2.17 (m, 5H), 2.11 (s, 6H), 1.36 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 248

Compound **248** was prepared following the protocol above for Compound **234** starting with a tert-butyl (((1s,3s)-3-aminocyclobutyl)methyl)carbamate instead of 2A followed by deprotection with TFA. Compound **248** (7.02 mg, 14.68 µmol, 2.52% yield, 99% purity) was obtained as a white solid. **LCMS**: RT=0.420min, m/z=474.2(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.96 - 8.80 (m, 1H), 8.71 - 8.55 (m, 1H), 8.51 - 8.40 (m, 1H), 7.93 (br s, 1H), 7.40 - 7.31 (m, 4H), 7.08 - 6.99 (m, 3H), 5.29 - 5.17 (m, 2H), 4.45 - 4.27 (m, 1H), 4.08 (br d, J = 6.4 Hz, 2H), 3.11 - 2.95 (m, 2H), 2.46 - 2.29 (m, 2H), 2.25 - 2.10 (m, 3H), 1.42 - 1.35 (m, 3H).

Synthesis of Compound 249

Compound **249** was prepared by reacting Compound **248** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **249** (17.72 mg, 34.27 µmol, 10.82% yield, 97% purity) was obtained as a white solid. **LCMS**: RT=0.427min, m/z=502.2(M+H+) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.21 - 11.96 (m, 1H), 9.12 (s, 1H), 8.44 (s, 1H), 8.26 (s, 1H), 7.40 - 7.31 (m, 4H), 7.05 (br t, J = 88 Hz, 1H), 6.98 - 6.92 (m, 2H), 5.23 - 5.04 (m, 2H), 4.32 - 4.18 (m, 1H), 4.10 - 4.03 (m, 2H), 2.48 - 2.34 (m, 2H), 2.33 - 2.20 (m, 6H), 2.19 - 2.12 (m, 2H), 2.02 (br d, J = 6.4 Hz, 3H), 1.38 (dt, J = 2.0, 6.8 Hz, 3H).

Synthesis of Compound 250

Compound **250** was prepared following the protocol above for Compound **234** starting with a tert-butyl ((1s,3s)-3-aminocyclobutyl)carbamate instead of 2A followed by deprotection with TFA. Compound **250** (17.33 mg, 37.80 µmol, 43.40% yield) was obtained

as a white solid. **LCMS**: RT=0.485 min, m/z=459.2 [M+H]+ **^{1}H NMR**(400 MHz, CHLOROFORM-d) δ = 8.49 (br s, 1H), 8.01 (br s, 1H), 7.70 (br d, J = 7.6 Hz, 1H), 7.44 (br d, J = 3.2 Hz, 1H), 7.40 - 7.28 (m, 4H), 7.15 (br t, J = 7.6 Hz, 1H), 7.04 (br t, J = 7.2 Hz, 1H), 7.00 - 6.92 (m, 2H), 5.26 - 5.09 (m, 2H), 4.04 (br d, J = 1.6 Hz, 3H), 3.27 - 2.91 (m, 1H), 2.46 - 2.30 (m, 2H), 2.29 - 2.10 (m, 2H), 1.36 (br s, 3H)

Synthesis of Compound 251

Compound **251** was prepared by reacting Compound **250** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **251** (54 mg, 110.98 µmol, 22.12% yield) was obtained as a white solid. **LCMS**: RT=0.497 min, m/z = 487.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.38 (s, 1H), 8.24 (s, 1H), 7.82 - 7.77 (m, 1H), 7.64 - 7.39 (m, 4H), 7.26 (br s, 5H), 5.21 - 4.97 (m, 2H), 4.39 - 4.13 (m, 2H), 2.36 (br s, 3H), 2.22 - 1.81 (m, 9H), 1.46 - 1.13 (m, 3H).

Synthesis of Compound 252

Compound **252** was prepared in a similar manner to Compound **234**. Compound **252** (65.97 mg, 126.83 µmol, 22.29% yield, 99.7% purity) was obtained as a white solid. **LCMS**: RT=0.501 min, m/z= 473.3 [M+H]+. **^{1}H NMR**(400 MHz, CHLOROFORM-d) δ = 8.63 (br s, 1H), 8.04 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.56 - 7.39 (m, 1H), 7.39 - 7.27 (m, 4H), 7.15 (t, J = 7.5 Hz, 1H), 7.07 - 6.99 (m, 3H), 5.22 (br s, 2H), 4.50 - 4.14 (m, 1H), 4.13 - 3.59 (m, 2H), 3.10 - 2.81 (m, 1H), 2.60 - 2.40 (m, 2H), 2.36 (br s, 5H), 1.46 - 1.22 (m, 3H).

Synthesis of Compound 253

Compound **253** was prepared in a similar manner to Compound **251**. Compound **253** (10.2 mg, 18.88 µmol, 59.91% yield, 93.3% purity) was obtained as a white solid. **LCMS**: RT=0.443 min, m/z=504.2 [M+H]+ **^{1}H NMR**(400 MHz, CHLOROFORM-d) δ = 12.47 - 11.89 (m, 1H), 9.10 (s, 1H), 8.52 (s, 1H), 8.25 (s, 1H), 7.56 (s, 1H), 7.44 (td, J = 1.8, 6.8 Hz, 1H), 7.37 - 7.30 (m, 3H), 6.97 - 6.92 (m, 2H), 5.13 (br s, 2H), 4.13 - 3.96 (m, 3H), 2.20 (br d, J = 8.1 Hz, 5H), 2.11 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 265

Compound **265** was prepared in a similar manner to Compound **251**. Compound **265** (78.16 mg, 158.09 µ mol, 23.88% yield, 97% purity) was obtained as a white solid. **LCMS**: RT=0.460 min, m/z= 480.2 [M+H]+. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.64 (s, 1H), 8.06 (s, 1H), 7.84 (br s, 1H), 7.75 (br d, J = 0.9 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.63 (br d, J = 7.6 Hz, 1H), 7.56 - 7.41 (m, 2H), 7.29 (br d, J = 5.4 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.04 (s, 2H), 5.20 (br s, 2H), 4.36 - 3.69 (m, 3H), 3.09 - 2.88 (m, 1H), 2.55 - 2.40 (m, 2H), 2.35 (br s, 5H), 1.39 - 1.24 (m, 3H).

Synthesis of Compound 266

Compound **266** was prepared in a similar manner to Compound **251**. Compound **266** (41.16 mg, 80.34 µmol, 19.20% yield, 94.98% purity) was obtained as a brown gum. **LCMS**:

RT=0.526 min, m/z = 487.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.64 (br s, 1H), 8.08 (s, 1H), 7.37 (br d, J = 6.0 Hz, 2H), 7.34 - 7.29 (m, 3H), 7.07 - 7.03 (m, 1H), 7.01 (br s, 2H), 6.91 (br d, J = 7.2 Hz, 1H), 5.16 (br s, 2H), 4.18 - 3.91 (m, 3H), 3.01 - 2.83 (m, 1H), 2.61 (s, 3H), 2.43 - 2.38 (m, 3H), 2.36 (br s, 4H), 1.34 (br d, J = 6.0 Hz, 3H).

Synthesis of Compound 277

Compound **277** was prepared in a similar manner to Compound **234**. Compound **277** (20.48 mg, 37.75 µmol, 23.10% yield, 92.9% purity) was obtained as a yellow solid. **LCMS**: RT=0.433 min, m/z=504.2 [M+H]+. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.57 - 11.61 (m, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 7.56 (s, 1H), 7.45 - 7.41 (m, 1H), 7.37 - 7.31 (m, 3H), 6.97 - 6.90 (m, 2H), 5.09 (br s, 2H), 4.11 - 3.99 (m, 3H), 2.85 (s, 3H), 2.74 (br t, J = 7.2 Hz, 1H), 2.32 (s, 5H), 2.10 - 1.99 (m, 2H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 278

Compound **278** was prepared in a similar manner to Compound **234**. Compound **278** (62.83 mg, 121.65 µmol, 39.70% yield, 94.4% purity) was obtained as a white solid. **LCMS**: RT=0.412 min, m/z = 488.2 [M+H]+. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.47 - 11.72 (m, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 7.40 - 7.28 (m, 4H), 7.08 - 7.01 (m, 1H), 6.97 - 6.91 (m, 2H), 5.08 (br s, 2H), 4.11 - 3.99 (m, 3H), 2.85 (s, 3H), 2.73 (s, 1H), 2.36 - 2.27 (m, 5H), 2.03 (td, J = 9.2, 11.3 Hz, 2H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 267

Compound **267** was prepared following the procedures of **GP2**, **GP3**, and **GP5** with (*R*)-2-methyl-*N*-((*S*)-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-c]pyridin-7-yl)(1-trityl-1*H*-imidazol-4-yl)methyl)propane-2-sulfinamide as starting material and MsOH / NH_2OH-HCl are reagents in GP3. Compound **267** was obtained as a white solid (45 mg, 94.71 µmol, 3.86% yield, 99.02% purity). **LCMS**: RT=0.420 min, m/z=471.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 13.07 - 12.82 (m, 1H), 9.76 - 9.56 (m, 1H), 9.13 (s, 1H), 8.77 - 8.54 (m, 1H), 8.26 (s, 1H), 7.83 (s, 1H), 7.61 - 7.40 (m, 1H), 7.39 - 7.33 (m, 1H), 7.33 (br s, 3H), 7.07 - 6.98 (m, 3H), 4.12 - 3.95 (m, 2H), 3.19 - 2.99 (m, 3H), 1.35 (t, 3H).

Synthesis of Compound 284

Compound **284** was prepared in a similar manner to Compound **250**. Compound **284** (9.02 mg, 18.31 µmol, 21.95% yield, 99.24% purity) was obtained as a yellow solid. **LCMS**: RT=0.526 min, m/z = 487.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.54 - 8.45 (m, 1H), 8.02 (br s, 1H), 7.55 (br s, 1H), 7.41 (br s, 1H), 7.37 - 7.29 (m, 4H), 7.01 - 6.94 (m, 2H), 6.91 (br d, J = 7.2 Hz, 1H), 5.19 - 5.06 (m, 2H), 4.15 - 3.89 (m, 3H), 3.21 - 2.98 (m, 1H), 2.60 (s, 3H), 2.43 - 2.19 (m, 4H), 1.35 (br s, 3H)

Synthesis of Compound 285

Compound **285** was prepared by reacting Compound **284** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **285** (63.32 mg, 122.46 µmol, 66.54% yield) was obtained as a yellow gum. **LCMS**: RT=0.522 min, m/z =517.1 [M+H] + **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.06 (s, 1H), 7.51 (br s, 1H), 7.39 (br s, 2H), 7.32 - 7.27 (m, 3H), 7.08 - 6.97 (m, 2H), 6.92 (br d, J = 7.2 Hz, 1H), 5.16 (br s, 2H), 4.24 - 3.58 (m, 2H), 2.74 - 2.56 (m, 8H), 2.51 (br s, 6H), 1.43 - 1.22 (m, 3H).

Synthesis of Compound 286

Compound **286** was prepared in a similar manner to Compound **234**. Compound **286** (4.23 mg, 8.41 µmol, 15.42% yield) was obtained as a yellow solid. **LCMS**: RT=0.515 min, m/z = 503.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.05 - 11.68 (m, 1H), 8.12 (s, 1H), 7.56 (s, 1H), 7.45 - 7.41 (m, 1H), 7.37 - 7.28 (m, 5H), 6.96 - 6.92 (m, 2H), 6.90 (d, J = 7.2 Hz, 1H), 5.11 (br s, 2H), 4.09 - 3.97 (m, 3H), 2.73 - 2.67 (m, 1H), 2.64 (s, 3H), 2.30 (s, 3H), 2.28 (br s, 1H), 2.03 - 1.95 (m, 2H), 1.36 (br t, J = 6.8 Hz, 3H).

Synthesis of Compound 287

Compound **287** was prepared in a similar manner to Compound **250**. Compound **287** (19.77 mg, 40.46 µmol, 14.29% yield, 97.4% purity) was obtained as an off-white solid. **LCMS**: RT=0.406 min, m/z=476.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.08 (br s, 1H), 8.66 - 8.33 (m, 1H), 8.24 (s, 1H), 7.56 (s, 1H), 7.46 - 7.41 (m, 1H), 7.37 - 7.29 (m, 3H), 7.10 - 6.89 (m, 2H), 5.26 - 4.90 (m, 2H), 4.16 - 3.68 (m, 4H), 2.22 - 2.05 (m, 1H), 1.82 - 1.69 (m, 2H), 1.35 (br t, J = 6.8 Hz, 3H), 1.27 - 1.13 (m, 1H).

Synthesis of Compound 288

Compound **288** was prepared by reacting Compound **287** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **288** (22.09 mg, 42.91 µmol, 14.59% yield, 97.9% purity) was obtained as a white solid. **LCMS**: RT=0.423 min, m/z=504.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.72 - 12.30 (m, 1H), 9.05 (br s, 1H), 8.61 - 8.28 (m, 1H), 8.19 (s, 1H), 7.49 (s, 1H), 7.36 (br d, J = 6.4 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.22 (s, 1H), 6.91 (br s, 2H), 5.23 (br d, J = 8.4 Hz, 1H), 4.87 (br d, J = 14.8 Hz, 1H), 4.28 (br d, J = 1.2 Hz, 1H), 4.13 - 3.83 (m, 2H), 3.24 (br d, J = 1.6 Hz, 1H), 1.98 - 1.70 (m, 9H), 1.29 (br s, 4H).

Synthesis of Compound 289

Compound **289** was prepared in a similar manner to Compound **250**. Compound **289** (42.13 mg, 89.49 µmol, 12.47% yield, 99.1% purity) was obtained as a white solid. **LCMS**: RT=0.409 min, m/z = 467.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.11 (s, 1H), 8.46 (s, 1H), 8.26 (s, 1H), 7.86 (d, J = 0.8 Hz, 1H), 7.77 (dd, J = 1.0, 7.9 Hz, 1H), 7.63 (dd, J = 1.0, 7.8 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.03 - 6.91 (m, 2H), 5.12 (br s, 2H), 4.12 - 4.03 (m, 2H), 3.92 (br s, 1H), 2.98 (br t, J = 7.6 Hz, 1H), 2.35 (br d, J = 6.4 Hz, 2H), 2.04 - 1.94 (m, 2H), 1.36 (t, J = 6.8 Hz, 3H)

Synthesis of Compound 290

Compound **290** was prepared by reacting Compound **289** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **290** (108.52 mg, 218.76 µmol, 51.03% yield, 99.7% purity) was obtained as a white solid. **LCMS**: RT=0.413 min, m/z = 495.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.16 (br d, J = 1.5 Hz, 1H), 9.11 (s, 1H), 8.52 (s, 1H), 8.25 (s, 1H), 7.87 (s, 1H), 7.82 - 7.74 (m, 1H), 7.68 - 7.60 (m, 1H), 7.57 - 7.49 (m, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.03 - 6.92 (m, 2H), 5.14 (br s, 2H), 4.15 - 3.95 (m, 3H), 2.28 - 2.14 (m, 5H), 2.11 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 291

Compound **291** was prepared in a similar manner to Compound **234**. Compound **291** (32.05 mg, 66.03 µmol, 31.29% yield, 99% purity) was obtained as a white solid. **LCMS**: RT=0.409 min, m/z = 481.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.11 (s, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 7.87 (s, 1H), 7.78 (br d, J = 8.0 Hz, 1H), 7.64 (br d, J = 7.6 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.01 - 6.94 (m, 2H), 5.14 (br s, 2H), 4.11 - 3.99 (m, 3H), 2.75 (br t, J = 7.2 Hz, 1H), 2.32 (s, 5H), 2.09 - 1.98 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 292

Compound **292** was prepared in a similar manner to Compound **250**. Compound **292** (32.32 mg, 65.26 µ mol, 12.76% yield, 94% purity) was obtained as a white solid. **LCMS**: RT=0.485 min, m/z= 466.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.10 (s, 1H), 7.85 (s, 1H), 7.79 - 7.71 (m, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.55 - 7.47 (m, 1H), 7.38 (br d, J = 6.8 Hz, 1H), 7.29 (br s, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.01 - 6.92 (m, 2H), 5.15 (br s, 2H), 4.03 (br s, 2H), 3.94 - 3.79 (m, 1H), 2.95 (br s, 1H), 2.30 (br s, 2H), 2.05 - 1.92 (m, 2H), 1.34 (br t, J = 6.1 Hz, 3H)

Synthesis of Compound 293

Compound **293** was prepared by reacting Compound **292** with formaldehyde in the presence of $NaBH(OAc)_3$. Compound **293** (44.03 mg, 82.96 µ mol, 9.66% yield, 93% purity) was obtained as a white solid. **LCMS**: RT=0.455 min, m/z= 494.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.09 (s, 1H), 7.82 (br s, 1H), 7.72 (br d, J = 8.1 Hz, 2H), 7.61 (br d, J = 7.6 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.35 - 7.27 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 - 6.96 (m, 2H), 5.25 (br s, 2H), 4.16 - 3.66 (m, 2H), 2.92 - 2.15 (m, 12H), 1.39 - 1.18 (m, 3H).

Synthesis of Compound 294

Compound **294** was prepared in a similar manner to Compound **250**. Compound **294** (32.37 mg, 69.39 µmol, 15.96% yield, 98.5% purity) was obtained as a white solid. **LCMS**: RT=0.392 min, m/z=460.1 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 13.39 - 12.31 (m, 1H), 9.03 (br s, 1H), 8.43 (br s, 1H), 8.19 (s, 1H), 7.36 - 7.30 (m, 1H), 7.29 (br s, 1H), 7.25 (br d, J = 7.2 Hz, 2H), 7.06 - 6.88 (m, 3H), 5.08 (br s, 1H), 4.92 (br d, J = 14.8 Hz, 1H),

3.98 (br s, 3H), 3.69 (q, J = 8.4 Hz, 1H), 2.07 (br s, 1H), 1.75 - 1.65 (m, 2H), 1.30 (br t, J = 6.4 Hz, 3H), 1.19 (br d, J = 17.6 Hz, 1H).

Synthesis of Compound 295

Compound **295** was prepared in a similar manner to Compound **250**. Compound **295** (15.26 mg, 31.42 µmol, 7.93% yield, 98% purity) was obtained as a white solid. **LCMS**: RT=0.431min, m/z=476.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.53 (s, 1H), 8.86 (br s, 1H), 8.33 (br s, 1H), 7.47 (s, 1H), 7.38 - 7.26 (m, 5H), 7.18 (d, J = 7.8 Hz, 1H), 5.49 - 5.19 (m, 2H), 4.84 - 4.79 (m, 1H), 4.29 - 4.15 (m, 1H), 4.13 - 3.97 (m, 2H), 2.96 (quin, J = 10.6 Hz, 1H), 2.43 - 2.29 (m, 1H), 2.19 (br d, J = 8.1 Hz, 1H), 2.09 - 1.97 (m, 1H), 1.31 (t, J = 7.0 Hz, 3H).

Synthesis of Compound 301

Compound **301** was prepared in a similar manner to Compound **250**. Compound **301** (10.14 mg, 30.88 µmol, 14.54% yield, 98% purity) was obtained as a white solid. **LCMS**: RT=0.424 min, m/z=476.2 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.30 - 11.90 (m, 1H), 9.11 (s, 1H), 8.47 (s, 1H), 8.26 (s, 1H), 7.55 (s, 1H), 7.45 - 7.41 (m, 1H), 7.36 - 7.30 (m, 3H), 6.97 - 6.91 (m, 2H), 5.13 (br s, 2H), 4.05 (q, J = 6.9 Hz, 2H), 3.98 - 3.88 (m, 1H), 3.04 - 2.92 (m, 1H), 2.41 - 2.29 (m, 2H), 2.05 - 1.93 (m, 2H), 1.37 (t, J = 6.8 Hz, 3H).

Synthesis of Compound 302

Compound **302** was prepared in a similar manner to Compound **240** using Compound **301** as starting material. Compound **302** (25.75 mg, 48.31 µmol, 11.84% yield, 97.2% purity) was obtained as a white solid. **LCMS**: RT=0.446 min, m/z=518.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.49 - 11.80 (m, 1H), 8.39 (s, 1H), 8.21 (s, 1H), 7.56 (s, 1H), 7.46 - 7.40 (m, 1H), 7.38 - 7.30 (m, 3H), 6.98 - 6.90 (m, 2H), 5.12 (br s, 2H), 4.05 (q, J = 7.0 Hz, 3H), 2.85 (s, 3H), 2.35 - 2.19 (m, 5H), 2.15 (br s, 6H), 1.37 (t, J = 6.9 Hz, 3H).

Synthesis of Compound 303

Compound **303** was prepared in a similar manner to Compound **250**. Compound **303** (15.59 mg, 31.87 µmol, 4.08% yield, 96.8% purity) was obtained as a white solid. **LCMS**: RT=0.417 min, m/z=474.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.25 - 11.90 (m, 1H), 8.31 (s, 1H), 8.22 (s, 1H), 7.40 - 7.32 (m, 2H), 7.32 - 7.27 (m, 2H), 7.08 - 7.01 (m, 1H), 6.96 - 6.90 (m, 2H), 5.08 (br s, 2H), 4.05 (q, J = 6.9 Hz, 2H), 3.96 - 3.86 (m, 1H), 3.02 - 2.90 (m, 1H), 2.86 (s, 3H), 2.40 - 2.28 (m, 2H), 2.02 - 1.92 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H).

Synthesis of Compound 304

Compound **304** was prepared in a similar manner to Compound **240** using Compound **303** as starting material. Compound **304** (108.54 mg, 213.79 µmol, 33.75% yield, 98.8% purity) was obtained as a white solid. **LCMS**: RT=0.413 min, m/z=502.3 [M+H]+ **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 12.15 (br s, 1H), 8.37 (s, 1H), 8.21 (s, 1H), 7.41 -

7.33 (m, 2H), 7.33 - 7.28 (m, 2H), 7.08 - 7.01 (m, 1H), 6.97 - 6.91 (m, 2H), 5.09 (br s, 2H), 4.10 - 3.97 (m, 3H), 2.85 (s, 3H), 2.27 - 2.15 (m, 5H), 2.10 (s, 6H), 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 / 55μM 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 (150μL) 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. 200μL 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 incubation, 10μM 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 10μM 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-1β (human; DuoSet; R&D) and for TNFα (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 4 below provides IC_{50} data for the compounds disclosed herein where “A” is indicative of an IC_{50} value of <100 nM, “B” is indicative of an IC_{50} value between 100 nM and 500 nM, “C” is indicative of an IC_{50} value between 500 nM and 1 uM, “D” is indicative of an IC_{50} value between 1 uM and 15 uM, and “E” is indicative of an IC_{50} value >15 uM.

Table 4

No.	IC_{50}	No.	IC_{50}	No.	IC_{50}
001	A	063	A	126	A
002	A	064	A	127	A
003	A	065	A	128	A
004	A	066	A	129	C
005	A	067	A	130	A
006	A	068	A	131	A
007	A	070	A	132	D
008	D	071	A	133	A
009	A	072	A	134	D
010	D	073	A	135	A
011	D	074	A	136	A

012	B	075	A	137	A
013	A	076	A	138	A
014	A	077	A	139	A
015	A	078	A	140	A
016	E	079	A	141	A
017	A	080	A	142	D
018	A	081	A	143	A
019	A	082	A	144	A
020	B	083	A	145	D
021	B	084	A	146	B
022	A	085	A	147	A
023	A	086	A	148	A
024	A	087	A	149	A
025	A	088	B	150	D
026	A	089	A	151	A
027	A	090	A	152	C
028	E	091	A	153	A
029	A	092	B	154	A
030	E	093	A	155	A
031	E	094	A	156	A
032	B	095	A	157	A
033	A	096	A	158	D
034	E	097	A	159	A
035	A	098	A	160	A
036	A	099	A	161	A
037	A	100	A	162	A
038	A	101	A	163	A
039	D	102	A	164	A
040	A	103	A	165	A
041	A	104	A	166	A
042	A	106	A	167	A
043	B	107	A	168	A
044	B	108	A	169	A
045	A	109	A	170	A
046	A	110	A	171	A
047	B	111	A	172	A
048	A	112	A	173	A
049	A	113	A	174	A
050	D	114	A	175	A
051	A	115	A	176	B
052	E	116	A	177	A
053	A	117	A	178	A
054	E	118	B	179	A
055	A	119	A	180	C
056	A	120	A	181	A
057	B	121	A	182	A

058	A	122	C	183	A
059	D	123	C	184	A
060	E	124	-	185	D
061	E	125	A	186	A
062	A				

Table 4 continued

No.	IC_{50}	No.	IC_{50}	No.	IC_{50}
187	A	223	A	257	A
188	A	224	A	258	B
189	A	225	A	259	A
190	A	226	B	260	D
192	B	227	A	261	A
193	A	228	A	262	A
194	A	229	A	263	A
195	A	230	A	264	A
196	A	231	A	265	A
197	A	232	A	266	A
198	A	233	A	267	B
199	A	234	D	277	A
200	B	235	B	278	A
201	B	236	A	279	A
202	A	237	D	280	A
203	A	238	A	281	D
204	B	239	A	282	A
205	A	240	C	283	A
206	A	241	A	284	A
207	A	242	B	285	A
208	D	243	D	286	A
209	A	244	A	287	C
210	D	245	A	288	B
211	A	246	A	289	A
212	A	247	A	290	A
213	A	248	A	291	A
214	A	249	A	292	A
215	A	250	A	293	A
216	A	251	A	294	C
217	A	252	A	295	B
218	A	253	A	297	B
219	A	254	A	298	A
220	B	255	A	299	D
221	A	256	B	300	B
222	C				

Example 3: Compound 007 NLRP3 Epitope Determination

NLRP3 belongs to the family of NOD-like receptors (NLRs), which are classified as AAA+ ATPases (ATPases associated with diverse cellular activities). AAA+ ATPases are triphosphate-nucleotide binding domains whose central β-sheet is defined by a characteristic parallel β2-β3-β4-β1-β5 topology, where the P-loop (or Walker A motif) is directly following the first β-strand (β1) and the Walker B motif is located on the third β-strand (β3) (Hochheiser and Geyer, 2023). The structure of the P-loop domain is characterized by a three-layered αβα sandwich of repeating β-loop-α units, also known as Rossmann-fold, where the β-strands are arranged in parallel orientation and surrounded by α-helices. NLRs constitute the subgroup of STAND ATPases within the AAA+ superfamily, which contain a C-terminal helical domain (HD1) followed by a winged helix domain (WHD) relative to the ATPase activity containing nucleotide-binding domain (NBD).

Compound 007 of the disclosure was used as an exemplary compound for determining the epitope to NLRP3, using cryogenic electron microscopy (cryo-EM).

The results of the cryo-EM assay found that Compound 007 binds in a pocket on the surface of the NACHT domain of NLRP3 (Fig. 1). The specific binding site is mostly composed of residues from the nucleotide-binding domain (NBD) but opposite to the ATP-binding site from the perspective of the central β-sheet (Fig. 2). The binding site is consistent with the finding that the 5-azaindazole-containing compounds either do not inhibit, or are very weak inhibitors of the intrinsic ATP-hydrolysis activity of NLRP3 (Fig. 6).

The defining feature of the interaction between the 5-azaindazole-containing compounds (Hartman et al., Bioorg. Med. Chem. Lett. 102: 129675. 2024) and NLRP3 is the formation of three hydrogen bonds to the backbone atoms of the terminal β-strand β2 in the NBD of NLRP3 (Fig. 3). The two nitrogen atoms (N32 and N31) form two donor-acceptor pairs with the backbone NH and CO groups of Tyr258 at a distance of 3.1 and 2.9 Angstroem, respectively, in perfect geometry (Fig. 3). This specific interaction is complemented by a third hydrogen bond between the CO moiety (O23) of the central peptide bond unit to the backbone NH group of His260 at 3.1 Angstroem (Fig. 3). The following biphenyl unit binds into a hydrophobic crevice formed by helices α2 and α4 of the NBD, where it interacts with the side chains of residues Leu275, Leu272, Leu335, Leu331, Leu332, Val264, the β-methylene group of Glu263, and Gly328 in a counterclockwise listing (Fig. 4). The ethoxy moiety in the meta-position of the first benzene ring of Compound 007 reaches out into a hydrophobic crevice formed by the side chains of Phe299, Leu272, Ile276 and Phe257 of NLRP3 contributing to the specificity of the interaction. The fluorine atom of the second benzene ring is embedded between the side chains of Leu331, Leu332 and L335 of NBD helix α4. The two benzene rings of the biphenyl unit are twisted relative to each other by 45° (Fig. 4).

The benzylic Ca position (C04) position of the 5-azaindiazole is chiral and in the (R)-

configuration. The hydroxy group of the 2-hydroxyethyl moiety forms a hydrogen bond to the carboxyl side chain group of Glu263 (Fig. 3). Additional interactions are made to residue Cys514 at the tip of the β-sandwich loop in the winged-helix-domain (WHD) of NLRP3 at a distance of 3.3 Angstroem between the oxygen (O01) and the sulfur atoms (Fig. 4). The methyl group at the NC position of the central peptide bond (C24) is in proximity (4.1 Angstroem) to the sidechain of Cys279 (Fig. 5).

The binding of Compound 007 to NLRP3 is complemented by an interaction of the nitrogen atom (N27) of the 5-azaindazole, which is in 3.4 and 4.6 Angstroem distance to the side chains of Arg147 and Tyr143 of the FISNA domain, respectively, coordinating the interaction of the inhibitor to the first subdomain of the NACHT (Fig. 4). Overall, the inhibitor Compound 007 performs interactions with 25 residues of the three subdomains NBD, FISNA and WHD, with Leu275 and Cys279 making the largest contribution to the buried surface area (BSA) of NLRP3 with 56 and 42 $Å^2$, respectively.

Methods – Example 3

Cloning, expression and purification of human NLRP3

Full length, human NLRP3 (3-1036, UniProt accession code Q96P20), codon-optimized for *Spodoptera frugiperda*, was cloned in an in-house modified pACE-Bac1 vector containing an N-terminal MBP-tag, followed by a Tobacco etch virus (TEV) protease cleavage site. For recombinant protein expression of MBP-NLRP3, 1L of *Sf9* insect cells were infected with 3% v/v viral stock of the second virus passage. The expression culture was incubated for 72 h at 27°C and 80 rpm, and was subsequently harvested by centrifugation at 2000 rpm for 20 min. Cell pellets were washed with PBS and subsequently used for protein purification or flash-frozen in liquid nitrogen and stored at -80°C. For protein purification, a 1L cell pellet was solubilized in lysis buffer (50 mM HEPES pH 7.5, 150 mM NaCl, 0.5 mM TCEP, 1 mM ADP, 10 mM $MgCl_2$) to which 1 µM Compound 007 from a 10 mM stock solution in DMSO was added. The lysis buffer was supplemented with 1 mM phenylmethylsulfonyl-fluoride (PMSF), followed by sonication (10 sec on; 5 sec off for 4 min at 40% intensity) on ice. The cell lysate was centrifuged at 25,000 rpm for 1 h and the supernatant was subsequently filtered with a 0.45 µm syringe filter, before it was applied onto a lysis buffer equilibrated 5 ml MBP-trap column (GE Healthcare) connected to an ÄKTA-Start FPLC system. The column was subsequently washed with 10 column volumes (CVs) of lysis buffer and the protein was eluted with 5 CVs of lysis buffer supplemented with 15 mM maltose. The NLRP3•Compound 007 complex was further purified using a Superose 6 increase 10/300 GL column (GE Healthcare) equilibrated with lysis buffer. Elution fractions were analyzed by SDS-PAGE and negative stain electron microscopy (EM), before they were plunge frozen for cryo-EM analysis.

A NACHT–transition LRR construct of human NLRP3 (aa 131-694) was subcloned into an in-house modified pACEBac1 vector containing an N-terminal MBP-tag, followed by a

Tobacco etch virus (TEV) protease cleavage site. The Bac-to-Bac system was used to generate baculovirus infected Sf9 insect cells. For the expression of recombinant human NLRP3, insect cells were infected with 3% v/v of a viral stock of the second passage. The expression culture was incubated for 72 h at 27°C and 80 rpm, and subsequently harvested by centrifugation at 2000 rpm for 20 min. The cell pellet was washed with PBS and either used for subsequent protein purification or frozen in liquid nitrogen and stored at -80°C till further use. For protein purification, cells were resuspended in buffer A (20 mM Tris-HCl pH 7.8, 150 mM NaCl, 5 mM β-mercaptoethanol, 10 mM $MgCl_2$, 1 mM ADP) supplemented with 1 mM PMSF and 1 µg/ml DNAse I, and lysed by sonication (6 sec on; 5 sec off for 4 min at 40% intensity on ice). The lysate was cleared from cell debris by centrifugation at 70,000 x g for >30 minutes. The protein containing an N-terminal MBP tag was captured using a MBPTrap column (GE Healthcare) and the unbound fraction was washed off with buffer A. After elution with buffer A containing 10 mM maltose, TEV protease (1:50 w/w) was added for cleavage of the MBP-tag and the protein was dialyzed against buffer B (20 mM HEPES pH 7.8, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM ADP, 1 mM TCEP, 500 mM L-Arginine); overnight at 4°C using the snake skin dialysis tubing with 3.5 kDa MWCO (Thermo Scientific). Protein was further purified using a Superdex 75 gel filtration column 16/600 (GE Healthcare) that was connected to a MBPTrap column for prolonged retention of the cleaved MBP tag and pre-equilibrated with buffer C (20 mM HEPES pH 7.8, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM ADP, 1 mM TCEP, 150 mM L-Arginine). Peak fractions containing monomeric NLRP3 were pooled, concentrated to 9.0 mg/ml (Amicon 10 kDa MWCO), snap frozen in liquid nitrogen, and stored at -80°C. For biochemical analysis, the protein was purified in absence of ADP and Compound 007. Due to lower solubility of the protein, the concentration was adjusted to 1 mg/ml.

Cryo-EM grid preparation, data collection and processing

The purified NLRP3• Compound 007 complex was applied onto glow-discharged EM-grids (Quantifoil Cu300 R2/1 + 2 nm carbon support film), incubated for 30s at 100% humidity and 4°C, before it was blotted for 5s with blot force 5 and plunge frozen into liquid ethane using a Vitrobot mark IV plunge freezing device (Thermo Fisher Scientific). For dataset acquisition using the SerialEM version 4 automation software, 4,720 electron-event representation (EER) movies each consisting of 1122 raw frames were recorded on a Cs-corrected Krios Titan microscope operated at 300 kV and equipped with a Falcon4i camera at a total dose of 66.22 e^-/A^2 and a defocus range of -0.80 to -1.80 µm. For Cryo-EM data processing in cryoSPARC, the raw EER data were fractioned onto 40 movie frames with a unsampling factor of 2. Resulting movie stacks were aligned using the patch motion correction and patch CTF correction jobs. Using the blob picker, 3,114,152 particles were picked and detected of which 2,058,399 were extracted (search particle diameter 280 nm, 588 box size), of which 559,748 particles remained after multiple rounds of 2D classification.

From these particles, three ab-initio models were generated, which were further subjected to heterogenous refinement. One model (468,974 particles) was further subjected to a non-uniform (NU)-refinement, followed by 3D classification allowing for ten 3D-classes. One class, comprising 30,200 particles, was further refined by another NU-refinement yielding a final reconstruction of the NLRP3•Compound 007 complex at 3.00 Å resolution (0.143 FSC). In this reconstruction, Compound 007 is clearly visible in the cryo-EM density map at a surface accessible binding pocket composed of the nucleotide-binding domain.

Thermal shift assay

Nano-differential scanning fluorimetry (nanoDSF) measurements were performed on a Prometheus NT.48 (NanoTemper) device to determine the thermal stability of the protein–ligand samples. For stability characterizations, NLRP3 was mixed with buffer or ligand in the presence of 2% DMSO. The sample was incubated for 30 minutes on ice before loading into capillaries (NanoTemper). The measurement was setup with a temperature ramp ranging from 15-95°C, a slope of 1.5°C/min, and 90% laser intensity.

HPLC-based ATPase assay

For the analysis of the intrinsic ATP hydrolysis, 3 µM full length, wild type NLRP3 (peak 1) was incubated for 30 minutes on ice in the presence of 2% DMSO or 100 µM BAL-0028 or 100 µM Compound 007. After incubation, 100 µM of ATP was added and the reaction was incubated for 60 minutes at 25°C. Every 10 minutes a 10 µl sample was injected onto a 1260 Infinity II LC system connected to a reversed phase C18-silica column (Chromolith Performance, Merck) that was pre-equilibrated with buffer D (30 mM K_2HPO_4, 70 mM KH_2PO_4, 10 mM TBA-Br, 4% v/v acetonitrile; pH 6.5). The detector was setup to measure at 259 nm wavelength. Detected peaks for ADP and ATP were integrated and the ratio was used to calculate the molar concentrations of educt and product.

Surface plasmon resonance spectroscopy

Surface plasmon resonance (SPR) spectroscopy experiments were performed on a Biacore 8K (GE Healthcare) device. The system was flushed with running buffer (10 mM HEPES pH 7.4, 200 mM NaCl, 0.5 mM ADP, 0.5 mM tris(2-carboxyethyl)phosphine (TCEP), 2 mM $MgCl_2$, 1 g/L carboxymethyl dextran (CMD), 0.05% Tween20, 2% DMSO) at 25°C. A streptavidin functionalized sensor chip (Series S Sensor Chip SA, Cytiva) was conditioned with three consecutive injections of 1 M NaCl in 50 mM NaOH (10 µL/min) for 1 min. After purification of biotinylated NLRP3 (131-694) that was expressed as wildtype or mutants in the FreeStyle™ 293-F expression system, the protein was immobilized onto the sensor chip at 2 µL/min for 3000 s. The flow system was washed using 50% isopropanol in 1 M NaCl and 50 mM NaOH. Free streptavidin binding sites were blocked by four consecutive injections of Biotin-PEG (1000 nM, Mn 2,300 Da) for 2 min at 10 µL/min. For binding measurements in the single cycle mode, increasing concentrations of 2.3 to 600 nM BAL compounds were injected at 30 µL/min (association 240 s, dissociation 60/360 s). Data were

collected at a rate of 10 Hz. The binding data were double referenced by blank cycle and reference flow cell subtraction. Data were corrected by a 4-point solvent correction. For determination of dissociation constants, processed data were fitted to a 1:1 interaction model using the Biacore Insight Evaluation Software (version 3.0.12.15655). For improved comparability of the NLRP3 variants and to account for their different immobilization levels, the measurements were normalized to the theoretical Rmax resulting in the bound fraction.

Example 4: Diet-Induced Obesity (DIO) Studies

Compound 040 ("Cmpd 40") was used to evaluate weight loss promotion in a diet-induced obesity (DIO) mouse model. The treatment groups were as follows:

0. Lean/vehicle (VEH) (50 mM Citrate buffer, PO), n=10
1. DIO/VEH (50 mM Citrate buffer, PO), n=12
2. DIO/Cmpd 40 (5 mpk, QD, PO), n=12
3. DIO/Cmpd 40 (20 mpk, QD, PO), n=12
4. DIO/Cmpd 40 (50 mpk, QD, PO), n=12
5. DIO/Cmpd 40 (100 mpk, QD, PO), n=16 (n=8 were ended earlier for PK, remaining n=8 were dosed at 75 mpk since day 9)
6. DIO/Semaglutide (10 ug/kg, QD, SC), n=12

Compound 040 was administered orally (PO) in a 50 mM citrate buffer (pH 4). Semaglutide was administered orally in a 20 mM citrate buffer (pH 7). The PO volume was 5 ul/gBW; and the subcutaneous (SC) volume was 4 ul/gBW. Mice were evaluated daily for body weight, food consumption, and water consumption. The mice were also evaluated weekly for body composition. Baseline and endpoint A1C and fasting glucose, endpoint HOMA-IR were also measured. The DIO mice were randomized for the drug treatment on the basis of equivalent body weight, body composition (fat mass, lean mass), 6 h fasting blood glucose, baseline blood A1C level, water consumption and food consumption as shown in Fig. 7.

The body weight change and body weight percentage changes are shown in Fig. 8 for mice receiving Compound 40 compared to a vehicle or semaglutide. Compound 40 showed a dose-dependent effect on reducing body weight of DIO mice. Table 5 summarizes the data shown in Fig. 8

Table 5.

Groups	Day 28 BW% change vs. baseline	Day 28 BW% change vs. DIO/VEH
DIO/VEH	4.0	0.0
DIO/Cmpd 40 (5 mpk, po, qd)	4.6	0.6
DIO/Cmpd 40 (20 mpk, po, qd)	1.3	-2.7

DIO/Cmpd 40 (50 mpk, po, qd)	-7.6	-11.6
DIO/Cmpd 40 (100/75 mpk, po, qd)	-17.9	-22.0
DIO/Semaglutide (10 µg/kg, sc, qd)	-8.2	-12.2

The changes in food consumption in mice receiving no treatment (VEH), Compound 40, and semaglutide are shown in Fig. 9. Compound 40 showed a dose-dependent effect on reducing food consumption.

The changes in fat and lean percentages in mice receiving no treatment (VEH), Compound 40, and semaglutide are shown in Fig. 10. Compound 40 showed a dose-dependent effect on reducing fat mass to body weight percentage and maintaining lean mass to body weight percentage.

Compound 40, at doses of 50 mpk or higher, significantly reduced fasting glucose and improved insulin sensitivity in DIO mice as shown in Fig. 11.

Fig. 12. depicts a weight loss comparison between DIO mice receiving vehicle, semaglutide, NT-0796, WTX3232, or Compound 40

Compound 40, at doses of 50 mpk or higher, significantly reduced liver weight and inguinal fat weight. The inguinal fat to body weight percentage or muscle tissues to body weight percentage of Compound 40-treated DIO mice had no significant difference from Semaglutide treated mice as shown in Fig. 13.

The body weight change and body weight percentage changes are shown in Figs. 14A and 14B for mice receiving Compound 096 or Compound 211 compared to a vehicle or semaglutide. Compounds 096 and 211 showed a dose-dependent effect on reducing body weight of DIO mice. Table 6 summarizes the data shown in Fig. 14

Table 6.

Groups	**Day 14 BW% change vs. baseline**
DIO/VEH	-2.8
DIO/Cmpd 096 (50 mpk, po, qd)	-11.9
DIO/Cmpd 211 (50 mpk, po, qd)	-14.9
DIO/Semaglutide (10 µg/kg, sc, qd)	-14.4

The changes in food consumption in mice receiving no treatment (VEH), Compound 096, Compound 211, and semaglutide are shown in Fig. 14. Compounds 096 and 211 showed a dose-dependent effect on reducing food consumption, which also caused a change in fat mass as shown in Fig. 15.

As can be seen in the above example and corresponding Figures, Compound 40, Compound 096, and Compound 211 signficantly reduced body weight and food consumption of high fat DIO mice, which is comparable to the effect of Semaglutide.

Example 5: Foot Gout Model

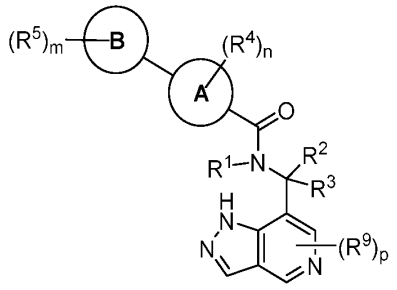
Compound 096 and Compound 040 reduce swelling in a foot gout mouse model in a dose dependent manner as shown in Fig. 16 and Fig. 17. Compound 040 can be used as both a preventative and therapeutic treatment.

The disclosed subject matter is not to be limited in scope by the specific embodiments and examples described herein. Indeed, various modifications of the 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 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:



(I)

or a pharmaceutically acceptable salt thereof;

wherein

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is independently optionally oxidized and independently optionally substituted by C_{1-6} alkyl; and the nitrogen atom of $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized and one or more carbon atoms of the alkyl groups on the nitrogen atom are optionally substituted with 1-6 deuterium atoms or C_{1-6} alkoxy;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

2. The compound of claim 1, wherein

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is C_{1-6} alkyl;

R^2 is H;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, halo, SO_2R^6, or C_{1-3} alkyene-5-10 membered heteroaryl;

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, both of which are substituted by OH C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl ;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, CN, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, and COR^6;

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, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHCOR^6$, CN, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, COR^6, and SO_2R^6;

each R^6 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, SO_2R^6, and halo;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

3. The compound of claim 1 or 2, wherein

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is C_{1-6} alkyl;

R^2 is H;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl, all of which are substituted by OH, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, or C_{1-6} alkoxy;

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, both of which is substituted by OH;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHC(O)C_{1-6}$ alkyl, CN, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $CONH_2$, $CONH(C_{1-6}$ alkyl), CN, and C_{1-6} haloalkyl;

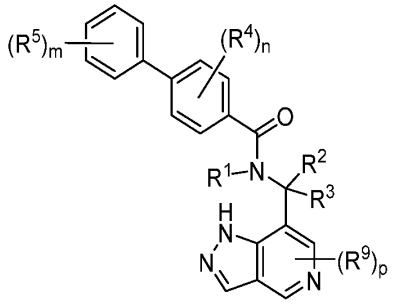
each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

4. The compound of any one of claims 1-3, wherein the compound of Formula I is a compound of Formula Ia:



(**Ia**)

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-3, wherein Ring A is phenyl.

6. The compound of claim 1 or 5, wherein Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl.

7. The compound of any one of claims 1-3, 5, and 6, wherein Ring B is phenyl.

8. The compound of claim 1, wherein Ring B and R^5 are absent.

9. The compound of any one of claims 1-8, wherein R^1 is C_{1-6} alkyl.

10. The compound of any one of claims 1 and 4-9, wherein R^2 is H.

11. The compound of any one of claims 1-10, wherein R^3 is C_{1-6} alkyl substituted by OH, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, or C_{1-3} alkoxy.

12. The compound of any one of claims 1-9, wherein R^2 and R^3, together with the atom to which they are attached, form a ring selected from the group consisting of C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, both of which is substituted by OH.

13. The compound of any one of claims 1-12, wherein each R^4 is independently selected from the group consisting of halo, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, and C_{1-6} haloalkyl.

14. The compound of any one of claims 1-7 and 9-13, wherein each R^5 is independently selected from the group consisting of C_{1-6} alkyl, halo, CN, and C(O)NH(C_{1-6} alkyl).

15. The compound of any one of claims 1-14, wherein each R^9 is independently selected from the group consisting of C_{1-3} alkyl, C_{1-6} alkoxy, C_{1-3} alkyl-OH, and halo.

16. The compound of any one of claims 1-7 and 9-15, wherein m is 0.

17. The compound of any one of claims 1-7 and 9-15, wherein m is 1.

18. The compound of any one of claims 1-7 and 9-15, wherein m is 2.

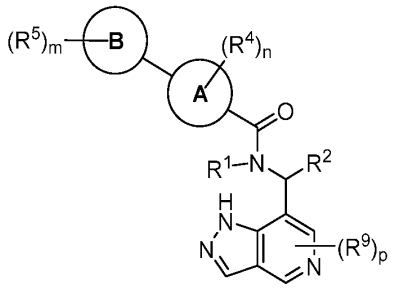
19. The compound of any one of claims 1-18, wherein n is 1.

20. The compound of any one of claims 1-19, wherein p is 0.

21. The compound of any one of claims 1-19, wherein p is 1.

22. The compound of any one of claims 1-21, wherein the compound of Formula I is selected from a compound in Table 1, Table 1A, Table 1B, and Table 1C, or a pharmaceutically acceptable salt thereof.

23. A compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof;

wherein

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} 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 and R^5 are absent;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{0-6} alkylene-C_{6-10} aryl, and 3-7 membered heterocycloalkyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{0-6} alkylene-C_{6-10} aryl are substituted with OH, halo, SO_2R^6, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, 3-6 membered heterocycloalkyl, and $N(R^a)_2$, wherein 3-6 membered heterocycloalkyl is optionally substituted by one or two halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, C_{1-6} alkyl-$NH(C_{1-3}$ alkyl), halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

24. The compound of claim 23, wherein

Ring A is C_{6-10} aryl;

Ring B is C_{6-10} aryl;

R^1 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, all of which are substituted with OH, halo, SO_2R^6, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, and $N(R^a)_2$;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

each R^4 is independently selected from the group consisting of halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, CN, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $CONH_2$, and $CONH(C_{1-6}$ alkyl);

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ 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. The compound of claim 23 or 24, wherein

Ring A is phenyl;

Ring B is phenyl;

R^1 is selected from the group consisting of C_{1-6} alkyl and C_{3-6} cycloalkyl, both of which are substituted with OH;

R^2 is H or C_{1-6} alkyl;

each R^4 is independently selected from the group consisting of halo, OH, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, and C_{1-6} haloalkyl;

each R^5 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $CONH_2$, and $CONH(C_{1-6}$ alkyl);

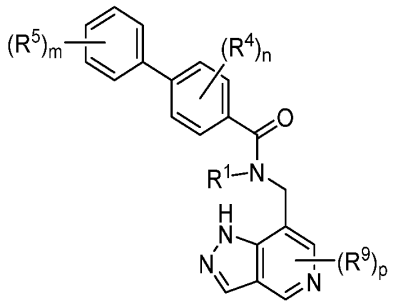
each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0 or 1.

26. The compound of any one of claims 23-25, wherein the compound of Formula II is a compound of Formula IIa:



(**IIa**)

or a pharmaceutically acceptable salt thereof.

27. The compound of claim 23 or 24, wherein Ring A is phenyl.

28. The compound of claim 23, wherein Ring B is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl.

29. The compound of any one of claims 23, 24, 27 and 28, wherein Ring B is phenyl.

30. The compound of claim 23, wherein Ring B and R^5 are absent.

31. The compound of any one of claims 23-30, wherein R^1 is C_{1-6} alkyl substituted by OH.

32. The compound of any one of claims 23-31, wherein each R^4 is independently selected from the group consisting of C_{1-6} alkoxy and OC_{3-6} cycloalkyl.

33. The compound of any one of claims 23-29, 31, and 32, wherein each R^5 is independently selected from the group consisting of halo, CN, $CONH_2$, and $CONH(C_{1-6}$ alkyl).

34. The compound of any one of claims 23-33, wherein each R^9 is independently selected from the group consisting of C_{1-6} alkyl-OH, halo, OH, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$.

35. The compound of any one of claims 23-29, 31, 32, and 34, wherein m is 0.

36. The compound of any one of claims 23-29 and 31-34, wherein m is 1.

37. The compound of any one of claims 23-29 and 31-34, wherein m is 2.

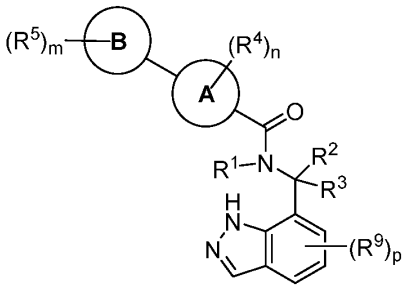
38. The compound of any one of claims 23-37, wherein n is 1.

39. The compound of any one of claims 23-33 and 35-38, wherein p is 0.

40. The compound of any one of claims 23-38, wherein p is 1.

41. The compound of any one of claims 23-40, wherein the compound of Formula II is selected from a compound in Table 2, Table 2A, or Table 2B, or a pharmaceutically acceptable salt thereof.

42. A compound of Formula III:



(III)

or a pharmaceutically acceptable salt thereof;

wherein

Ring A is selected from the group consisting of C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 4-10 membered heterocycloalkyl;

Ring B is selected from the group consisting of C_{6-10} aryl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered heterocycloalkyl;

alternatively, Ring B and R^5 are absent;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OC_{3-6} cycloalkyl, $O(C_{0-6}$ alkylene-C_{6-10} aryl), and C_{0-6} alkylene-C_{6-10} aryl, wherein alkyl and cycloalkyl are optionally substituted with OH, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $N(R^a)_2$, and halo;

each R^a is independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $C(O)C_{1-6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, and 5-10 membered heteroaryl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are substituted by OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, $N(C_{1-6}$ haloalkyl)$_2$, halo, SO_2R^6, $NHCOR^6$, 3-6 membered heterocycloalkyl optionally substituted with one or two halo or OH, or C_{0-3} alkyene-5-10 membered heteroaryl, wherein 3-6 membered heterocycloalkyl is independently optionally oxidized and independently optionally substituted by C_{1-6} alkyl; and the nitrogen atom of NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)(C_{1-6} haloalkyl), $NH(C_{1-6}$ haloalkyl), $N(C_{1-6}$ alkyl)$_2$, and $N(C_{1-6}$ haloalkyl)$_2$ is optionally oxidized and one or more carbon atoms of the alkyl groups on the nitrogen atom are optionally substituted with 1-6 deuterium atoms or C_{1-6} alkoxy;

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, both of which are substituted by OH, C_{1-6} alkoxy, or C_{1-4} alkylene-O-C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkylene-$NHCOR^6$, $NHCOR^6$, 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 C_{1-6} alkyl, C_{1-6} haloalkyl, halo, OH, OR^6, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ 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_{2-6} alkenyl, C_{0-6} alkylene-C_{6-10} aryl, C_{0-6} alkylene-5-10 membered heteroaryl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, halo, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

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

each R^9 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-OH, halo, CN, OH, SO_2R^6, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

m is 0, 1, 2, or 3;

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

p is 0, 1, 2, or 3.

43. The compound of claim 42, wherein the compound of Formula III is a compound selected from a compound in Table 3 and Table 3A, or a pharmaceutically acceptable salt thereof.

44. The compound of any one of claims 1-43, wherein the compound binds to one or more amino acids of Y143, R147, F257, Y258, H260, E263, V264, L272, L275, I276, C279, F299, G328, L331, L332, L335, and C514 of a NLRP3 amino acid sequence of SEQ ID NO: 1.

45. The compound of any one of claims 1-44, wherein the compound binds to at least amino acids of L275 and C279 of a NLRP3 amino acid sequence of SEQ ID NO: 1.

46. The compound of any one of claims 1-45, wherein the compound binds to amino acids of Y143, R147, F257, Y258, H260, E263, V264, L272, L275, I276, C279, F299, G328, L331, L332, L335, and C514 of a NLRP3 amino acid sequence of SEQ ID NO: 1.

47. A pharmaceutical composition comprising a compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

48. 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 1-46, or the pharmaceutical composition of claim 47.

49. 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 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

50. 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 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

51. A method of treating a disease or disorder of the inner ear in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

52. The method of claim 51, wherein 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.

53. A method of treating a neurosensory disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

54. The method of claim 53, wherein the neurosensory disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), traumatic brain injury, Parkinson's disease, and Alzheimer's disease.

55. The method of claim 53 or 54, wherein the neurosensory disease is ALS.

56. The method of claim 53 or 54, wherein the neurosensory disease is traumatic brain injury.

57. The method of claim 53 or 54, wherein the neurosensory disease is Parkinson's disease.

58. The method of claim 53 or 54, wherein the neurosensory disease is Alzheimer's disease.

59. A method of treating, preventing, or mitigating an adverse effect related to the administration of a T cell engaging agent in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to

any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

60. The method of claim 59, wherein the adverse effect is cytokine release syndrome (CRS).

61. The method of claim 59, wherein the adverse effect is fever, hypotension and/or hypoxia.

62. The method of claim 59, wherein the adverse effect is an elevated serum level of one of more cytokine(s), particularly one or more cytokine(s) selected from the group consisting of IL-1b, IL-6, and IL-18.

63. A method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

64. The method of claim 63, wherein the cancer is a CD20-expressing cancer.

65. The method of claim 63 or 64, wherein the cancer is a B-cell cancer.

66. The method of claim 63, wherein the cancer is selected from the group consisting of Non-Hodgkin lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), high grade B cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL) and marginal zone lymphoma (MZL).

67. A method of treating obesity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

68. A method of improving lipid metabolism in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

69. A method of reducing hypothalamic gliosis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

70. A method of reducing leptin levels in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

71. A method of reducing low-density lipoprotein cholesterol levels in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.

72. The method of any one of claims 68-71, wherein the method treats obesity in the subject.

73. A method of treating an ocular disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-46, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 47.