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(54) Title: DERIVATIVES AND METHODS OF TREATING HEPATITIS B INFECTIONS

(57) Abstract: Provided herein are compounds useful for the treatment of HBV infection in a subject in need thereof, pharmaceutical compositions thereof, and methods of inhibiting, suppressing, or preventing HBV infection in the subject.

DERIVATIVES
AND METHODS OF TREATING HEPATITIS B INFECTIONS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/097,835, filed December 30, 2014, and U.S. Provisional Application No. 62/163,150, filed May 18, 2015. The contents of these provisional applications are incorporated herein by reference in their entirety.

BACKGROUND

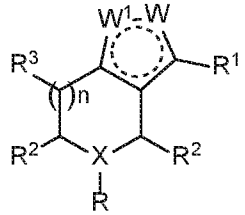
Chronic hepatitis B virus (HBV) infection is a significant global health problem, affecting over 5% of the world population (over 350 million people worldwide and 1.25 million individuals in the U.S.).

Despite the availability of a prophylactic HBV vaccine, the burden of chronic HBV infection continues to be a significant unmet worldwide medical problem, due to suboptimal treatment options and sustained rates of new infections in most parts of the developing world. Current treatments do not provide a cure and are limited to only two classes of agents (interferon alpha and nucleoside analogues/inhibitors of the viral polymerase); drug resistance, low efficacy, and tolerability issues limit their impact. The low cure rates of HBV are attributed at least in part to the fact that complete suppression of virus production is difficult to achieve with a single antiviral agent. However, persistent suppression of HBV DNA slows liver disease progression and helps to prevent hepatocellular carcinoma. Current therapy goals for HBV-infected patients are directed to reducing serum HBV DNA to low or undetectable levels, and to ultimately reducing or preventing the development of cirrhosis and hepatocellular carcinoma.

There is a need in the art for therapeutic agents that can increase the suppression of virus production and that can treat, ameliorate and/or prevent HBV infection. Administration of such therapeutic agents to an HBV infected patient, either as monotherapy or in combination with other HBV treatments or ancillary treatments, will lead to significantly reduced virus burden, improved prognosis, diminished progression of the disease and enhanced seroconversion rates.

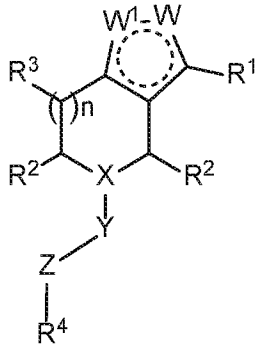
SUMMARY

Provided herein are compounds useful for the treatment of HBV infection in a subject in need thereof, having the structure:



or a pharmaceutically acceptable salt thereof.

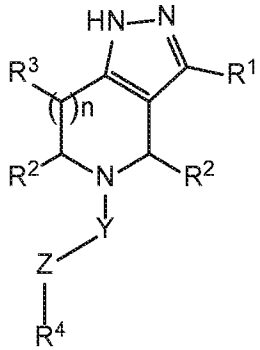
In one aspect, provided herein is a compound of Formula I:



I,

or a pharmaceutically acceptable salt thereof.

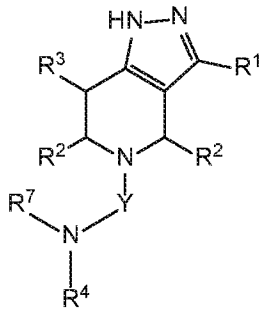
In an embodiment, the compound of Formula I is a compound of Formula II:



II,

or a pharmaceutically acceptable salt thereof.

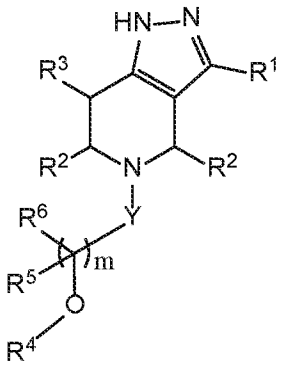
In another embodiment, the compound of Formula I is a compound of Formula III:



III,

or a pharmaceutically acceptable salt thereof.

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



IV,

or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein are pharmaceutical compositions comprising a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

In one aspect, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of eradicating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of reducing the viral load associated with an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of reducing reoccurrence of an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of inhibiting or reducing the formation or presence of HBV DNA-containing particles or HBV RNA-containing particles in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of reducing an adverse physiological impact of an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of inducing remission of hepatic injury from an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of reducing the physiological impact of long-term antiviral therapy for HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of prophylactically treating an HBV infection in an individual in need thereof, wherein the individual is afflicted with a latent HBV infection, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

In an embodiment, the methods provided herein can further comprise administering to the individual at least one additional therapeutic agent selected from the group consisting of an HBV polymerase inhibitor, immunomodulatory agents, pegylated interferon, viral entry inhibitor, viral maturation inhibitor, literature-described capsid assembly modulator, reverse transcriptase inhibitor, a cyclophilin/TNF inhibitor, a TLR-agonist, an HBV vaccine,agents of distinct or unknown mechanism, and a combination thereof. In a further embodiment, the methods provided herein allow for administering of the at least one additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one

additional therapeutic agent alone that is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

In another embodiment, the methods provided herein reduce the viral load in the individual to a greater extent or at a faster rate compared to the administering of a compound selected from the group consisting of an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and any combination thereof.

In another embodiment, the methods provided herein cause a lower incidence of viral mutation and/or viral resistance than the administering of a compound selected from the group consisting of an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof.

In another embodiment, the methods provided herein further comprise administering to the individual at least one HBV vaccine, a nucleoside HBV inhibitor, an interferon or any combination thereof.

In an aspect, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising reducing the HBV viral load by administering to the individual a therapeutically effective amount of a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, alone or in combination with a reverse transcriptase inhibitor; and further administering to the individual a therapeutically effective amount of HBV vaccine.

In an embodiment, the methods provided herein further comprise monitoring the HBV viral load of the subject, wherein the method is carried out for a period of time such that the HBV virus is undetectable.

DETAILED DESCRIPTION

Provided herein are compounds, e.g., the compounds of Formulas I, II, III, or IV, or pharmaceutically acceptable salts thereof, that are useful in the treatment and prevention of HBV infection in subject. In a non-limiting aspect, these compounds may modulate or disrupt HBV assembly and other HBV core protein functions necessary for HBV replication or the generation of infectious particles, may inhibit the production of infectious virus particles or infection or may interact with HBV capsid to afford defective viral particles with greatly reduced infectivity or replication capacity. In other words, the compounds provided herein may act as capsid assembly modulators. The compounds provided herein have potent

antiviral activity, exhibit favorable metabolic properties, tissue distribution, safety and pharmaceutical profiles, and are suitable for use in humans.

The HBV capsid protein plays essential functions during the viral life cycle. HBV capsid/core proteins form metastable viral particles or protein shells that protect the viral genome during intercellular passage, and also play a central role in viral replication processes, including genome encapsidation, genome replication, and virion morphogenesis and egress. Capsid structures also respond to environmental cues to allow un-coating after viral entry. Consistently, the appropriate timing of capsid assembly and dis-assembly, the appropriate capsid stability and the function of core protein have been found to be critical for viral infectivity.

The crucial function of HBV capsid proteins imposes stringent evolutionary constraints on the viral capsid protein sequence, leading to the observed low sequence variability and high conservation. Consistently, mutations in HBV capsid that disrupt its assembly are lethal, and mutations that perturb capsid stability severely attenuate viral replication. The high functional constraints on the multi-functional HBV core/capsid protein is consistent with a high sequence conservation, as many mutations are deleterious to function. Indeed, the core/capsid protein sequences are >90% identical across HBV genotypes and show only a small number of polymorphic residues. Resistance selection to HBV core/capsid protein binding compounds may therefore be difficult to select without large impacts on virus replication fitness.

Reports describing compounds that bind viral capsids and inhibit replication of HIV, rhinovirus and HBV provide strong pharmacological proof of concept for viral capsid proteins as antiviral drug targets.

In one aspect, the compounds provided herein are useful in HBV treatment by disrupting, accelerating, reducing, delaying and/or inhibiting normal viral capsid assembly and/or disassembly of immature or mature particles, thereby inducing aberrant capsid morphology and leading to antiviral effects such as disruption of virion assembly and/or disassembly, virion maturation, virus egress and/or infection of target cells. In one embodiment, a disruptor of capsid assembly interacts with mature or immature viral capsid to perturb the stability of the capsid, thus affecting assembly and/or disassembly. In another embodiment, a disruptor of capsid assembly perturbs protein folding and/or salt bridges required for stability, function and/or normal morphology of the viral capsid, thereby disrupting and/or accelerating capsid assembly and/or disassembly. In yet another embodiment, the compounds of the invention bind capsid and alter metabolism of cellular

polyproteins and precursors, leading to abnormal accumulation of protein monomers and/or oligomers and/or abnormal particles, which causes cellular toxicity and death of infected cells. In another embodiment, the compounds provided herein cause failure of the formation of capsids of optimal stability, affecting efficient uncoating and/or disassembly of viruses (e.g., during infectivity).

In one embodiment, the compounds provided herein disrupt and/or accelerate capsid assembly and/or disassembly when the capsid protein is immature. In another embodiment, the compounds provided herein disrupt and/or accelerate capsid assembly and/or disassembly when the capsid protein is mature. In yet another embodiment, the compounds provided herein disrupt and/or accelerate capsid assembly and/or disassembly during viral infectivity. In yet another embodiment, the disruption and/or acceleration of capsid assembly and/or disassembly attenuates HBV viral infectivity and/or reduces viral load. In yet another embodiment, disruption, acceleration, inhibition, delay and/or reduction of capsid assembly and/or disassembly eradicates the virus from the host organism. In yet another embodiment, eradication of the HBV from a host advantageously obviates the need for chronic long-term therapy and/or reduces the duration of long-term therapy.

In one embodiment, the compounds described herein are suitable for monotherapy and are effective against natural or native HBV strains and against HBV strains resistant to currently known drugs. In another embodiment, the compounds described herein are suitable for use in combination therapy.

In another embodiment, the compounds proided herein can be used in methods of modulating (e.g., inhibiting or disrupting) the activity, stability, function, and viral replication properties of HBV cccDNA. In yet another embodiment, the compounds of the invention can be used in methods of diminishing or preventing the formation of HBV cccDNA.

In another embodiment, the the compounds provided herein can be used in methods of modulating (e.g., inhibiting or disrupting) the activity of HBV cccDNA. In yet another embodiment, the compounds of the invention can be used in methods of diminishing the formation of HBV cccDNA.

In another embodiment, the the compounds provided herein can be used in methods of modulating, inhibiting, or disrupting the generation or release of HBV RNA particles from within the infected cell. In a further embodiment, the total burden (or concentration) of HBV RNA particles is modulated. In a preferred embodiment, the total burden of HBV RNA is diminished.

Definitions

Listed below are definitions of various terms used to describe this invention. 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 to which this invention belongs. 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 ±20% or ±10%, including ±5%, ±1%, and ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

As used herein, the term "capsid assembly modulator" refers to a compound that disrupts or accelerates or inhibits or hinders or delays or reduces or modifies normal capsid assembly (e.g., during maturation) or normal capsid disassembly (e.g., during infectivity) or perturbs capsid stability, thereby inducing aberrant capsid morphology and function. In one embodiment, a capsid assembly modulator accelerates capsid assembly or disassembly, thereby inducing aberrant capsid morphology. In another embodiment, a capsid assembly modulator interacts (e.g. binds at an active site, binds at an allosteric site, modifies and/or hinders folding and the like) with the major capsid assembly protein (CA), thereby disrupting capsid assembly or disassembly. In yet another embodiment, a capsid assembly modulator causes a perturbation in structure or function of CA (e.g., ability of CA to assemble, disassemble, bind to a substrate, fold into a suitable conformation, or the like), which attenuates viral infectivity and/or is lethal to the virus.

As used herein, the term "treatment" or "treating," is defined as the application or administration of a therapeutic agent, i.e., a compound of the invention (alone or in

combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (e.g., for diagnosis or ex vivo applications), who has an HBV infection, a symptom of HBV infection or the potential to develop an HBV infection, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the HBV infection, the symptoms of HBV infection or the potential to develop an HBV infection. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

As used herein, the term "prevent" or "prevention" means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term "patient," "individual" or "subject" refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine 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 and/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 invention 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 invention 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, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. 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 invention 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 invention 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 invention, 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 invention, 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 useful within the invention. Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention 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, 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 one to six carbon atoms) and includes straight, branched chain. 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.

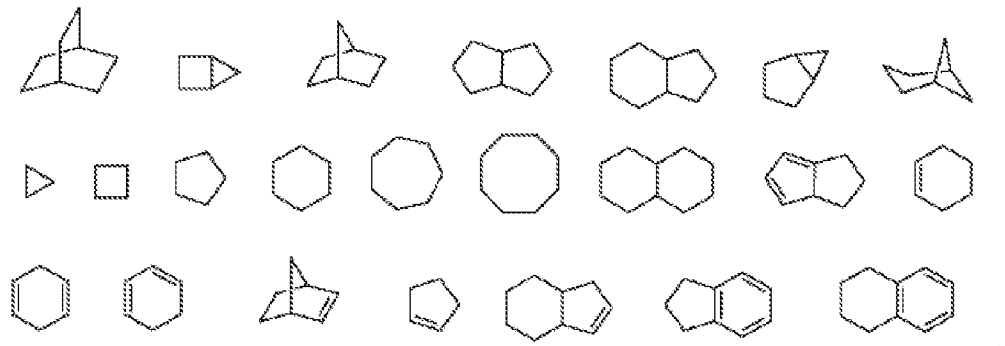
As used herein, the term "alkenyl," denotes a monovalent group derived from a hydrocarbon moiety containing at least two carbon atoms and at least one carbon-carbon double bond. The double bond may or may not be the point of attachment to another group. Alkenyl groups (e.g., C_2-C_8-alkenyl) include, but are not limited to, for example, ethenyl, propenyl, prop-1-en-2-yl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl 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 "haloalkyl" refers to alkl radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Haloalkyl embraces monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. The term "haloalkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, and pentafluoroethyl.

As used herein, the term "cycloalkyl" refers to a mono cyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e., skeletal atoms) is a carbon atom. In one embodiment, the cycloalkyl group is saturated or partially unsaturated. In another embodiment, the cycloalkyl group is fused with an aromatic ring. Cycloalkyl groups

include groups having 3 to 10 ring atoms (C_3-C_{10}-cycloalkyl), groups having 3 to 8 ring atoms (C_3-C_8-cycloalkyl), groups having 3 to 7 ring atoms (C_3-C_7-cycloalkyl), and groups having 3 to 6 ring atoms (C_3-C_6-cycloalkyl). Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



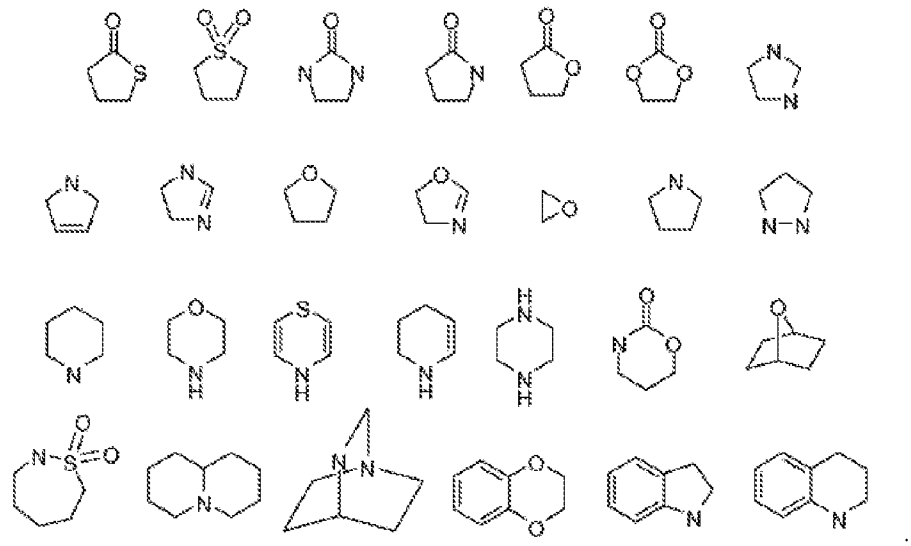
Monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Dicyclic cycloalkyls include, but are not limited to, tetrahydronaphthyl, indanyl, and tetrahydropentalene. Polycyclic cycloalkyls include adamantine and norbornane. The term cycloalkyl includes "unsaturated nonaromatic carbocyclyl" or "nonaromatic unsaturated carbocyclyl" groups, both of which refer to a nonaromatic carbocycle as defined herein, which contains at least one carbon carbon double bond or one carbon carbon triple bond.

As used herein, the term "heterocycloalkyl" or "heterocyclyl" refers to a heteroalicyclic group containing one to four ring heteroatoms each selected from O, S and N. In one embodiment, each heterocyclyl group has from 3 to 10 atoms in its ring system, with the proviso that the ring of said group does not contain two adjacent O or S atoms. Heterocyclyl substituents may be alternatively defined by the number of carbon atoms, e.g., C_2-C_8-heterocyclyl indicates the number of carbon atoms contained in the heterocyclic group without including the number of heteroatoms. For example, a C_2-C_8-heterocyclyl will include an additional one to four heteroatoms. In another embodiment, the heterocycloalkyl group is fused with an aromatic ring. In one embodiment, the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure.

An example of a 3-membered heterocyclyl group includes, and is not limited to, aziridine. Examples of 4-membered heterocyclyl groups include, and are not limited to, azetidine and a beta lactam. Examples of 5-membered heterocyclyl groups include, and are

not limited to, pyrrolidine, oxazolidine and thiazolidinedione. Examples of 6-membered heterocycloalkyl groups include, and are not limited to, piperidine, morpholine and piperazine.

Other non-limiting examples of heterocycloalkyl groups are:



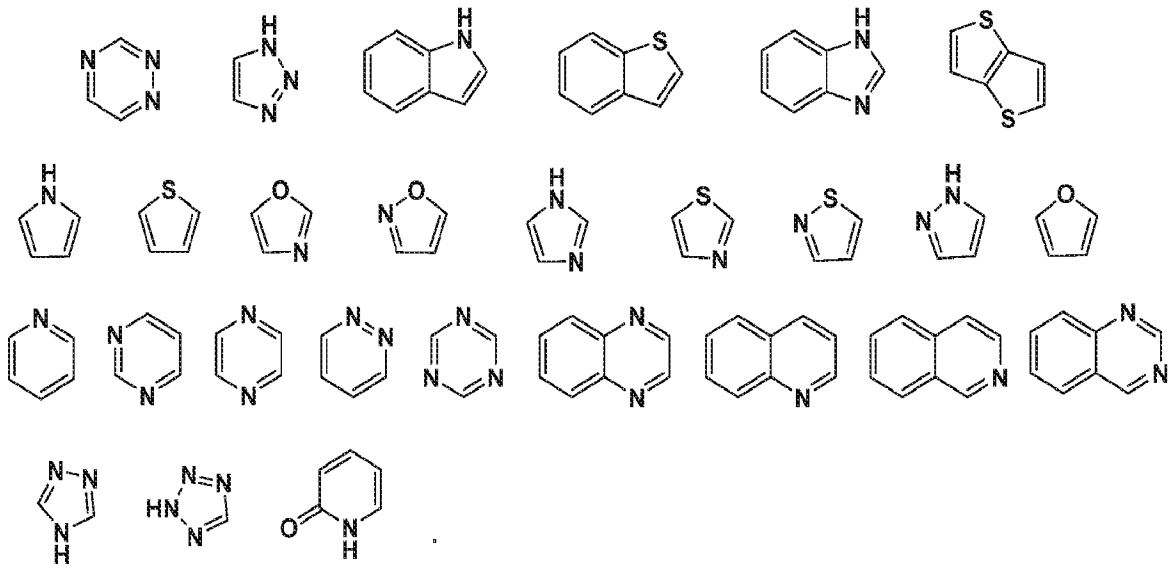
Examples of heterocycles include monocyclic groups such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, pyrazolidine, imidazoline, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dihydropyridine, piperazine, morpholine, thiomorpholine, pyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane, homopiperazine, homopiperidine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethyleneoxide.

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," employed alone or in combination with other terms, means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (typically one, two, or three rings), wherein such rings may be attached together in a pendent manner, such as a biphenyl, or may be fused, such as naphthalene. Examples of aryl groups include phenyl, anthracyl, and naphthyl. Preferred examples are phenyl (e.g., C_6-aryl) and biphenyl (e.g., C_{12}-aryl). In some embodiments, aryl groups have from six to sixteen carbon atoms. In some embodiments, aryl groups have from six to twelve carbon atoms (e.g., C_6-C_{12}-aryl). In some embodiments, aryl groups have six carbon atoms (e.g., C_6-aryl).

As used herein, the term "heteroaryl" or "heteroaromatic" refers to a heterocycle having aromatic character. Heteroaryl substituents may be defined by the number of carbon

atoms, e.g., C_1-C_9-heteroaryl indicates the number of carbon atoms contained in the heteroaryl group without including the number of heteroatoms. For example, a C_1-C_9-heteroaryl will include an additional one to four heteroatoms. A polycyclic heteroaryl may include one or more rings that are partially saturated. Non-limiting examples of heteroaryls include:



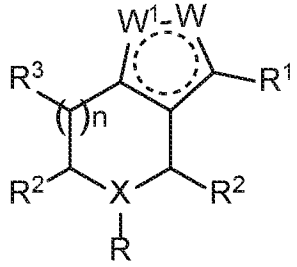
Additional non-limiting examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl (including, e.g., 2- and 4-pyrimidinyl), pyridazinyl, thienyl, furyl, pyrrolyl (including, e.g., 2-pyrrolyl), imidazolyl, thiazolyl, oxazolyl, pyrazolyl (including, e.g., 3- and 5-pyrazolyl), isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

Non-limiting examples of polycyclic heterocycles and heteroaryls include indolyl (including, e.g., 3-, 4-, 5-, 6- and 7-indolyl), indolinyl, quinolyl, tetrahydroquinolyl, isoquinolyl (including, e.g., 1- and 5-isoquinolyl), 1,2,3,4-tetrahydroisoquinolyl, cinnolinyl, quinoxalinyl (including, e.g., 2- and 5-quinoxalinyl), quinazolinyl, phthalazinyl, 1,8-naphthyridinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarin, 1,5-naphthyridinyl, benzofuryl (including, e.g., 3-, 4-, 5-, 6- and 7-benzofuryl), 2,3-dihydrobenzofuryl, 1,2-benzisoxazolyl, benzothienyl (including, e.g., 3-, 4-, 5-, 6-, and 7-benzothienyl), benzoxazolyl, benzothiazolyl (including, e.g., 2-benzothiazolyl and 5-benzothiazolyl), purinyl, benzimidazolyl (including, e.g., 2-benzimidazolyl), benzotriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

As used herein, the term "substituted" means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

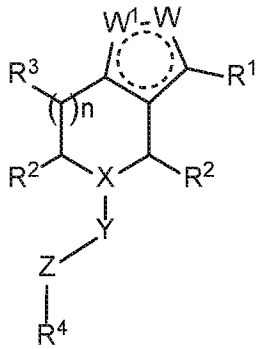
Compounds of the Invention

Provided herein are compounds useful for the treatment of HBV infection in a subject in need thereof, having the structure:



or pharmaceutically acceptable salts thereof.

In one aspect, provided herein is a compound of Formula Ia



Ia,

or a pharmaceutically acceptable salt thereof,

wherein

W^1 and W are each independently selected from N, NR^a, and CR^a, wherein one of W^1 and W is NR^a;

X is N or CR^b;

Y is selected from a bond, –C(O)–, and $–SO_2–$;

Z is selected from $–(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$, $–(CR^5R^6)_mCR^5=CR^5–$, $–(CR^5R^6)_m$-C_3-C_6-cycloalkylene–, and $–(CR^5R^6)_m$-$NR^7–$;

R^1 is selected from C_6-C_{12}-aryl, C_1-C_9-heteroaryl, C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, $–OR^c$, C_1-C_6-alkyl, $C(O)OR^c$, $C(O)R^c$, $C(O)NR^dR^e$, $NR^dC(O)R^c$, $–OC(O)R^c$, halo, and C_2-C_8-alkenyl, wherein alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, $–O$-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, $–O$-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from C_1-C_6-alkyl, $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, and $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, C_1-C_6-alkyl-OH, and C_3-C_8-cycloalkyl;

R^5 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

alternatively, R^4 and R^5 are optionally joined to form a ring;

R^6 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^a is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^b is selected from H and C_1-C_6-alkyl;

R^c is selected from H, C_1-C_6-alkyl, C_1-C_6-alkyl-OH, C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_6-C_{12}-aryl, and C_1-C_9-heteroaryl;

R^d is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^e is selected from H, C_1-C_6-alkyl, C_1-C_6-alkyl-OH, C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_6-C_{12}-aryl, C_1-C_9-heteroaryl, and –O-C_1-C_6-alkyl;

alternatively, R^d and R^e are optionally joined to form a heterocyclic ring;

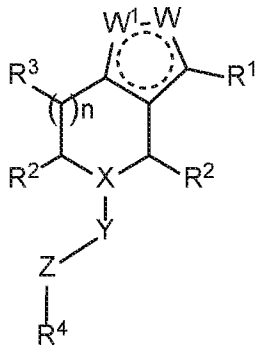
R^f is, at each occurrence, independently selected from H and C_1-C_6-alkyl;

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

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

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

In another aspect, provided herein is a compound of Formula I



I,

or a pharmaceutically acceptable salt thereof,

wherein

W^1 and W are each independently selected from N, NR^a, and CR^a, wherein one of W^1 and W is NR^a;

X is N or CR^b;

Y is selected from a bond, –C(O)–, and $–SO_2–$;

Z is selected from $–(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$, $–(CR^5R^6)_mCR^5=CR^5–$, $–(CR^5R^6)_m$-C_3-C_6-cycloalkylene–, and $–(CR^5R^6)_m$-$NR^7–$;

R^1 is selected from C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, $–OR^c$, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from C_1-C_6-alkyl, $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, and $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH;

R^5 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

alternatively, R^4 and R^5 are optionally joined to form a heterocyclic ring;

R^6 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^a is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^b is selected from H and C_1-C_6-alkyl;

R^c is selected from H, C_1-C_6-alkyl, C_1-C_6-alkyl-OH, C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_6-C_{12}-aryl, and C_1-C_9-heteroaryl;

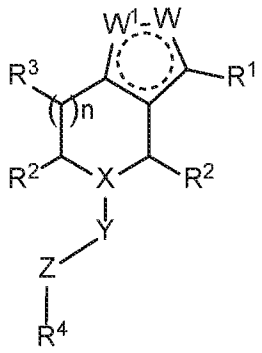
R^f is, at each occurrence, independently selected from H and C_1-C_6-alkyl;

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

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

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

In an embodiment of the compound of Formula I



I,

or a pharmaceutically acceptable salt thereof,

W^1 and W are each independently selected from N, NR^a, and CR^a, wherein one of W^1 and W is NR^a;

X is N or CR^b;

Y is selected from a bond, –C(O)–, and $–SO_2–$;

Z is selected from $–(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$, $–(CR^5R^6)_mCR^5=CR^5–$, $–(CR^5R^6)_m$-C_3-C_6-cycloalkylene–, and $–(CR^5R^6)_m-NR^7–$;

R^1 is selected from C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-

C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from C_1-C_6-alkyl, $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, and $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH;

R^5 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

alternatively, R^4 and R^5 are optionally joined to form a ring;

R^6 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^a is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^b is selected from H and C_1-C_6-alkyl;

R^f is, at each occurrence, independently selected from H and C_1-C_6-alkyl;

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

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

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

In another embodiment of the compound of Formula I, W^1 is NR^a and W is N or CR^a. In a further embodiment, W^1 is NH.

In another embodiment of the compound of Formula I, W^1 is N or CR^a and W is NR^a.

In another embodiment of the compound of Formula I, X is N.

In an embodiment of the compound of Formula I, Y is –C(O)– or $–SO_2–$.

In a further embodiment of the compound of Formula I, Z is $–(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$, or $–(CR^5R^6)_m-NR^7–$.

In an embodiment of the compound of Formula I,

m is 0 or 1;

R^5 is H, –OH, or C_1-C_6-alkyl;

R^6 is H or C_1-C_6-alkyl; and

R^7 is H or C_1-C_6-alkyl.

In another embodiment of the compound of Formula I, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, or C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula I, R^1 is C_3-C_8-cycloalkyl or C_2-C_8-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula I, R^1 is C_3-C_6-cycloalkyl or C_2-C_5-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In an embodiment of the compound of Formula I, each R^2 is independently selected from H or C_1-C_4-alkyl. In a further embodiment of the compound of Formula I, R^2 is H.

In an embodiment of the compound of Formula I, R^3 is H.

In an embodiment of the compound of Formula I, R^4 is $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula I, R^4 is $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula I,

p is 0 or 1;

R^8 is H, –OH, or C_1-C_6-alkyl; and

R^9 is H or C_1-C_6-alkyl.

In an embodiment of the compound of Formula I, n is 1.

In another embodiment of the compound of Formula I,

X is N;

Y is –C(O)–;

Z is NR^7; and

R^7 is H or C_{1-4}-alkyl.

In a further embodiment of the compound of Formula I,

X is N;

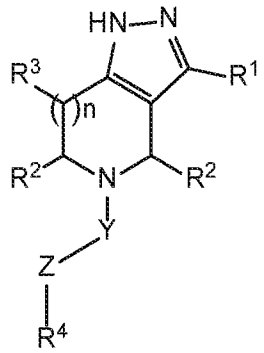
Y is –C(O)–;

Z is NR^7;

R^7 is H or C_{1-4}-alkyl; and

n is 1.

Also provided herein is a compound of Formula I, having the structure of Formula II (also referred to as "a compound of Formula II"):



II,

or a pharmaceutically acceptable salt thereof.

In an embodiment of the compound of Formula II, Y is –C(O)– or $–SO_2–$.

In an embodiment of the compound of Formula II, Z is $–(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$ or $–(CR^5R^6)_m-NR^7–$.

In an embodiment of the the compound of Formula II,

m is 0 or 1;

R^5 is H, –OH, or C_1-C_6-alkyl;

R^6 is H or C_1-C_6-alkyl; and

R^7 is H or C_1-C_6-alkyl.

In an embodiment of the compound of Formula II, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula II, R^1 is C_3-C_8-cycloalkyl or C_2-C_8-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1, 2, 3,

or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula II, R^1 is C_3-C_6-cycloalkyl or C_2-C_5-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula II, R^1 is selected from –OH, -Br, methyl, ethyl, ethenyl, propyl, propenyl, isopropyl, butyl, t-butyl, butenyl, pentanyl, 2-methylpentan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, bicyclo[3.1.0]hexanyl, wherein methyl, ethyl, ethenyl, propyl, propenyl, isopropyl, butyl, t-butyl, butenyl, pentanyl, and 2-methylpentan-2-yl are optionally substituted with 1 or 2 groups independently selected from –OH, and halo, or wherein cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, and bicyclo[3.1.0]hexanyl are optionally substituted with 1 or 2 groups independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula II, R^1 is selected from methyl, ethyl, ethenyl, propyl, propenyl, isopropyl, butyl, t-butyl, butenyl, pentanyl, 2-methylpentan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, bicyclo[3.1.0]hexanyl, any of which are optionally substituted with 1 or 2 groups independently selected from –OH and halo.

In an embodiment of the compound of Formula II, each R^2 is independently selected from H or C_1-C_4-alkyl. In a further embodiment of the compound of Formula II, R^2 is H.

In an embodiment of the compound of Formula II R^3 is H.

In an embodiment of the compound of Formula II, R^4 is $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH.

In an embodiment of the compound of Formula II, R^4 is $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, and wherein aryl and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-

haloalkyl, –O-C_1-C_6-alkyl, C(O)N(R^f)$_2$, C(O)OR^f, –OCH_2C(O)OR^f, –SO_2R^f, and C_1-C_6-alkyl-OH.

In an embodiment of the compound of Formula II,

Y is –C(O)–;

Z is –(CR^5R^6)$_m$–, –(CR^5R^6)$_m$O– or –(CR^5R^6)$_m$-NR^7–;

R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, –OH, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 and R^3 are H;

R^4 is (CR^8R^9)$_p$-C_6-C_{12}-aryl, or (CR^8R^9)$_p$-C_1-C_9-heteroaryl, and wherein aryl and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, C(O)N(R^f)$_2$, C(O)OR^f, –OCH_2C(O)OR^f, –SO_2R^f, and C_1-C_6-alkyl-OH;

R^5 is H, –OH, or C_1-C_6-alkyl;

R^6 is H or C_1-C_6-alkyl;

R^7 is H or C_1-C_6-alkyl;

R^8 is, at each occurrence, independently selected from H, –OH, halo, and C_1-C_6-alkyl;

R^9 is, at each occurrence, independently selected from H, –OH, halo, and C_1-C_6-alkyl;

R^c is C_1-C_6-alkyl;

R^f is, at each occurrence, independently selected from H and C_1-C_6-alkyl;

m is 1, or 2;

n is 1; and

p is 0, 1, or 2.

In an embodiment of this embodiment, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In an embodiment of this embodiment, R^4 is (CR^8R^9)$_p$-C_6-C_{12}-aryl, or (CR^8R^9)$_p$-C_1-C_9-heteroaryl, and wherein aryl and heteroaryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In an embodiment of the compound of Formula II,

p is 0 or 1;

R^8 is independently selected from H, –OH, and C_1-C_6-alkyl; and

R^9 is independently selected from H and C_1-C_6-alkyl.

In an embodiment of the compound of Formula II, n is 1.

In an embodiment of the compound of Formula II,

Y is –C(O)–;

Z is NR^7; and

R^7 is H or C_{1-4}-alkyl.

In an embodiment of the compound of Formula II,

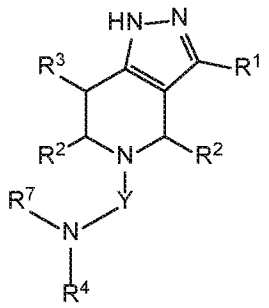
Y is –C(O)–;

Z is NR^7;

R^7 is H or C_{1-4}-alkyl; and

n is 1.

Also provided herein is a compound of Formula I, having the structure of Formula III (also referred to as "a compound of Formula III"):



III,

or a pharmaceutically acceptable salt thereof, wherein

Y is –C(O)– or $–SO_2–$;

R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, -OH, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from $(CR^8R^9)_p$-C_1-C_9-heteroaryl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, and C_3-C_8-cycloalkyl wherein heteroaryl, aryl, and cycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-

C_1-C_6-alkyl, C_1-C_6-alkyl-OH, and C_3-C_8-cycloalkyl.

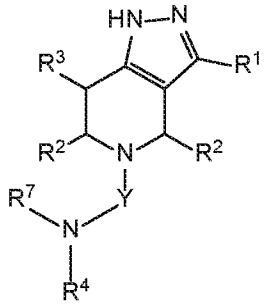
R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H and C_1-C_6-alkyl; and

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

In an embodiment of the Compound of Formula III,



III,

or a pharmaceutically acceptable salt thereof,

Y is –C(O)– or –SO_2–;

R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from $(CR^8R^9)_p$-C_1-C_9-heteroaryl and $(CR^8R^9)_p$-C_6-C_{12}-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H and C_1-C_6-alkyl; and

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

In an embodiment of the compound of Formula III, Y is –C(O)–.

In an embodiment of the compound of Formula III, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, –OH, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In an embodiment of the compound of Formula III, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

In an embodiment of the compound of Formula III, R^1 is C_3-C_8-cycloalkyl or C_2-C_8-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula III, R^1 is C_3-C_6-cycloalkyl or C_2-C_5-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula III, R^1 is selected from –OH, -Br, methyl, ethyl, ethenyl, propyl, propenyl, isopropyl, butyl, t-butyl, butenyl, pentanyl, 2-methylpentan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, bicyclo[3.1.0]hexanyl, wherein methyl, ethyl, ethenyl, propyl, propenyl, isopropyl, butyl, t-butyl, butenyl, pentanyl, and 2-methylpentan-2-yl are optionally substituted with 1 or 2 groups independently selected from –OH, and halo, or wherein cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, and bicyclo[3.1.0]hexanyl are optionally substituted with 1 or 2 groups independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In another embodiment of the compound of Formula III, R^1 is selected from methyl, ethyl, ethenyl, propyl, propenyl, isopropyl, butyl, t-butyl, butenyl, pentanyl, 2-methylpentan-2-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, pyrrolidinyl, bicyclo[3.1.0]hexanyl, any of which are optionally substituted with 1 or 2 groups independently selected from –OH and halo.

In an embodiment of the compound of Formula III, each R^2 is independently selected

from H or C_1-C_4-alkyl. In a further embodiment of the compound of Formula III, R^2 is H.

In an embodiment of the compound of Formula III, R^3 is H.

In an embodiment of the compound of Formula III, R^7 is H or C_1-C_4-alkyl. In a further embodiment, R^7 is H or $-CH_3$. In yet another embodiment, R^7 is H.

In an embodiment of the compound of Formula III, R^4 is $(CR^8R^9)_p$-C_1-C_5-heteroaryl or $(CR^8R^9)_p$-C_6-aryl, or C_3-C_8-cycloalkyl, wherein heteroaryl, aryl and cycloalkyl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, and C_1-C_6-alkyl;

R^8 is H or C_1-C_6-alkyl;

R^9 is H or C_1-C_6-alkyl; and

p is 0 or 1.

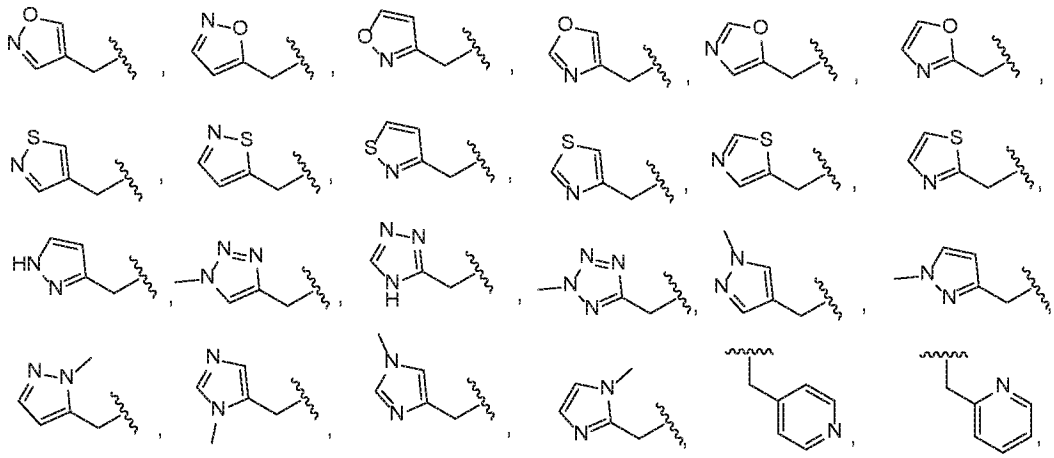
In an embodiment of the compound of Formula III, R^4 is $(CR^8R^9)_p$-C_1-C_5-heteroaryl or $(CR^8R^9)_p$-C_6-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, and C_1-C_6-alkyl;

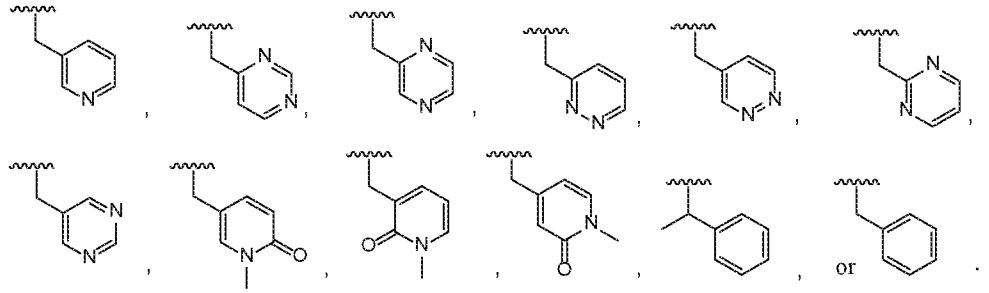
R^8 is H or C_1-C_6-alkyl;

R^9 is H or C_1-C_6-alkyl; and

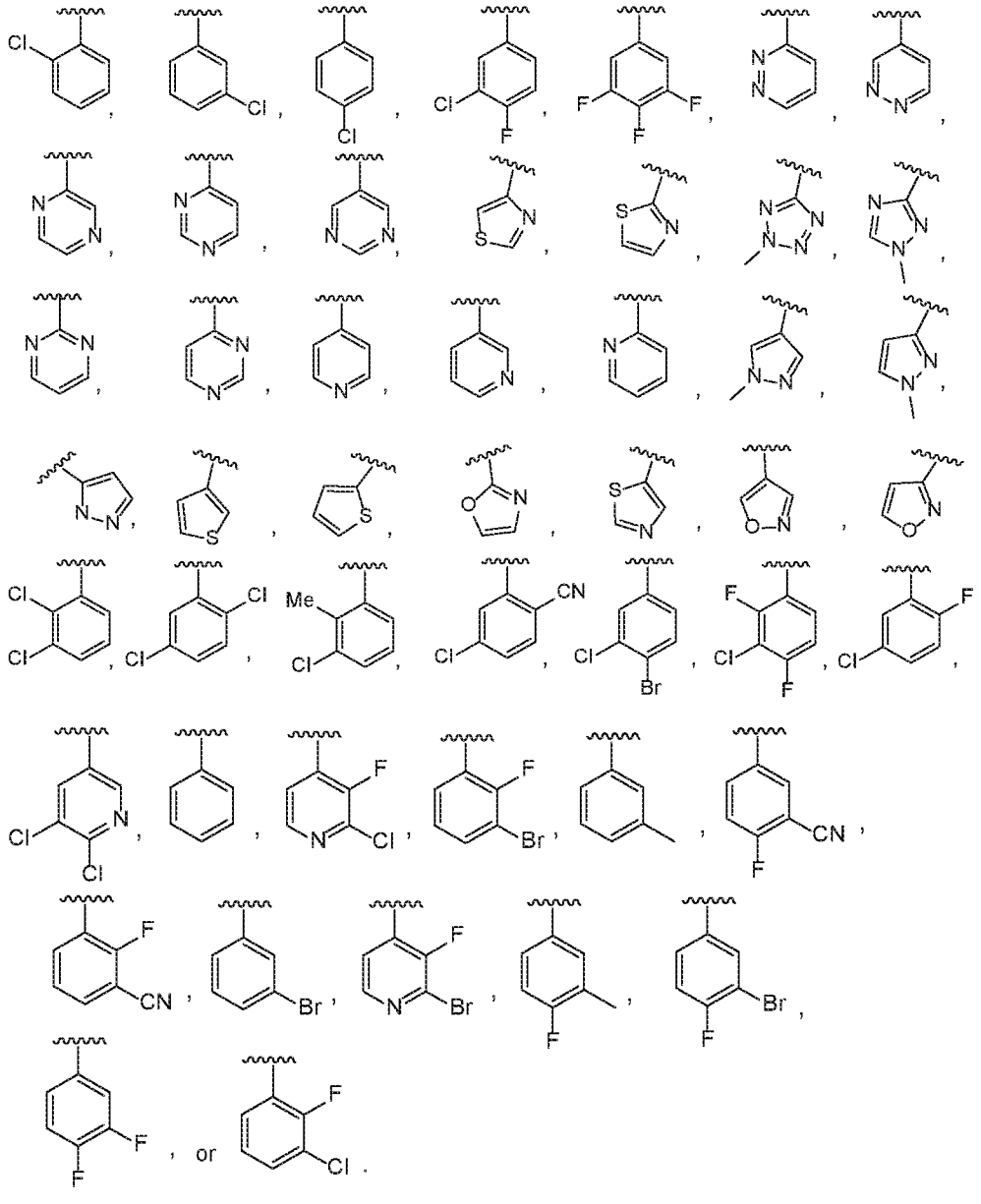
p is 0 or 1.

In an embodiment of the compound of Formula III, R^4 is C_1-C_5-heteroaryl or C_6-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, and C_1-C_6-alkyl. In a particular embodiment of the compound of Formula III, R^4 is

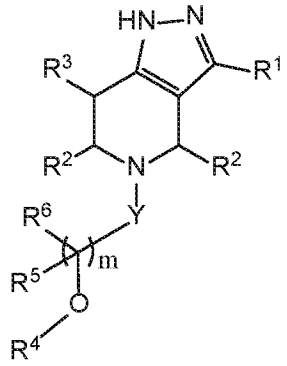




In another particular embodiment of the compound of Formula III, R^4 is



Also provided herein is a compound of Formula I, having the structure of Formula IV (also referred to as "a compound of Formula IV"):



IV,

or a pharmaceutically acceptable salt thereof wherein,

Y is –C(O)– or $–SO_2–$; and

m is 0, 1, or 2.

In an embodiment of the compound of Formula IV, Y is –C(O)–.

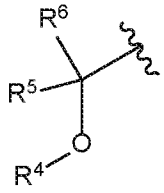
In an embodiment of the compound of Formula IV, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, –OH, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

In an embodiment of the compound of Formula IV, R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

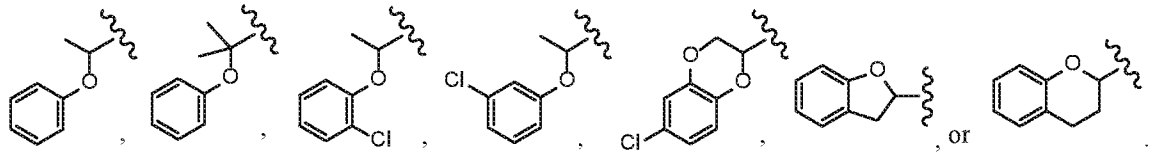
In an embodiment of the compound of Formula IV, each R^2 is independently selected from H or C_1-C_4-alkyl. In a further embodiment of the compound of Formula IV, R^2 is H.

In an embodiment of the compound of Formula IV, R^3 is H.

In another embodiment of the compound of Formula IV, m is 1, R^5 is H or C_1-C_6-alkyl, R^6 is H or C_1-C_6-alkyl, and wherein R^5 and R^4 are optionally joined to form a ring. In another embodiment of the compound of Formula IV, m is 1; R^5 is C_1-C_6-alkyl; R^6 is H or C_1-C_6-alkyl; and R^5 and R^4 are optionally joined to form a ring. For example, in an embodiment,

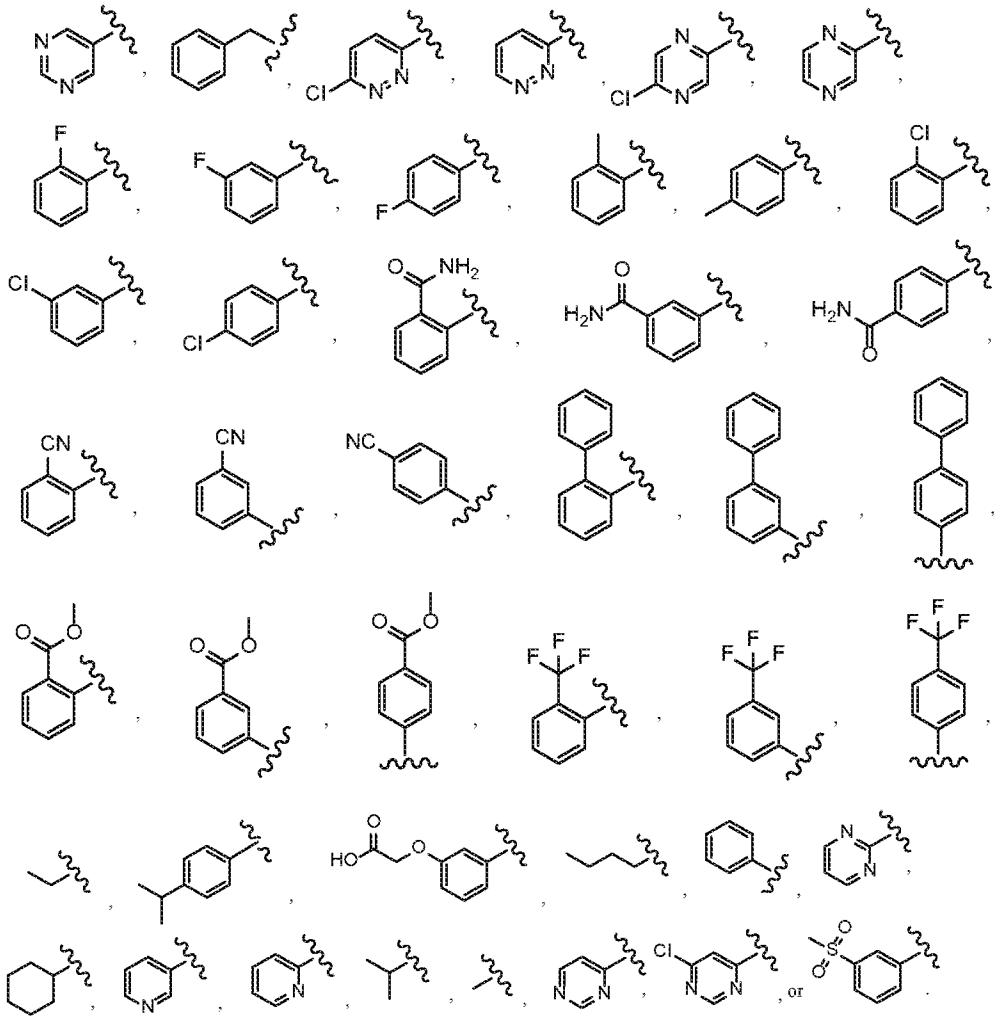


is



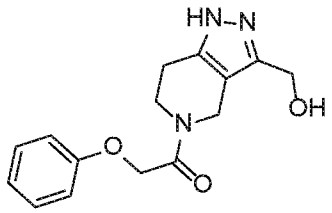
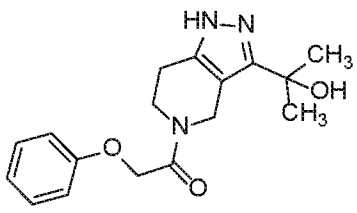
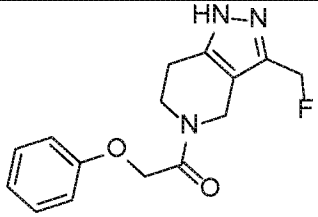
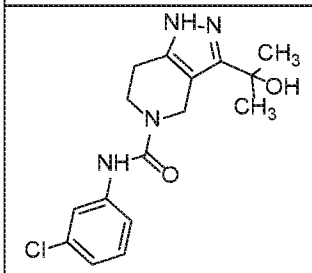
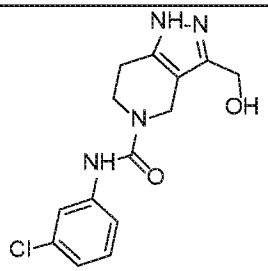
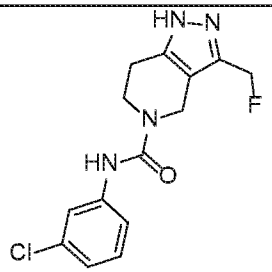
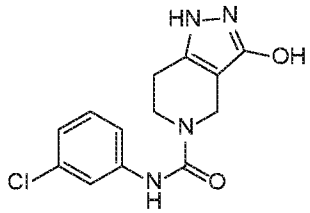
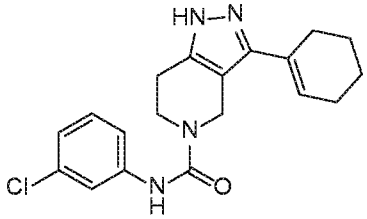
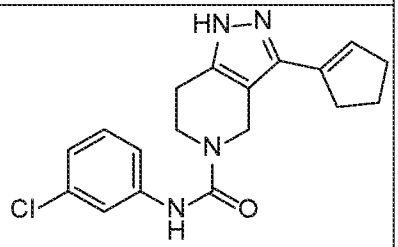
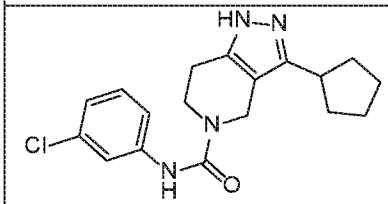
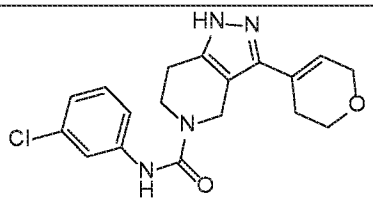
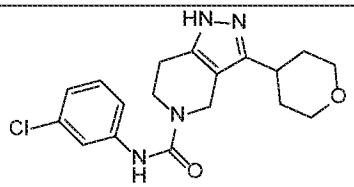
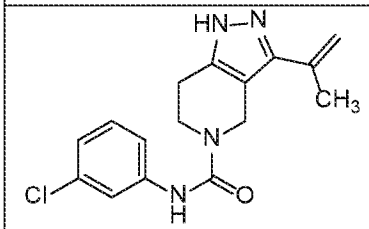
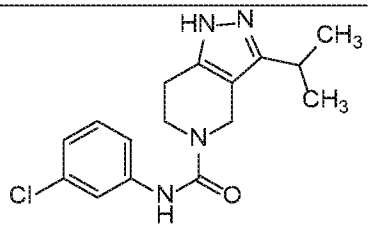
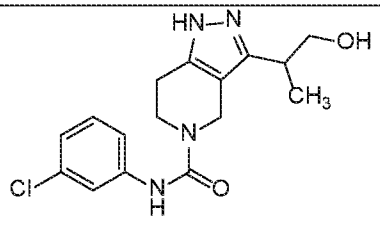
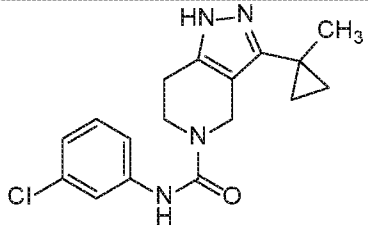
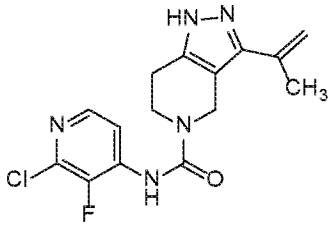
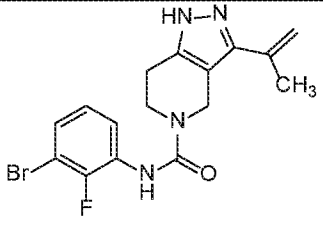
In another embodiment of the compound of Formula IV, R^4 is C_1-C_6-alkyl or $(CR^8R^9)_p$-C_6-C_{12}-aryl, wherein alkyl and aryl are optionally substituted with 1, 2, or 3, groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH.

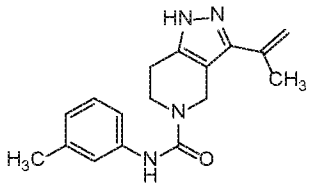
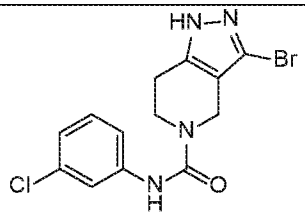
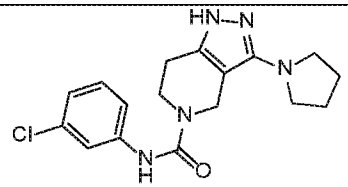
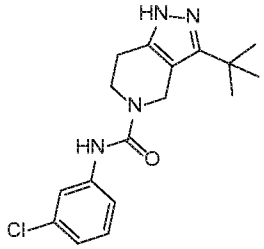
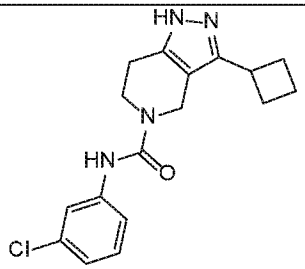
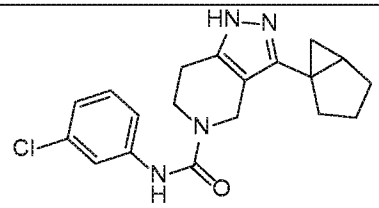
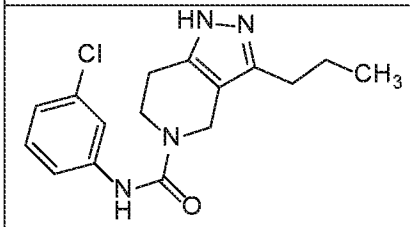
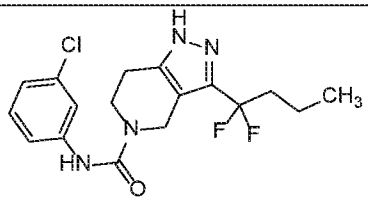
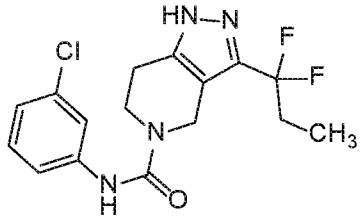
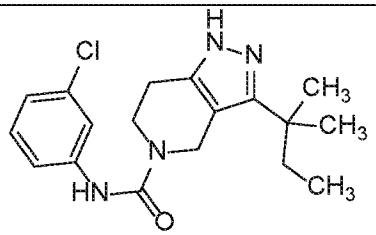
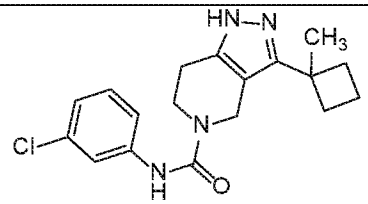
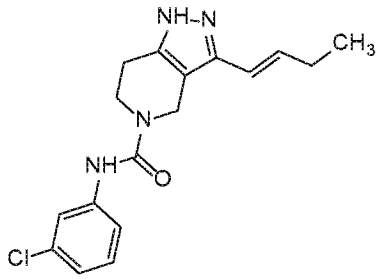
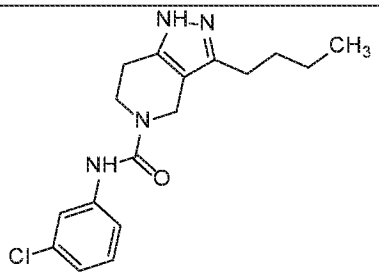
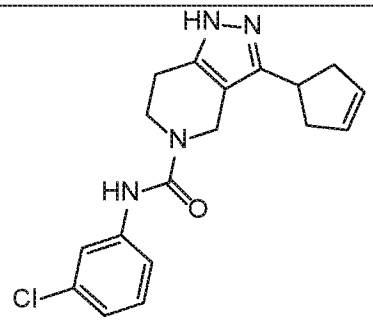
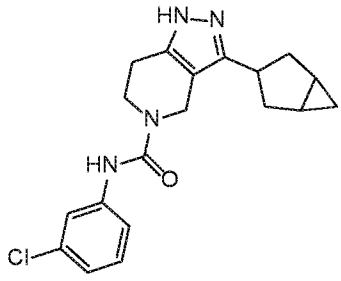
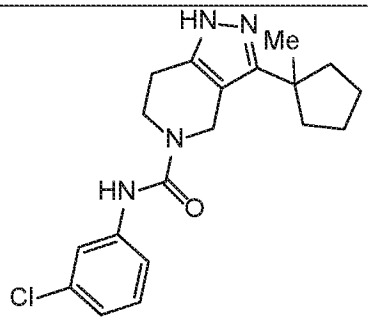
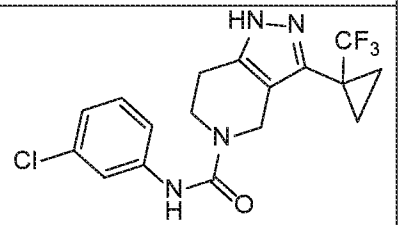
In further embodiments of the compound of Formula IV, R^4 is

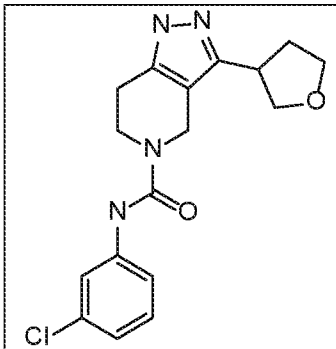
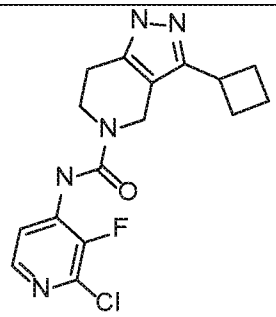
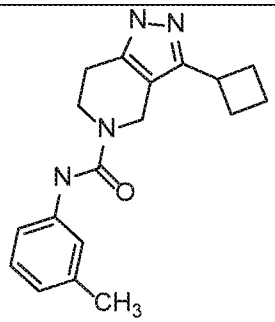
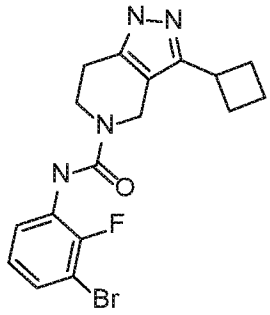
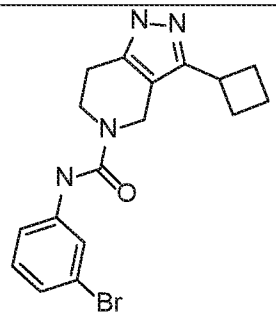
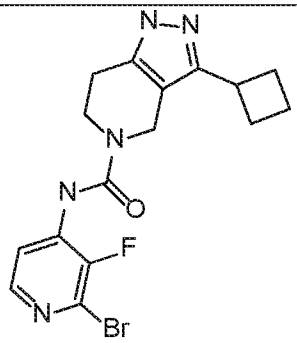
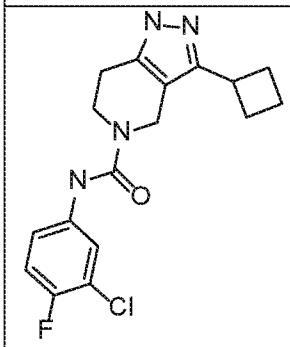
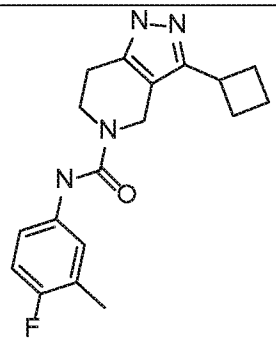
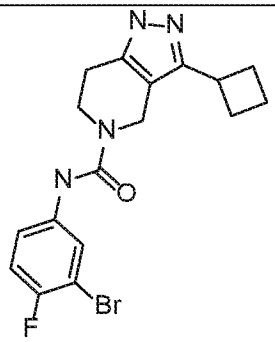
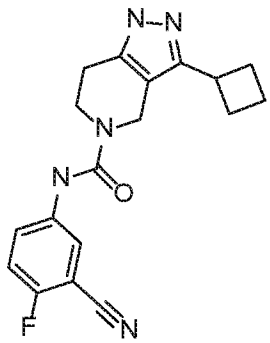
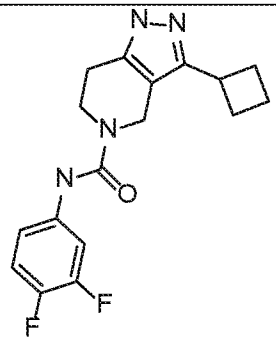
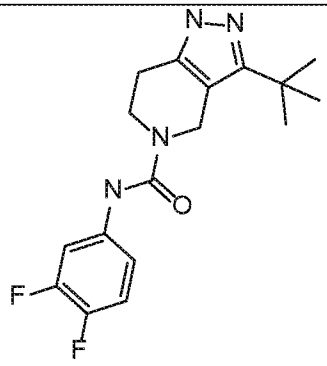


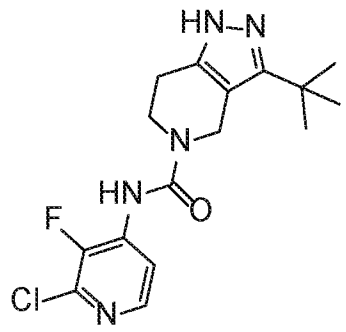
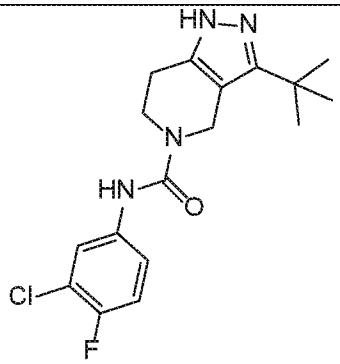
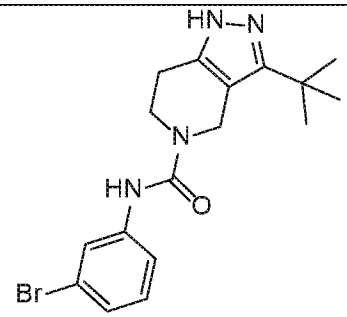
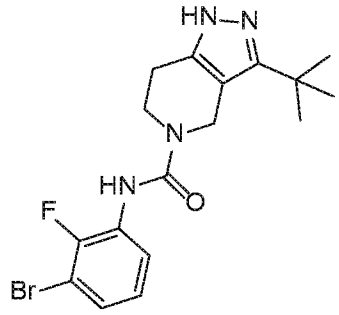
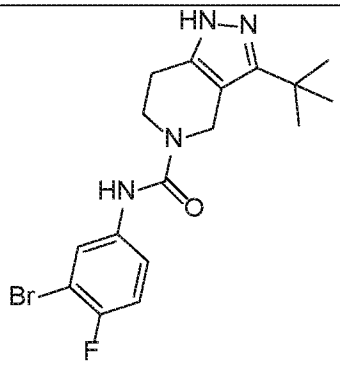
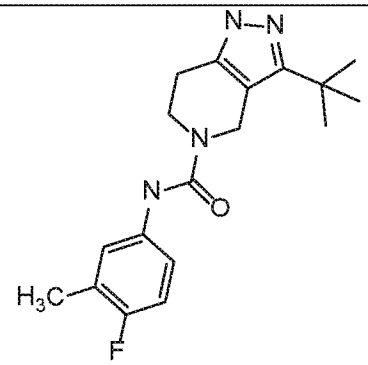
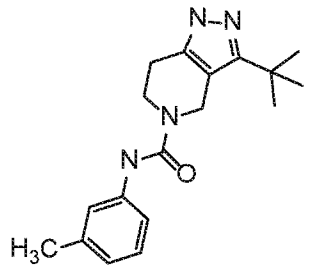
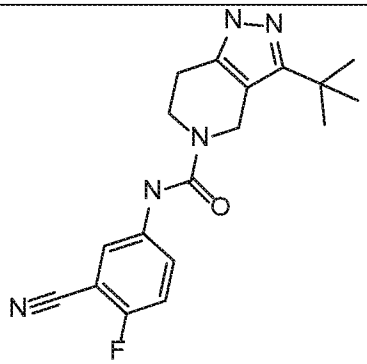
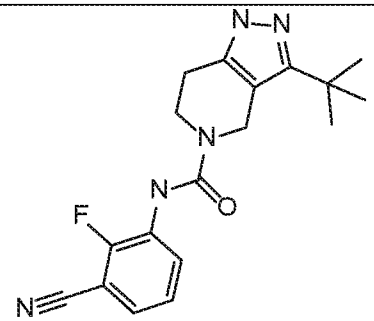
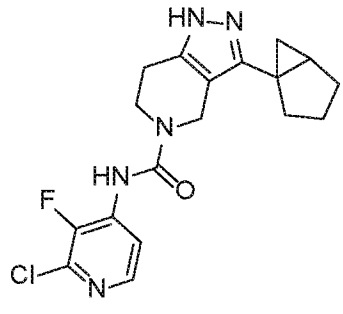
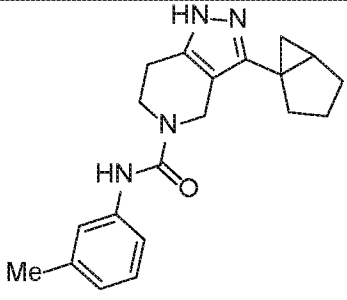
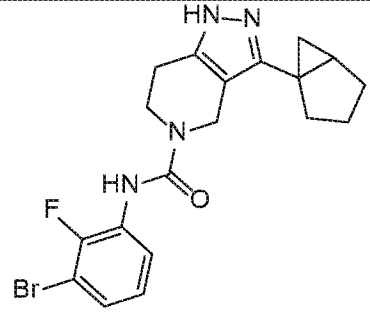
Certain embodiments of Formulas I-IV, including pharmaceutically acceptable salts thereof, are shown below in **Table 1**. All compounds of Formula I, II, III, and IV as well as pharmaceutically acceptable salts thereof, and the compounds of **Table 1**, as well as pharmaceutically acceptable salts thereof, are considered to be "compounds of the invention."

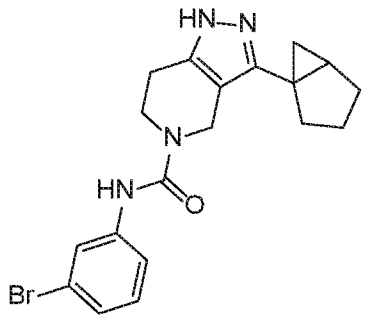
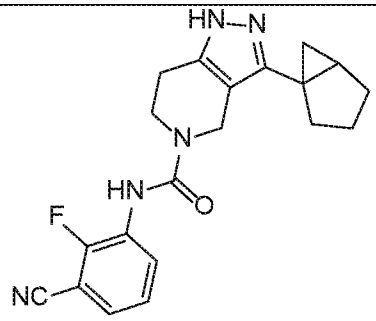
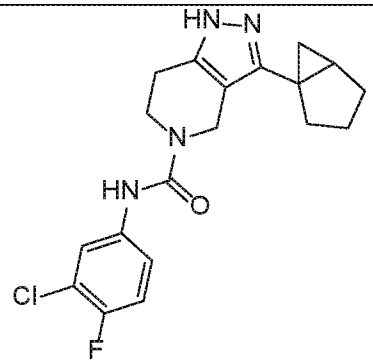
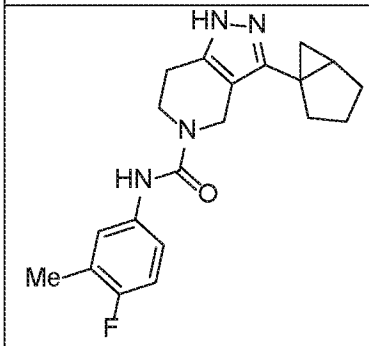
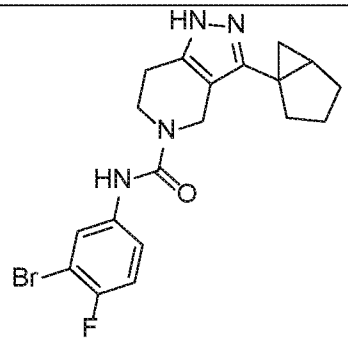
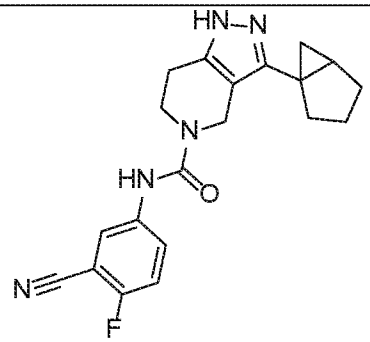
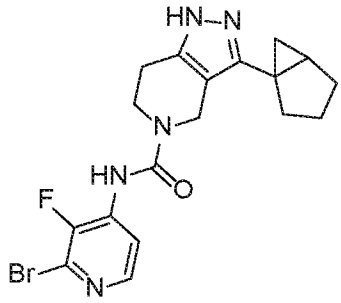
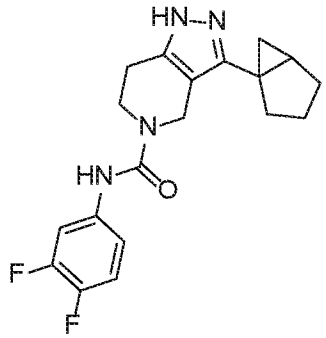
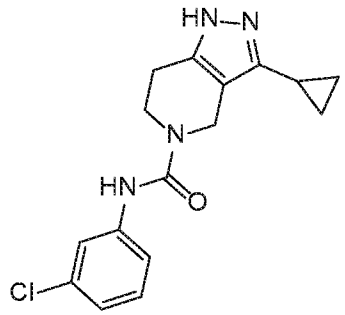
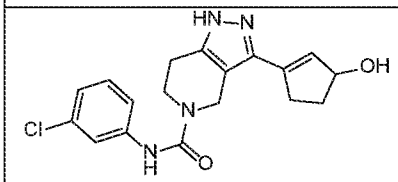
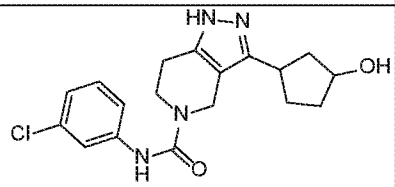
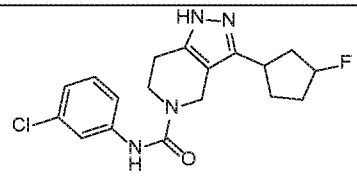
Table 1.

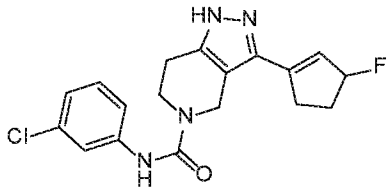
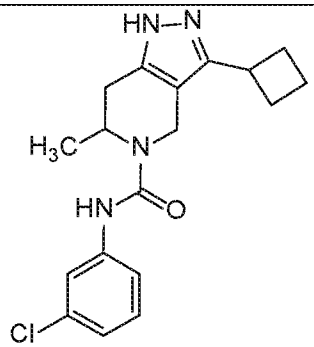
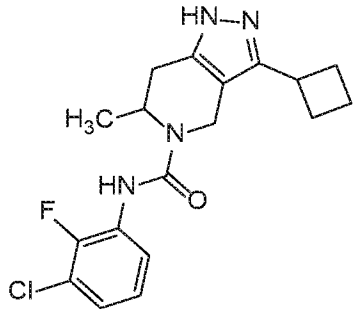
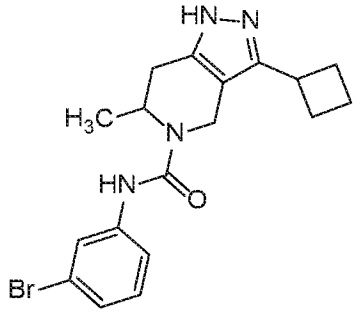
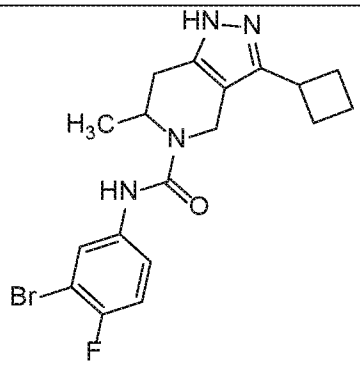
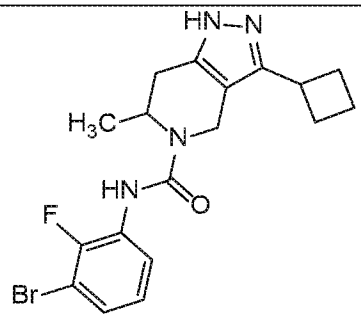
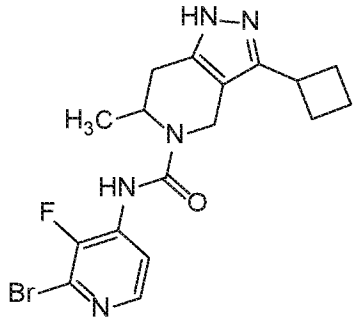
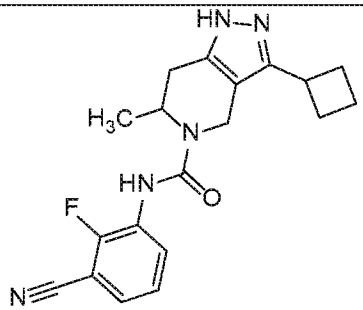
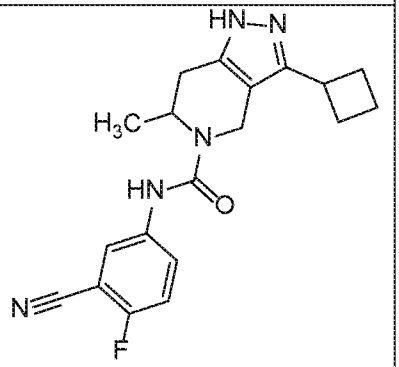
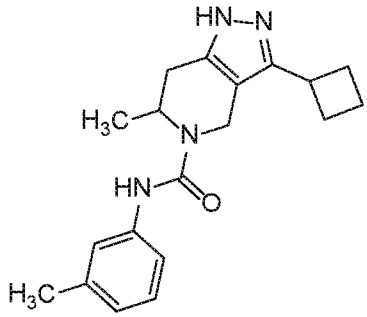
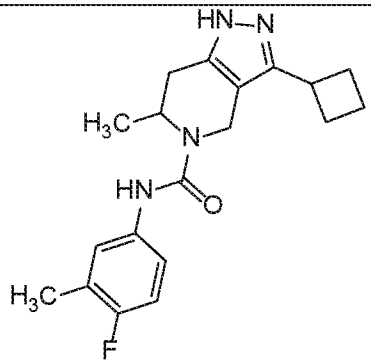
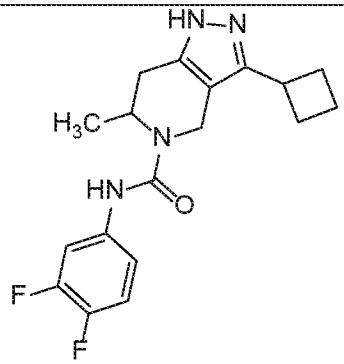
 040	 041	 042
 238	 239	 324
 241	 337	 338
 264	 274	 275
 336	 267	 388
 441	 547	 548

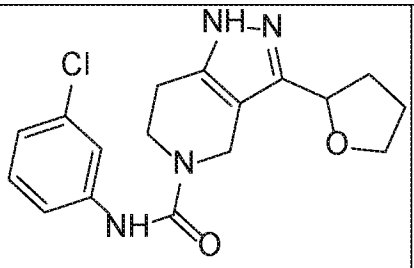
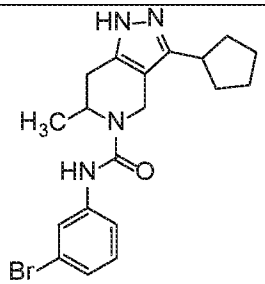
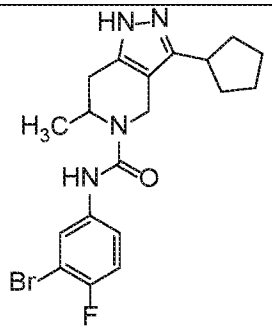
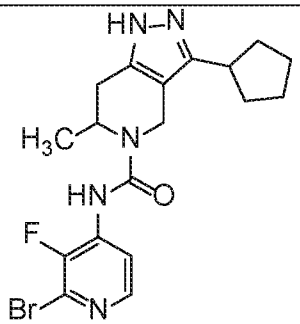
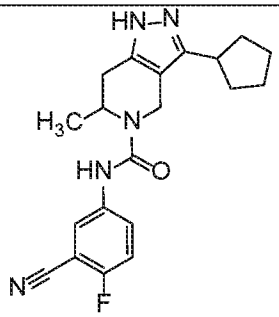
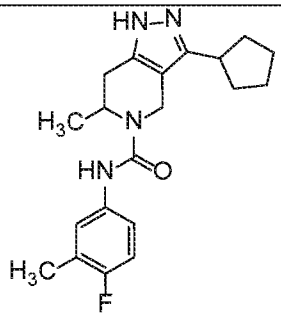
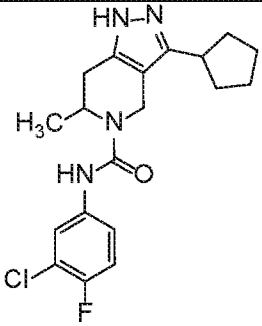
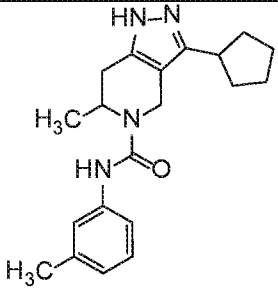
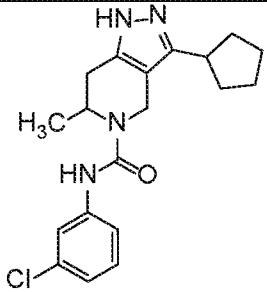
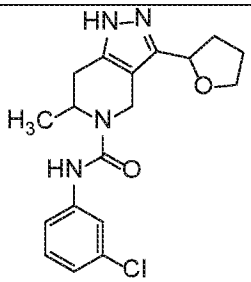
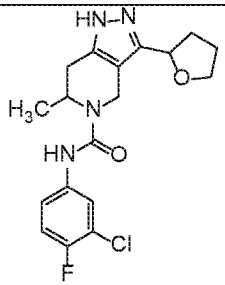
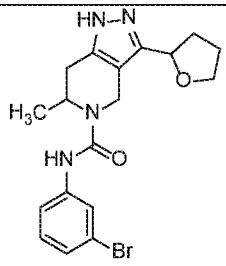
 549	 260	 455
 515	 554	 546
 644	 642	
 696	 604	 694
 508 (E & Z)	 509	 693
 734	 827	 700

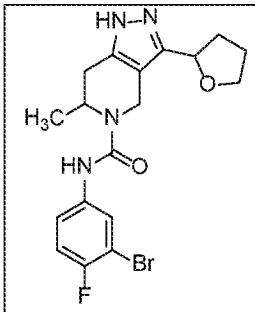
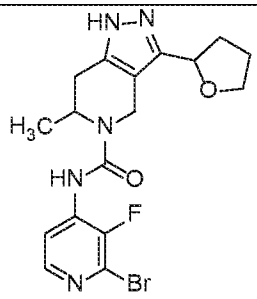
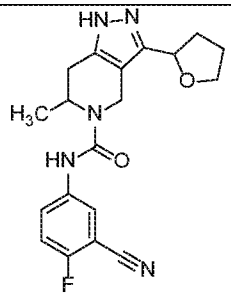
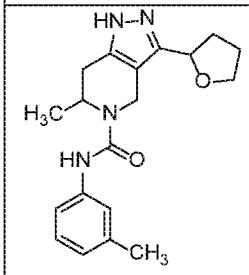
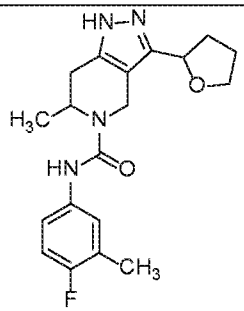
 446	 660	 661
 662	 663	 664
 665	 666	 667
 668	 669	 648

 649	 650	 651
 652	 653	 654
 655	 656	 657
 782	 783	 784

 785	 786	 787
 788	 789	 790
 791	 792	 440
 535	 742	 743

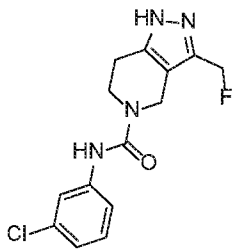
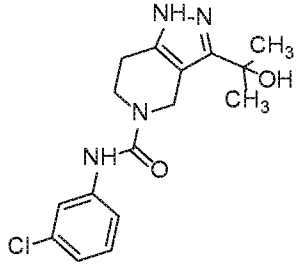
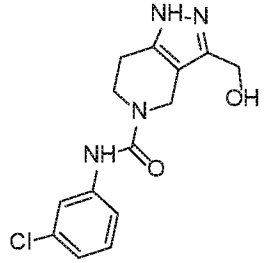
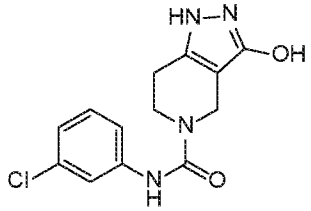
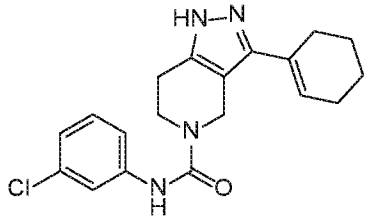
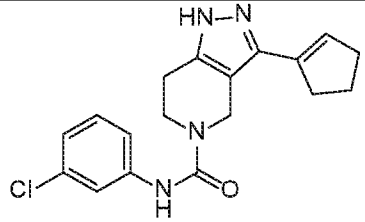
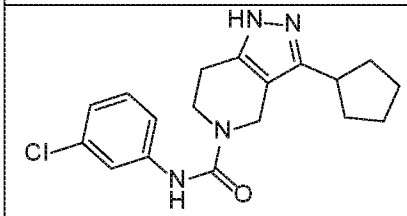
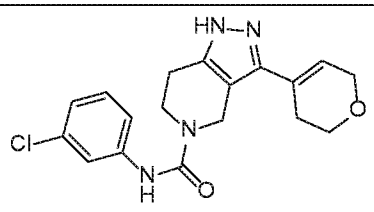
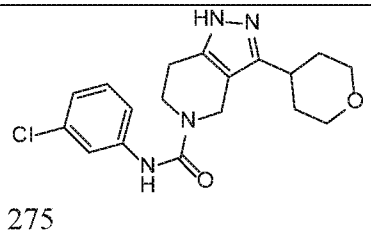
 744	 704	 756
 757	 758	 759
 760	 761	 762
 763	 764	 765

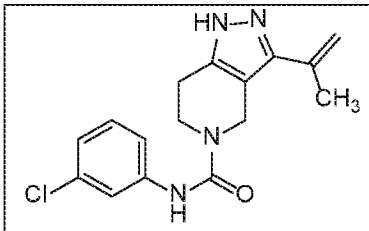
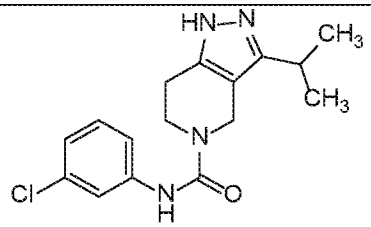
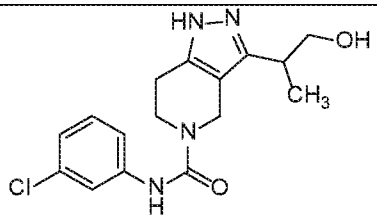
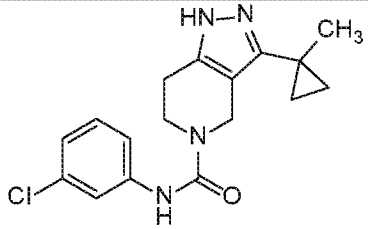
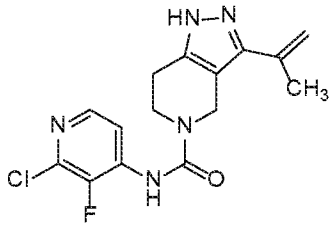
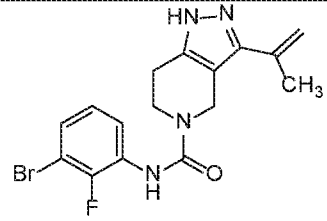
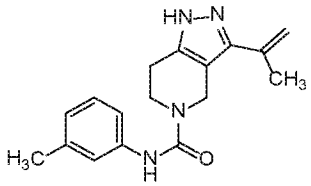
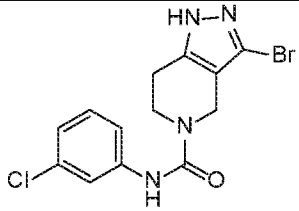
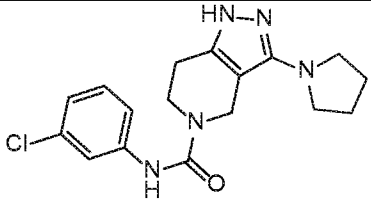
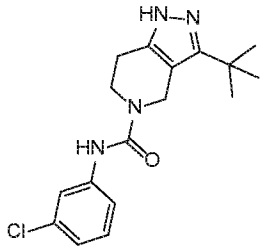
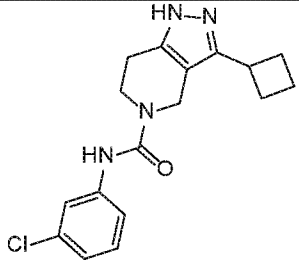
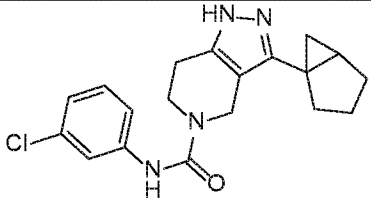
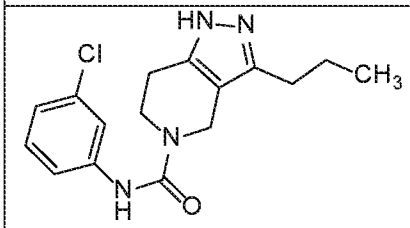
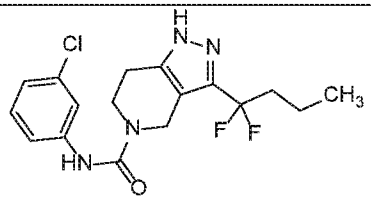
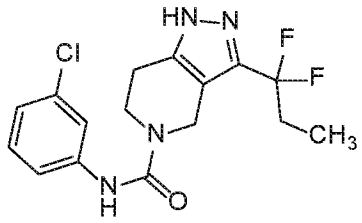
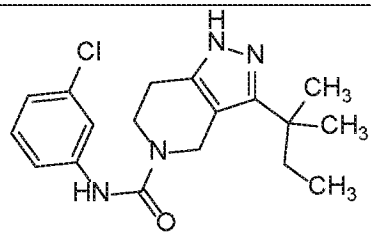
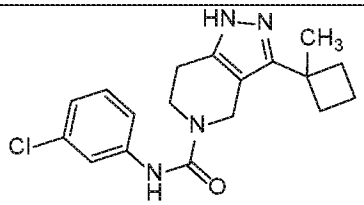
 861	 927	 928
 929	 930	 931
 932	 933	 934
 964	 965	 966

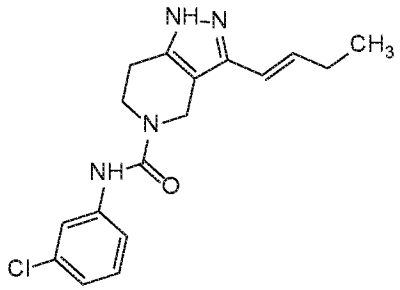
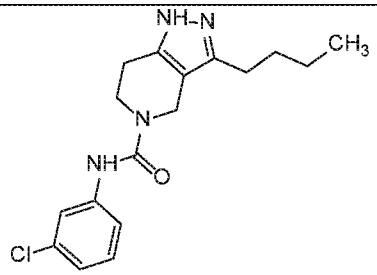
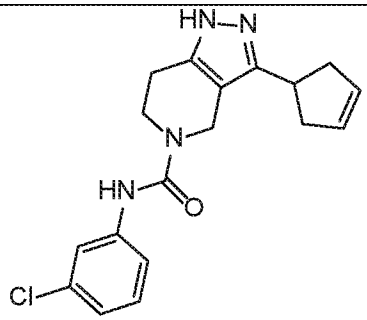
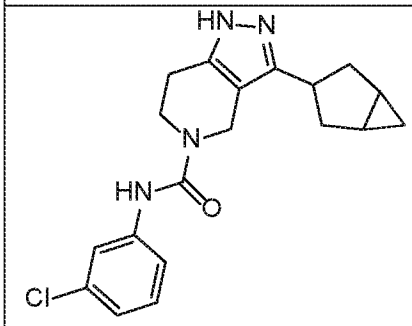
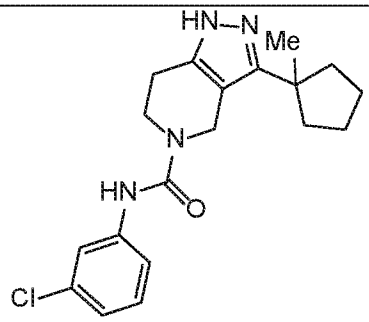
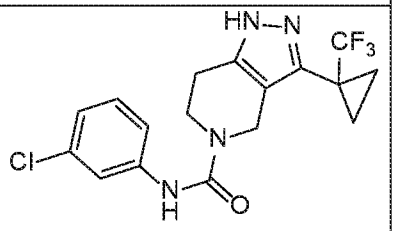
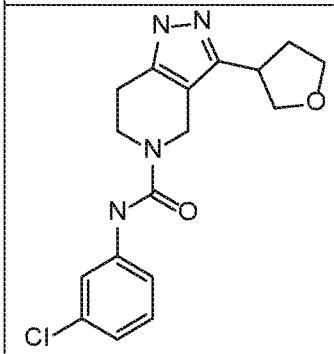
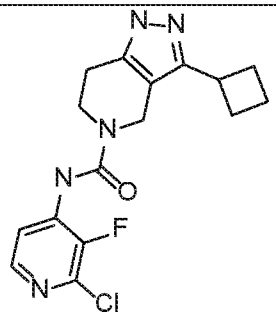
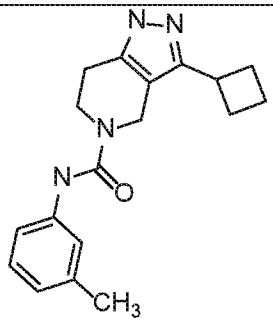
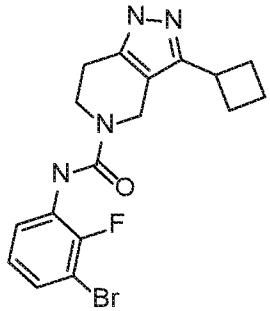
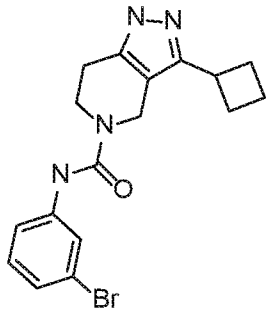
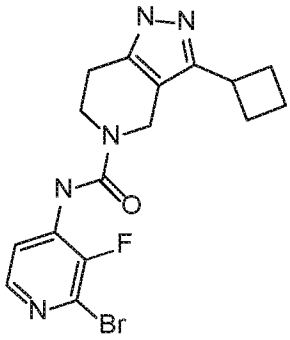
 967	 968	 969
 970	 971	

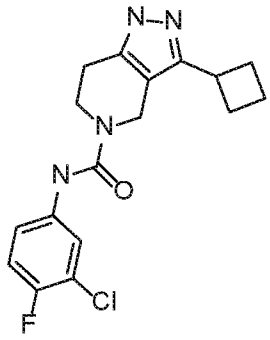
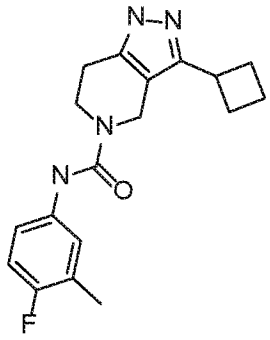
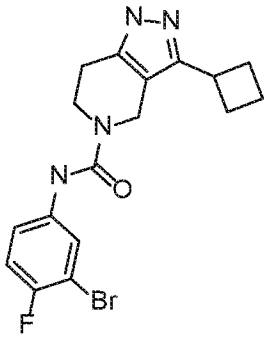
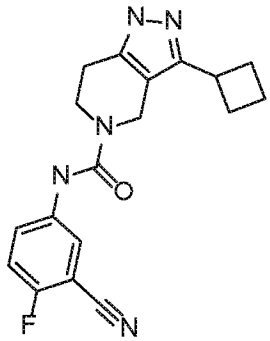
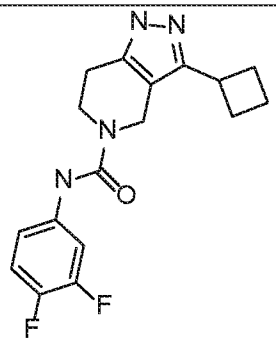
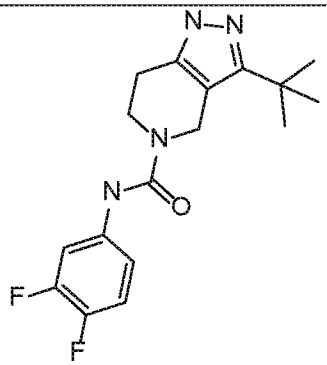
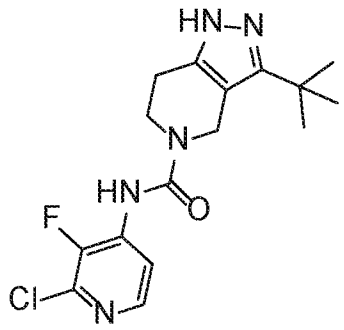
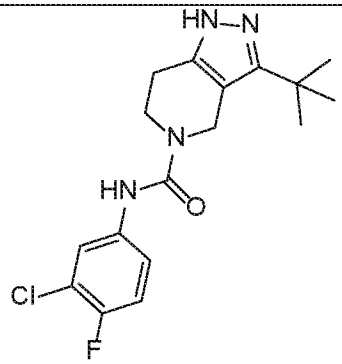
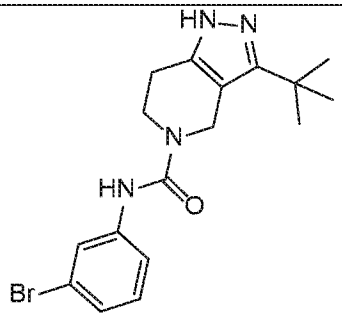
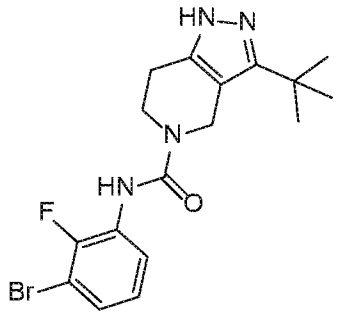
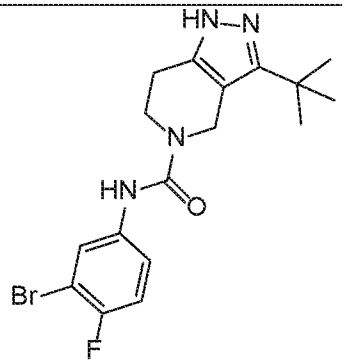
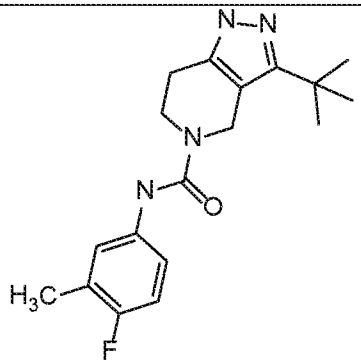
In yet another embodiment of Formula I provided herein, the compound of Formula III, or a pharmaceutically acceptable salt thereof, is selected from compounds shown in **Table 2** and pharmaceutically acceptable salts thereof.

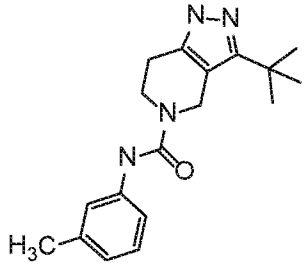
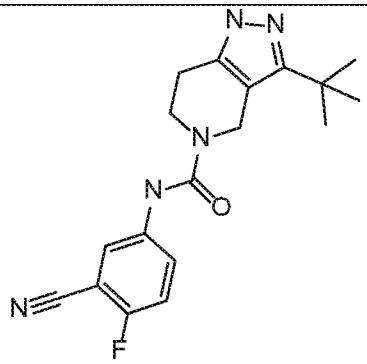
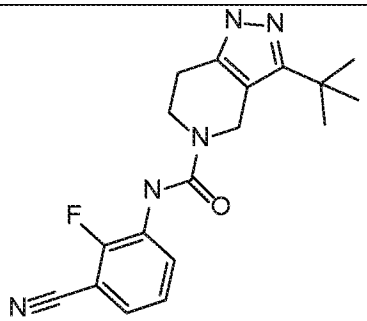
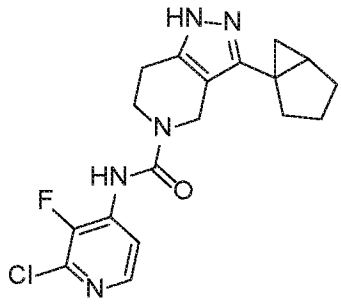
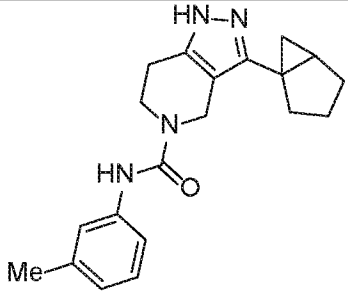
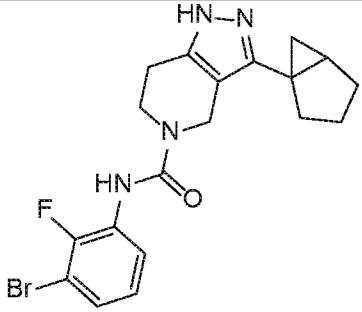
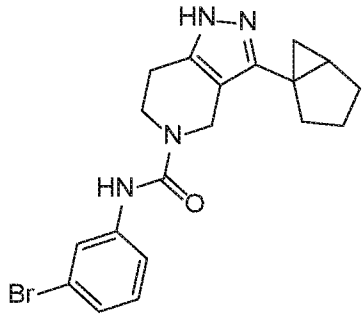
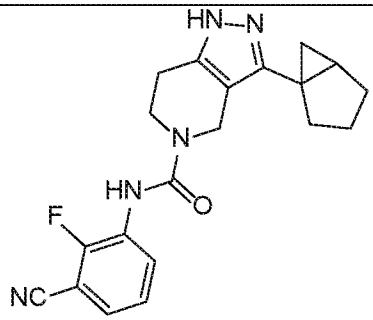
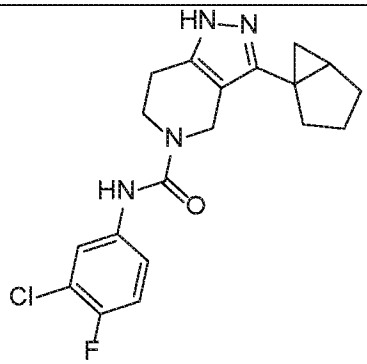
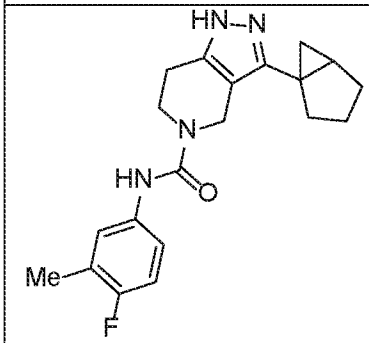
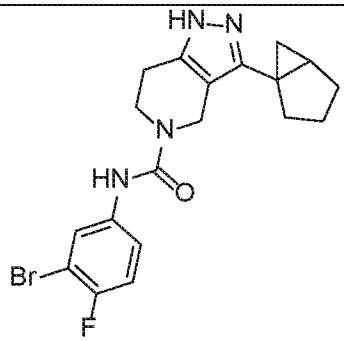
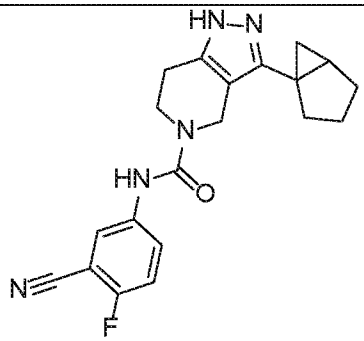
Table 2.

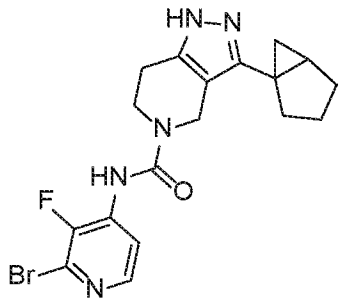
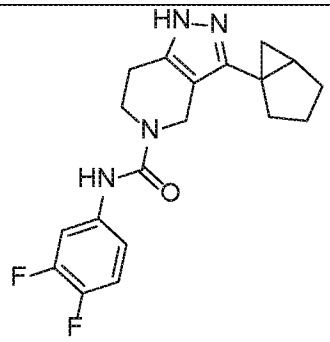
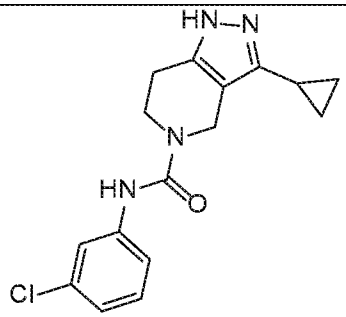
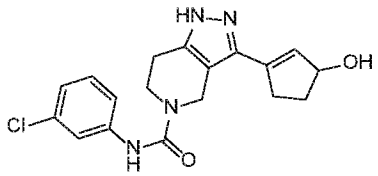
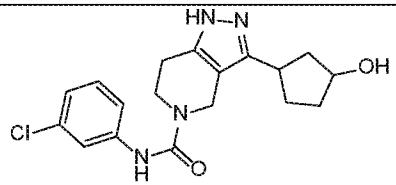
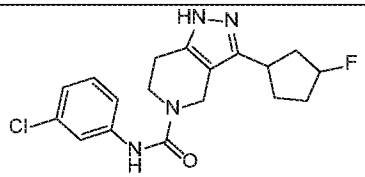
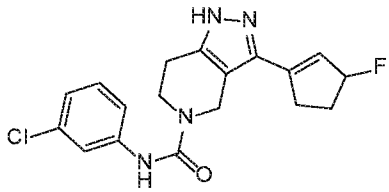
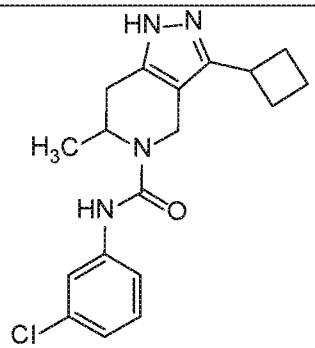
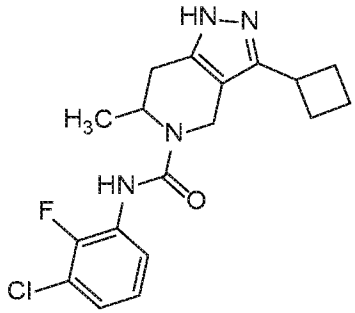
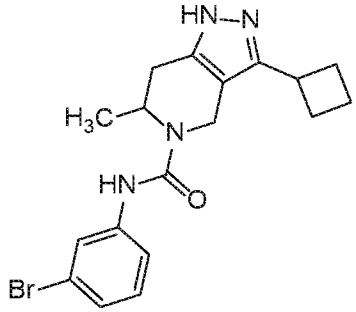
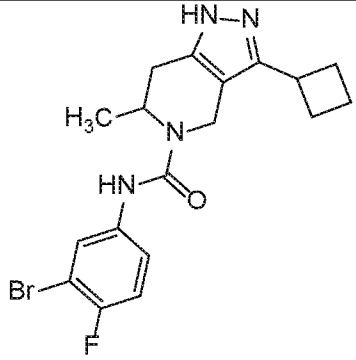
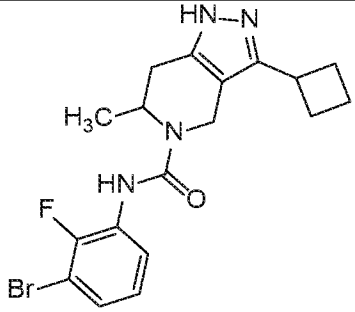
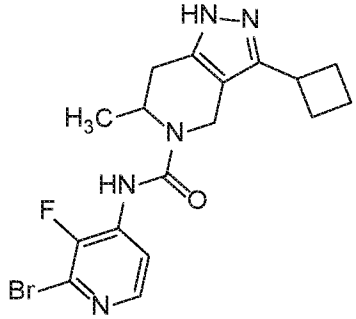
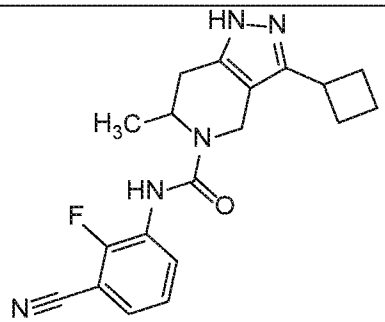
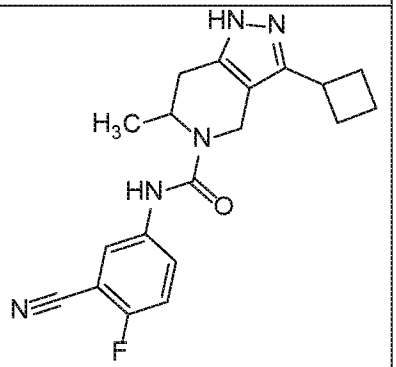
 324	 238	 239
 241	 337	 338
 264	 274	 275

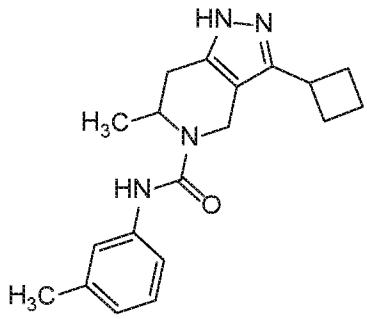
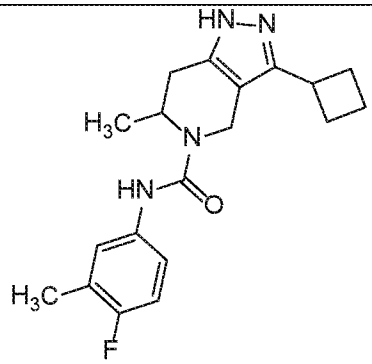
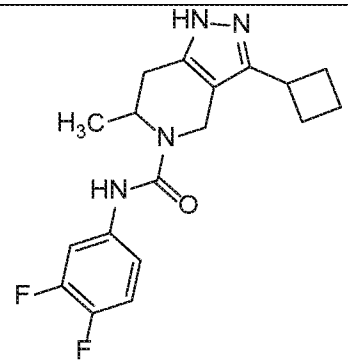
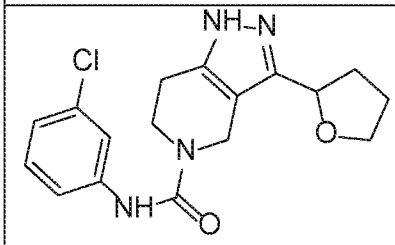
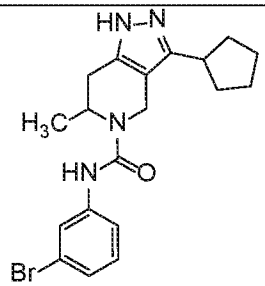
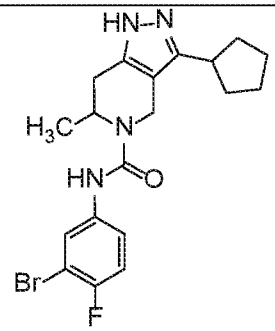
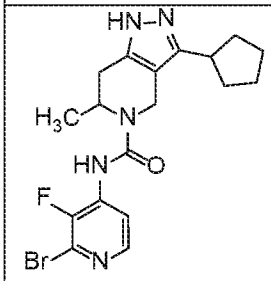
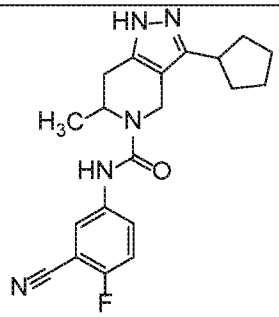
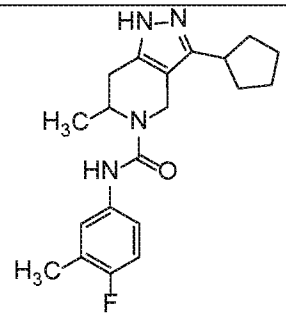
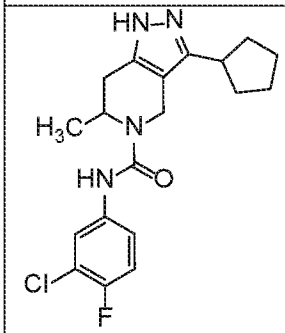
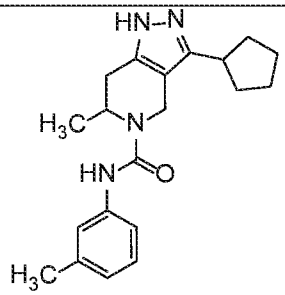
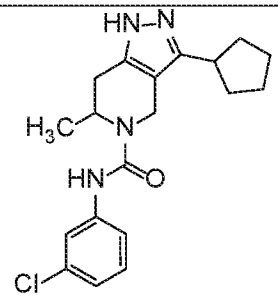
 336	 267	 388
 441	 547	 548
 549	 260	 455
 515	 554	 546
 644	 642	
 696	 604	 694

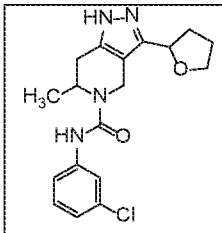
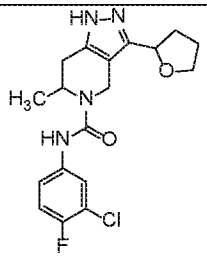
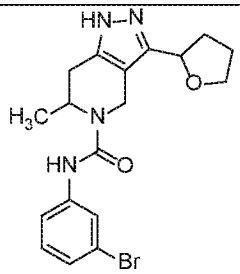
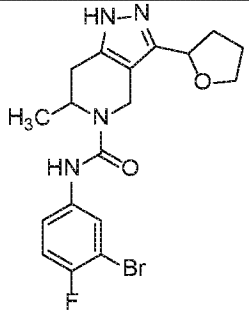
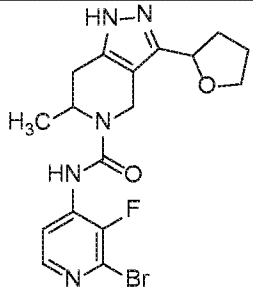
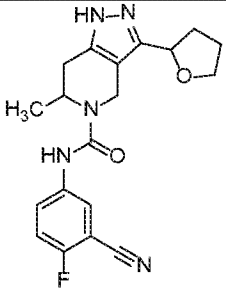
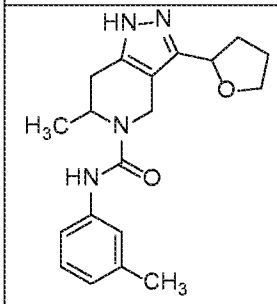
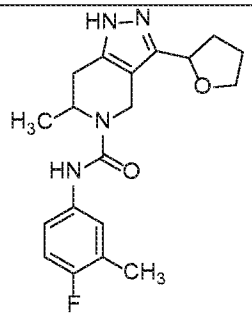
 508	 509	 693
 734	 827	 700
 446	 660	 661
 662	 663	 664

 665	 666	 667
 668	 669	 648
 649	 650	 651
 652	 653	 654

 655	 656	 657
 782	 783	 784
 785	 786	 787
 788	 789	 790

 791	 792	 440
 535	 742	 743
 744	 704	 756
 757	 758	 759
 760	 761	 762

 763	 764	 765
 861	 927	 928
 929	 930	 931
 932	 933	 934

 964	 965	 966
 967	 968	 969
 970	 971	

and pharmaceutically acceptable salts thereof.

The compounds of the invention may possess one or more stereocenters, and each stereocenter may exist independently in either the R or S configuration. In one embodiment, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds described herein encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein.

Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In one embodiment, a mixture of one or more isomer is utilized as the therapeutic compound described herein. In another

embodiment, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis and/or separation of a mixture of enantiomers and/or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

In one embodiment, the compounds of the invention may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

Compounds described herein also include isotopically-labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{36}Cl, ^{18}F, ^{123}I, ^{125}I, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, and ^{35}S. In one embodiment, isotopically-labeled compounds are useful in drug and/or substrate tissue distribution studies. In another embodiment, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements). In yet another embodiment, substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

In one embodiment, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein and as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey and Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000,2001), and Green and Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of

compound as described herein are modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formula as provided herein.

Compounds described herein are synthesized using any suitable procedures starting from compounds that are available from commercial sources, or are prepared using procedures described herein.

In one embodiment, reactive functional groups, such as hydroxyl, amino, imino, thio or carboxy groups, are protected in order to avoid their unwanted participation in reactions. Protecting groups are used to block some or all of the reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In another embodiment, each protective group is removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal.

Methods of the Invention

The invention provides a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention also provides a method of eradicating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention also provides a method of reducing viral load associated with an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention further provides a method of reducing reoccurrence of an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

In another aspect, provided herein is a method of inhibiting and/or reducing the formation or presence of HBV DNA-containing particles and/or HBV RNA-containing particles in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention also provides a method of reducing an adverse physiological impact of an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention further provides a method of reducing, slowing, or inhibiting an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention also provides a method of inducing remission of hepatic injury from an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention further provides a method of reducing the physiological impact of long-term antiviral therapy for HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

The invention further provides a method of prophylactically treating an HBV infection in an individual in need thereof, wherein the individual is afflicted with a latent HBV infection, comprising administering to the individual a therapeutically effective amount of a compound of the invention.

In one embodiment, the methods described herein further comprise administering at least one additional therapeutic agent selected from the group consisting of nucleotide/nucleoside analogs, entry inhibitors, fusion inhibitors, and any combination of these or other antiviral mechanisms. In another embodiment, the compound of the invention and the at least one additional therapeutic agent are co-formulated. In yet another embodiment, the compound of the invention and the at least one additional therapeutic agent are co-administered.

In one embodiment, the individual is refractory to other therapeutic classes of HBV drugs (e.g, HBV polymerase inhibitors, interferons, viral entry inhibitors, viral maturation inhibitors, literature-described capsid assembly modulators, antiviral compounds of distinct or unknown mechanism, and the like, or combinations thereof). In another embodiment, the method of the invention reduces viral load in an individual suffering from an HBV infection to a greater extent or at a faster rate compared to the extent that other therapeutic classes of HBV drugs reduce viral load in the individual.

In one embodiment, the administering of a compound of the invention, or a pharmaceutically acceptable salt thereof, allows for administering of the at least one additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one additional therapeutic agent alone that is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

In one embodiment, the administering of a compound of the invention, or a pharmaceutically acceptable salt thereof, reduces the viral load in the individual to a greater extent or at a faster rate compared to the administering of a compound selected from the group consisting of an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and any combination thereof.

In one embodiment, the method of the invention reduces viral load in an individual suffering from an HBV infection, thus allowing lower doses or varying regimens of combination therapies to be used.

In one embodiment, the method of the invention causes a lower incidence of viral mutation and/or viral resistance compared to other classes of HBV drugs, thereby allowing for long term therapy and minimizing the need for changes in treatment regimens.

In one embodiment, the administering of a compound the invention, or a pharmaceutically acceptable salt thereof, causes a lower incidence of viral mutation and/or viral resistance than the administering of a compound selected from the group consisting of an HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof.

In one embodiment, the method of the invention increases the seroconversion rate beyond that of current treatment regimens.

In one embodiment, the method of the invention increases and/or normalizes and/or restores normal health, elicits full recovery of normal health, restores life expectancy, and/or resolves the viral infection in the individual in need thereof.

In one embodiment, the method of the invention eliminates or decreases the number of HBV RNA particles that are released from HBV infected cells thus enhancing, prolonging, or increasing the therapeutic benefit of the compounds of the invention.

In one embodiment, the method of the invention eradicates HBV from an individual infected with HBV, thereby obviating the need for long term and/or life-long treatment, or shortening the duration of treatment, and/or allowing for reduction in dosing of other antiviral agents.

In another embodiment, the method of the invention further comprises monitoring the HBV viral load of the subject, and wherein the method is carried out for a period of time such that the HBV virus is undetectable.

Accordingly, in one embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula II, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula III, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of **Table 1**, or a pharmaceutically acceptable salt thereof.

In another embodiment, provided herein is a method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of **Table 2**, or a pharmaceutically acceptable salt thereof.

In an embodiment of any of the methods provided herein, the method can further comprise monitoring the HBV viral load of the subject, wherein the method is carried out for a period of time such that the HBV virus is undetectable.

Combination Therapies

The compounds of the present invention are intended to be useful in combination with one or more additional compounds useful for treating HBV infection. These additional compounds may comprise compounds of the present invention or compounds known to treat, prevent, or reduce the symptoms or effects of HBV infection. Such compounds include but are not limited to HBV polymerase inhibitors, interferons, viral entry inhibitors, viral maturation inhibitors, literature-described capsid assembly modulators, reverse transcriptase inhibitor, immunomodulatory agents, a TLR-agonist, and other agents with distinct or unknown mechanisms that affect the HBV life cycle and/or affect the consequences of HBV infection.

In non-limiting examples, the compounds of the invention may be used in combination with one or more drugs (or a salt thereof) selected from the group consisting of

HBV reverse transcriptase inhibitors, and DNA and RNA polymerase inhibitors, including but not limited to: lamivudine (3TC, Zeffix, Heptovir, Epivir, and Epivir-HBV), entecavir (Baraclude, Entavir), adefovir dipivoxil (Hepsara, Preveon, bis-POM PMEA), tenofovir disoproxil fumarate (Viread, TDF or PMPA);

interferons, including but not limited to interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), and interferon gamma (IFN-γ);

viral entry inhibitors;

viral maturation inhibitors;

literature-described capsid assembly modulators, such as, but not limited to BAY 41-4109;

reverse transcriptase inhibitor;

an immunomodulatory agent such as a TLR-agonist; and

agents of distinct or unknown mechanism, such as but not limited to AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT-130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), and similar analogs.

In one embodiment, the additional therapeutic agent is an interferon. The term "interferon" or "IFN" refers to any member the famly of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation, and modulate immune response. Human interferons are grouped into three classes; Type I, which include interferon-alpha (IFN-α), interferon-beta (IFN-β), and interferon-omega (IFN-ω), Type II, which includes interferon-gamma (IFN-γ), and Type III, which includes interferon-lambda (IFN-λ). Recombinant forms of interferons that have been developed and are commercially available are encompassed by the term "interferon" as used herein. Subtypes of interferons, such as chemically modified or mutated interferons, are also encompassed by the term "interferon" as used herein. Chemically modified interferons include pegylated interferons and glycosylated interferons. Examples of interferons also include, but are not limited to, interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-n1, interferon-beta-1a, interferon-beta-1b, interferon-lamda-1, interferon-lamda-2, and interferon-lamda-3. Examples of pegylated interferons include pegylated interferon-alpha-2a and pegylated interferson alpha-2b.

Accordingly, in one embodiment, the compounds of Formula I, II, III, or IV, can be administered in combination with an interferon selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), and interferon gamma (IFN-γ). In one specific embodiment, the interferon is interferon-alpha-2a, interferon-alpha-2b, or interferon-alpha-n1. In another specific embodiment, the interferon-alpha-2a or interferon-alpha-2b is pegylated. In a preferred embodiment, the interferon-alpha-2a is pegylated interferon-alpha-2a (PEGASYS).

In another embodiment, the additional therapeutic agent is selected from immune modulator or immune stimulator therapies, which includes biological agents belonging to the interferon class.

Further, the additional therapeutic agent may be an agent of distinct or unknown mechanism including agents that disrupt the function of other essential viral protein(s) or host proteins required for HBV replication or persistence.

In another embodiment, the additional therapeutic agent is an antiviral agent that blocks viral entry or maturation or targets the HBV polymerase such as nucleoside or nucleotide or non-nucleos(t)ide polymerase inhibitors. In a further embodiment of the combination therapy, the reverse transcriptase inhibitor and/or DNA and/or RNA polymerase inhibitor is Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

In an embodiment, the additional therapeutic agent is an immunomodulatory agent that induces a natural, limited immune response leading to induction of immune responses against unrelated viruses. In other words, the immunomodulatory agent can effect maturation of antigen presenting cells, proliferation of T-cells and cytokine release (e.g., IL-12, IL-18, IFN-alpha, -beta, and –gamma and TNF-alpha among others),

In a further embodiment, the additional therapeutic agent is a TLR modulator or a TLR agonist, such as a TLR-7 agonist or TLR-9 agonist. In further embodiment of the combination therapy, the TLR-7 agonist is selected from the group consisting of SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine) and AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate).

In any of the methods provided herein, the method may further comprise administering to the individual at least one HBV vaccine, a nucleoside HBV inhibitor, an

interferon or any combination thereof. In an embodiment, the HBV vaccine is at least one of RECOMBIVAX HB, ENGERIX-B, ELOVAC B, GENEVAC-B, or SHANVAC B.

In another aspect, provided herein is method of treating an HBV infection in an individual in need thereof, comprising reducing the HBV viral load by administering to the individual a therapeutically effective amount of a compound of the invention alone or in combination with a reverse transcriptase inhibitor; and further administering to the individual a therapeutically effective amount of HBV vaccine. The reverse transcriptase inhibitor may be one of Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

For any combination therapy described herein, synergistic effect may be calculated, for example, using suitable methods such as the Sigmoid-E_{max} equation (Holford & Scheiner, 19981, Clin. Pharmacokinet. 6: 429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, Arch. Exp. Pathol Pharmacol. 114: 313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22: 27-55). Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

In an embodiment of any of the methods of administering combination therapies provided herein, the method can further comprise monitoring the HBV viral load of the subject, wherein the method is carried out for a period of time such that the HBV virus is undetectable.

Administration/Dosage/Formulations

In another aspect, provided herein is pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well, known in the medical arts.

A medical doctor, e.g., physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a therapeutic compound for the treatment of HBV infection in a patient.

In one embodiment, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

In some embodiments, the dose of a compound of the invention is from about 1 mg to about 2,500 mg. In some embodiments, a dose of a compound of the invention used in compositions described herein is less than about 10,000 mg, or less than about 8,000 mg, or less than about 6,000 mg, or less than about 5,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg. Similarly, in some embodiments, a dose of a second compound (i.e., another drug for HBV treatment) as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about

100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof.

In one embodiment, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention, alone or in combination with a second pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of HBV infection in a patient.

Routes of administration of any of the compositions of the invention include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds for use in the invention may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (*e.g.*, sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to

delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For parenteral administration, the compounds of the invention may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing and/or dispersing agents may be used.

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 invention 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.

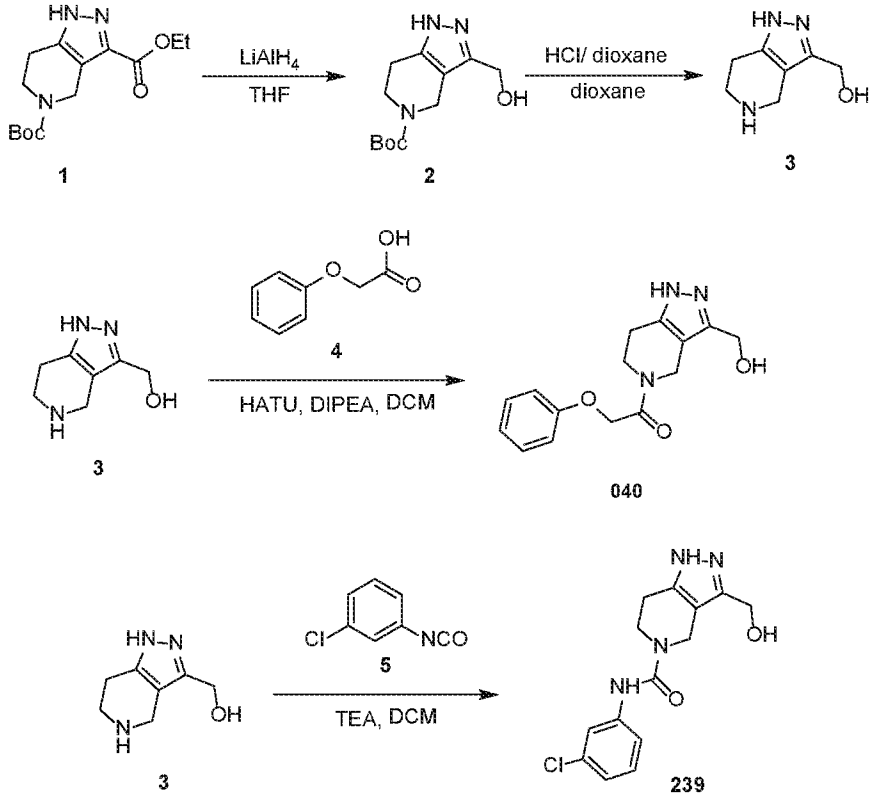
It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of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

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

EXAMPLES

The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only, and the invention is not limited to these Examples, but rather encompasses all variations that are evident as a result of the teachings provided herein.

Example 1: Procedure for the Preparation of Compounds 040 and 239



Step 1: Preparation of Compound 2

Cool the three-necked round bottom flask to -78 °C, LiAlH4 (192.75 mg, 5.08 mmol, 3.00 *eq*) was added under N_2, then a solution of O5-tert-butyl O3-ethyl 1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (500.00 mg, 1.69 mmol, 1.00 *eq*) in THF (5.00 mL) was added dropwise, after addition the reaction mixture was warmed to 0 °C and stirred at 0 °C for 5 hours. LCMS showed starting material was consumed completely and one main peak with desired MS was detected. The reaction was quenched with water (10 mL) and then extracted with EA (30 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compound tert-butyl 3-(hydroxymethyl)-1,4,6,7- tetrahydropyrazolo[4,3-c]pyridine -5-carboxylate (350.00 mg, crude) was obtained as yellow oil. The crude product was used into next step directly without further purification. LCMS: 254 [M+1].

Step 2: Preparation of Compound 3

To a mixture of tert-butyl 3-(hydroxymethyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (350.00 mg, 1.38 mmol, 1.00 *eq*) in dioxane (5.00 mL) was added HCl/dioxane (3.00 mL) in one portion, the reaction mixture was stirred at 20 °C for one hour, solid was precipitate out. TLC (Petroleum ether : Ethyl acetate=0:1) showed the reaction was completed. The solution was concentrated on a water bath under reduced pressure using a

rotary evaporator. 4,5,6,7- tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-ylmethanol (165.00 mg, crude) was obtained as yellow solid. The crude product was used into next step directly without further purification.

Preparation of Compound 040

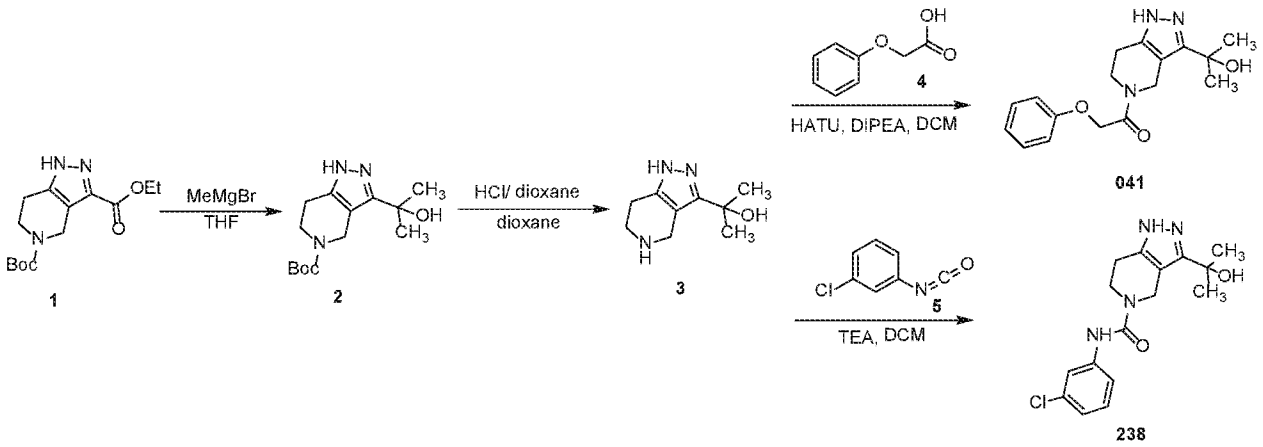
To a mixture of 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-ylmethanol (100.00 mg, 527.31 umol, 1.00 *eq*) and HATU (201.60 mg, 530.19 umol, 1.00 *eq*) in DCM (5.00 mL) was added DIPEA (102.78 mg, 795.29 umol, 1.50 *eq*) and 2- phenoxyacetic acid (80.23 mg, 527.31 umol, 1.00 *eq*) in one portion, the mixture was stirred at 20 °C for one hour. The desired compound was detected by LCMS. The mixture was extracted with DCM (10 mL*3) and water (10 mL), the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by pre-HPLC(FA) to afford Compound 040 (40.00 mg, 139.22 umol, 26.26% yield) as yellow oil. LCMS: 288 [M+1].

Preparation of Compound 239

To a solution of 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-ylmethanol (85.00 mg, 448.22 umol, 1.00 *eq*, HCl) in DCM (5.00 mL) was added TEA (136.07 mg, 1.34 mmol, 3.00 *eq*) at 0 °C, followed by 1-chloro-3-isocyanato-benzene (75.72 mg, 493.04 umol, 1.10 *eq*) , the reaction mixture was stirred at 0 °C for 30 minutes. LCMS showed compound 3 was consumed completely and one main peak with desired MS was detected. The mixture was extracted with DCM (15 mL*3) and water (15 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by prep-HPLC(FA) to afford Compound 239 (41.00 mg, 127.24 umol, 28.39% yield, 95.2% purity) as white solid.

^{1}H NMR (400MHz, METHANOL-d_4) 7.52 - 7.53 (t, *J*=2.01 Hz, 1 H) 7.21 - 7.28 (m, 2 H) 6.99 - 7.01 (m, 1 H) 4.61 (s, 4 H) 3.79 - 3.82 (t, *J*=5.77 Hz, 2 H) 2.79 - 2.82 (t, *J*=5.71 Hz, 2 H). LCMS: 307 [M+1].

Example 2: Procedure for the Preparation of Compounds 041 and 238



Step 1: Preparation of Compound 2

Cooled the three-necked round bottom flask in an ice bath to 0 °C, MeMgBr (3 M, 2.82 mL, 5.00 *eq*) was added under N_2, then a solution of 5-tert-butyl 3-ethyl 1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (500.00 mg, 1.69 mmol, 1.00 *eq*) in THF (10.00 mL) was added dropwise under N_2, after addition the reaction mixture was warmed to 20 °C and stirred at 20 °C for 3 hours. LCMS showed starting material was consumed completely and one main peak with desired MS was detected. The reaction was quenched with aqueous solution of NH_4Cl (15 mL) and then extracted with EA (20 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Tert-butyl 3-(1-hydroxy-1-methyl-ethyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylae (350.00 mg, crude) was obtained as yellow oil. The crude product was used into next step directly without further purification. LCMS: 282 [M+1].

Step 2: Preparation of Compound 3

To a solution of tert-butyl 3-(1-hydroxy-1-methyl-ethyl)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (350.00 mg, 1.24 mmol, 1.00 *eq*) in dioxane (5.00 mL) was added HCl/dioxane (3.00 mL) in one portion, the reaction mixture was stirred at 20 °C for one hour, solid was precipitate out. TLC (Petroleum ether : Ethyl acetate=0:1) showed the reaction was completed. The mixture was evaporated on a water bath under reduced pressure using a rotary evaporator. 2-(4,5,6,7- tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-yl)propan-2-ol (200.00 mg, crude) was obtained as yellow solid. The crude product was used into next step directly without further purification.

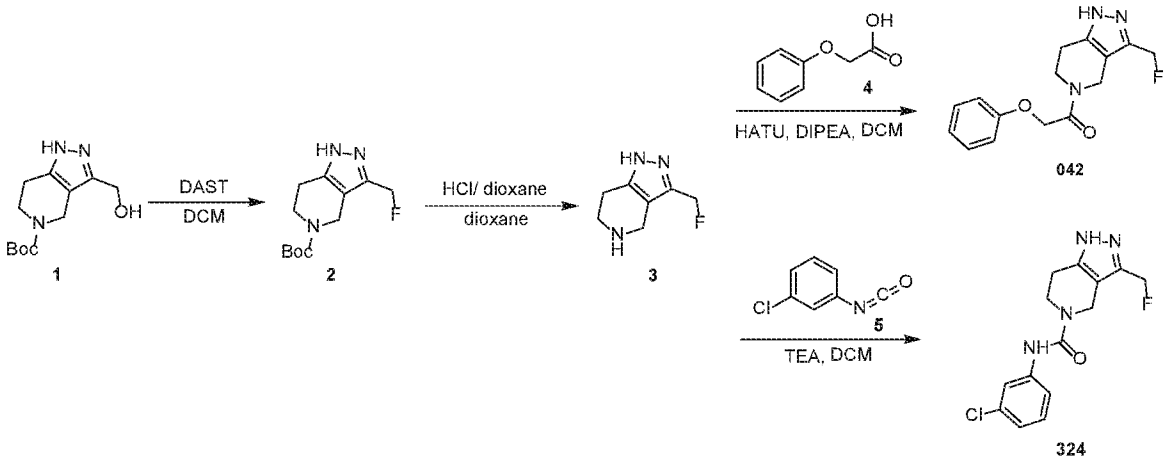
Preparation of Compound 041

To a mixture of 2-(4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-yl)propan-2-ol (100.00 mg, 551.79 umol, 1.00 *eq*) and HATU (314.71 mg, 827.68 umol, 1.50 *eq*) in DCM (5.00 mL) was added DIPEA (71.31 mg, 551.79 umol, 1.00 *eq*) and 2- phenoxyacetic acid (83.95 mg, 551.79 umol, 1.00 *eq*) in one portion, the reaction mixture was stirred at 20 °C for one hour. The desired product was detected by LCMS. The reaction mixture was extracted with DCM (15 mL*3) and water (15 mL), the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by prep-HPLC(FA) to afford Compound 041 (40.00 mg, 125.57 umol, 22.76% yield, 99% purity) as yellow oil. ^{1}H NMR (400MHz, METHANOL-d_4) 7.24 - 7.30 (m, 2 H) 6.94 - 6.99 (m, 3 H) 4.86 (s, 2 H) 4.73 (s, 2 H) 3.80 - 3.89 (m, 2 H) 2.72 - 2.83 (m, 2 H) 1.53 (s, 6 H). LCMS: 316 [M+1].

Preparation of Compound 238

To a solution of 2-(4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-yl)propan-2-ol (85.00 mg, 390.45 umol, 1.00 *eq*, HCl) in DCM (5.00 mL) was added TEA (118.53 mg, 1.17 mmol, 3.00 *eq*) at 0 °C, followed by 1-chloro-3-isocyanato-benzene (65.96mg, 429.49 umol, 1.10 *eq*) , the reaction mixture was stirred at 0 °C for 30 minutes. LCMS (EW1350-180-P1C) showed the desired compound was obtained. The mixture was extracted with DCM (15 mL*3) and water (15 mL), the organic phase was dried over with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by prep-HPLC(FA) to afford Compound 238(48.00 mg, 142.94 umol, 36.61% yield, 99.7% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d_4) 7.51 - 7.52 (t, *J*=2.01 Hz, 1 H) 7.23 - 7.28 (m, 2 H) 6.99 - 7.01 (m, 1 H) 4.68 (s, 2 H) 3.77 - 3.80 (t, *J*=5.84 Hz, 2 H) 2.77 - 2.80 (t, *J*=5.77 Hz, 2 H) 1.55 (s, 6 H). LCMS: 335 [M+1].

Example 3: Proccedure for the Preparation of Compound 042 and 324



Step 1: Preparation of Compound 2

To a solution of tert-butyl 3-(hydroxymethyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (200.00 mg, 789.58 umol, 1.00 *eq*) in DCM (5.00 mL) was added DAST (152.73 mg, 947.50 umol, 1.20 *eq*) dropwise at -78 °C, the reaction mixture was stirred at -78 °C for 5 hours. TLC (Ethyl acetate:Methanol=20:1) showed the starting material was consumed completely, The desired product was detected by LCMS. The reaction was quenched with saturated aqueous of $NaHCO_3$ (10 mL) and extracted with DCM (15 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compound tert-butyl 3-(fluoromethyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (180.00 mg, crude) was obtained as yellow oil. The crude product was used into next step directly without further purification. LCMS: 256 [M+1].

Step 2: Preparation of Compound 3

To a solution of tert-butyl 3-(fluoromethyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine -5-carboxylate (180.00 mg, 705.08 umol, 1.00 *eq*) in dioxane (5.00 mL) was added HCl/dioxane (3.00 mL) in one portion, the reaction mixture was stirred at 10 °C for one hour, solid was precipitate out. TLC (Ethyl acetate: Methanol=20:1) showed the reaction was completed. The solution was removed on a water bath under reduced pressure using a rotary evaporator. 3-(fluoromethyl)-4,5,6,7-tetrahydro -1H-pyrazolo[4,3-c]pyridine (120.00 mg, crude, HCl) was obtained as light yellow solid. The crude product was used into next step directly without further purification.

Preparation of Compound 042

To a mixture of 2-phenoxyacetic acid (63.52 mg, 417.47 umol, 1.00 *eq*) and HATU (158.74 mg, 417.47 umol, 1.00 *eq*) in DCM (5.00 mL) was added DIPEA (80.93 mg, 626.21

umol, 1.50 *eq*) and 3-(fluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3- c]pyridine (80.00 mg, 417.47 umol, 1.00 *eq*, HCl) in one portion, the reaction mixture was stirred at 10 °C for one hour. LCMS (EW1350-204-P1A) showed the desired compound was obtained. The mixture was extracted with DCM (15 mL*3) and water (15 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by pre-HPLC(FA) to afford Compound 042 (20.00 mg, 65.68 umol, 15.73% yield, 95% purity) as yellow solid.

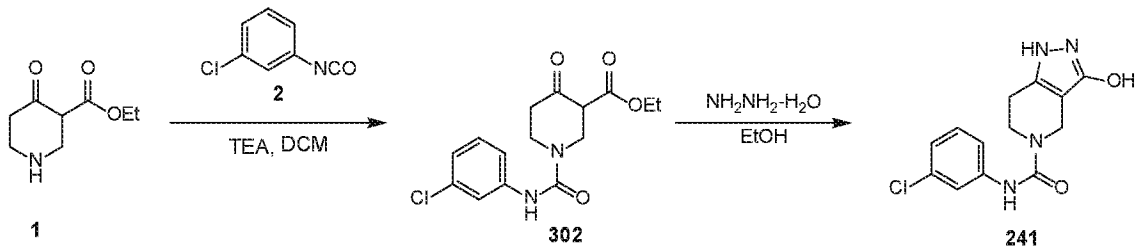
^{1}H NMR (400MHz, METHANOL-d_4) 7.24 - 7.30 (m, 2 H) 6.94 - 6.99 (m, 3 H) 5.29 - 5.43 (m, 2 H) 4.90 (br. s., 2 H) 4.66 - 4.68 (m, 2 H) 3.84 - 3.93 (m, 2 H) 2.75 - 2.88 (m, 2 H).

LCMS: 290 [M+1].

Preparation of Compound 324

To a smixture of 3-(fluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (40.00 mg, 208.74 umol, 1.00 *eq*, HCl) in DCM (5.00 mL) was added TEA (63.37 mg, 626.22 umol, 3.00 *eq*) at 0 °C, followed by 1-chloro-3-isocyanato-benzene (32.06 mg, 208.74 umol, 1.00 *eq*) , the reaction mixture was stirred at 0 °C for 30 minutes. The desired product was detected by LCMS. The mixture was extracted with DCM (15 mL*3) and water (15 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by pre-HPLC(FA) to afford Compound 324 (23.00 mg, 72.48 umol, 34.72% yield, 97.3% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d_4) 7.52 - 7.53 (t, *J*=2.01 Hz, 1 H) 7.21 - 7.29 (m, 2 H) 7.01 - 7.02 (m, 1 H) 5.31 - 5.43 (m, 2 H) 4.62 (s, 2 H) 3.81 - 3.84 (t, *J*=5.77 Hz, 2 H) 2.82 - 2.85 (t, *J*=5.71 Hz, 2 H). LCMS: 309 [M+1].

Example 4: Procedure for the Preparation of Compound 241



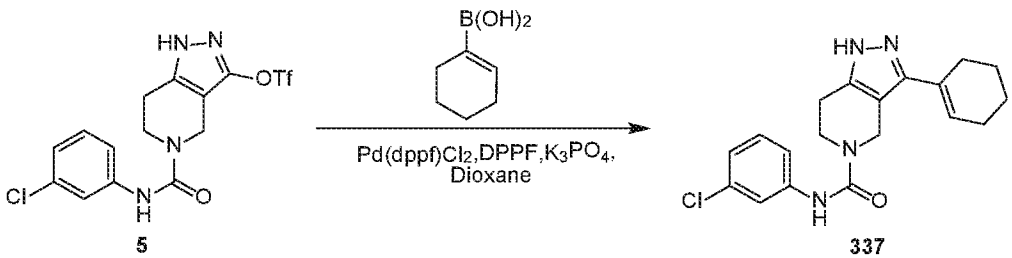
Step 1: Preparation of Compound 302

To a mixture of ethyl 4-oxopiperidine-3-carboxylate (10.00 g, 48.16 mmol, 1.00 *eq*, HCl) and TEA (19.49 g, 192.64 mmol, 4.00 *eq*) in DCM (150.00 mL) was added 1-chloro-3-isocyanato-benzene (7.40 g, 48.16 mmol, 1.00 *eq*) dropwise at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, then heated to 15 °C and stirred for 4 hours. TLC showed the reaction was completed. The mixture was poured into water (100 mL) and stirred for 5 min. The aqueous phase was extracted with DCM (100 mL*2). The combined organic phase was washed with saturated brine (50 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=4/1) to afford ethyl 1-[(3-chlorophenyl)carbamoyl]-4-oxo-piperidine-3-carboxylate(15.60 g, 47.31 mmol, 98.25% yield, 98.5% purity) as yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4) 7.44-7.60 (m, 1H), 7.17-7.35 (m, 2H), 6.95-7.08 (m, 1H), 4.28 (d, *J*=7.15 Hz, 1H), 4.18 (s, 2H), 3.90-4.03 (m, 1H), 3.68 (s, 2H), 2.56-2.64 (m, 1H), 2.40-2.51 (m, 1H), 1.29-1.38 (m, 2H), 1.21-1.28 (m, 1H). LCMS: 325 [M+1].

Step. 2: Preparation of Compound 241

To a mixture of ethyl 1-[(3-chlorophenyl)carbamoyl]-4-oxo-piperidine-3-carboxylate (2.00 g, 6.16 mmol, 1.00 *eq*) in EtOH (20.00 mL) was added N_2H_4-H_2O (501.10 mg, 8.01 mmol, 1.30 *eq*) in one portion under N_2. The mixture was stirred at 80 °C for 3 hours. LCMS showed the reaction was completed. The mixture was concentrated in vacuum to afford N-(3-chlorophenyl)-3-hydroxy-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxamide (1.78 g, 6.02 mmol, 97.78% yield, 99.05% purity) as white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) 7.49-7.60 (m, 1H), 7.20-7.33 (m, 2H), 6.99-7.04 (m, 1H), 4.35 (s, 2H), 3.78 (s, 2H), 2.65-2.76 (m, 2H). LCMS: 293 [M+1].

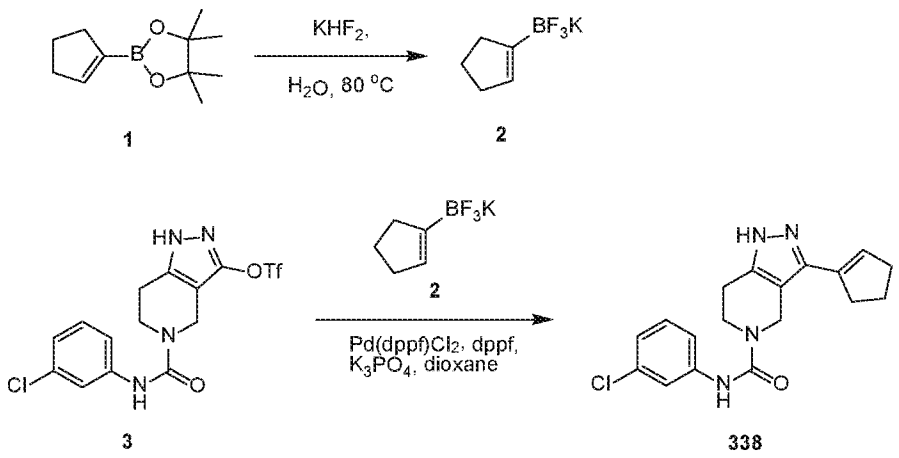
Example 5: Procedure for the Preparation of Compound 337



To a mixture of [5-[(3-chlorophenyl)carbamoyl]-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridin-3-yl] trifluoromethanesulfonate (400.00 mg, 941.66 umol, 1.00 *eq*) and cyclohexen-1-ylboronic acid (237.22 mg, 1.88 mmol, 2.00 *eq*) in dioxane (15.00 mL) was added

$Pd(dppf)Cl_2$ (68.90 mg, 94.17 umol, 0.10 *eq*), DPPF (52.20 mg, 94.17 umol, 0.10 *eq*) and K_3PO_4 (599.66 mg, 2.82 mmol, 3.00 *eq*) in one portion under N_2. The reaction vessel was sealed and heated in microwave at 130 °C for 2 hr. LCMS showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford N-(3-chlorophenyl)-3-(cyclohexen-1-yl)-1,4,6,7-tetrahydro pyrazolo[4,3-c]pyridine-5-carboxamide (195.00 mg, 510.93 umol, 54.26% yield, 93.5% purity) as white solid. ^1H NMR (400 MHz, METHANOL-d_4) □7.52-7.56 (m, 1H), 7.22-7.35 (m, 2H), 7.00-7.06 (m, 1H), 6.04-6.10 (m, 1H), 4.64 (s, 3H), 3.79-3.89 (m, 2H), 2.82 (s, 2H), 2.39-2.49 (m, 2H), 2.23-2.33 (m, 2H), 1.66-1.87 (m, 4H). LCMS: 357 [M+1].

Example 6: Preparation of Compounds 338



Step 1: Preparation of Compound 2

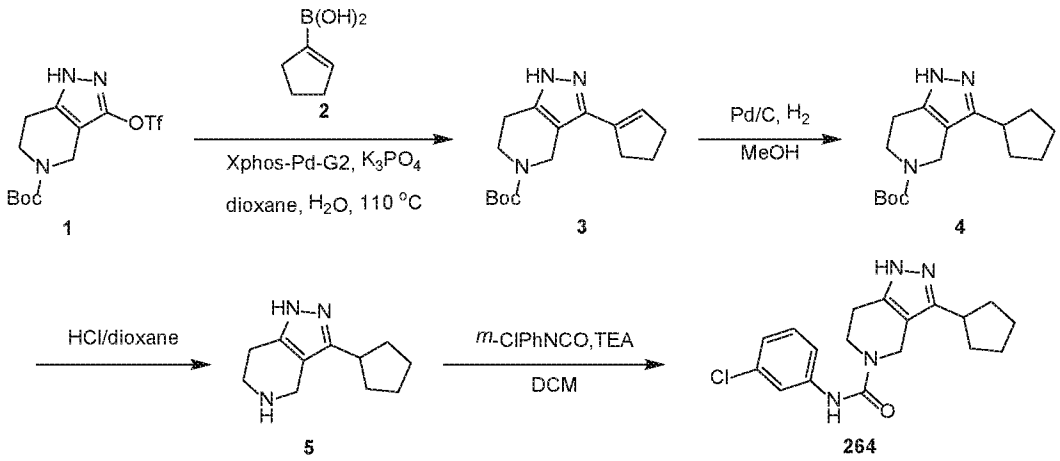
To a mixture of 2-(cyclopenten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200.00 mg, 1.03 mmol, 1.00 *eq*) in H_2O (5.00 mL) was added KHF_2 (241.45 mg, 3.09 mmol, 3.00 *eq*) in one portion under N_2. The reaction stirred at 20 °C for 13 h. TLC showed the reaction was completed. The mixture was concentrated in vacuum to afford potassium cyclopent-1-en-1-yltrifluoroborate (445.00 mg, crude) as yellow solid.

Step 2: Preparation of Compound 338

To a mixture of [5-[(3-chlorophenyl)carbamoyl]-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridin-3-yl] trifluoromethanesulfonate (50.00 mg, 117.71 umol, 1.00 *eq*) and potassium cyclopent-1-en-1-yltrifluoroborate (40.97 mg, 235.42 umol, 2.00 *eq*) in dioxane (3.00 mL) was added $Pd(dppf)Cl_2$ (8.61 mg, 11.77 umol, 0.10 *eq*), DPPF (6.53 mg, 11.77 umol, 0.10 *eq*)

and K_3PO_4 (74.96 mg, 353.12 umol, 3.00 *eq*) in one portion under N_2. The mixture was stirred at 145 °C for 1.5 hour. LCMS showed the starting material was consumed completely and the desired compound was detected. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2).The combined organic phase was washed with saturated brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford N-(3-chlorophenyl)-3-(cyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxamide (10.23 mg, 28.11 umol, 23.88% yield, 94.2% purity) as white solid. LCMS: 343 [M+1].

Example 7: Preparation of Compound 264



Step 1: Preparation of Compound 3

To a mixture of tert-butyl 3-(trifluoromethylsulfonyloxy)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (300.00 mg, 807.91 umol, 1.00 *eq*) and cyclopenten- 1-ylboronic acid (135.64 mg, 1.21 mmol, 1.50 *eq*) in dioxane (2.00 mL) and H_2O (200.00 uL) was added XPHOS-PD-G_2 (63.57 mg, 80.79 umol, 0.10 *eq*), K_3PO_4 (342.99 mg, 1.62 mmol, 2.00 *eq*) in one portion under N_2. The mixture was stirred at 110 °C for 10 hour. TLC (Ethyl acetate:Petroleum ether=2:1) showed the reaction was completed and the desired product was detected. The mixture was poured into water (20 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL*2). The combined organic phase was washed with brine (20 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=2/1) to afford tert-butyl 3-(cyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (Compound 3) (200.00 mg, 691.16 umol, 85.55% yield) as white solid.

Step 2: Preparation of Compound 4

To a solution of tert-butyl 3-(cyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (50.00 mg, 172.79 umol, 1.00 *eq*) in MeOH (5.00 mL) was added Pd/C (10%, 5 mg) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 12 hours. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filter was concentrated to give tert-butyl 3-cyclopentyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (Compound 4) (44.00 mg, 151.00 umol, 87.39% yield) as yellow solid. LCMS: 292 [M+1].

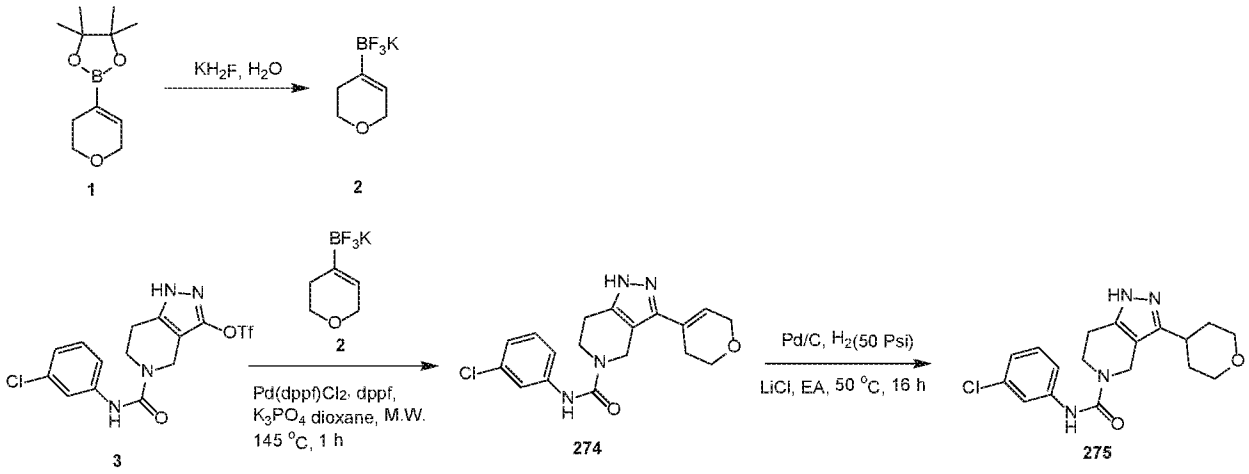
Step 3: Preparation of Compound 5

To a mixture of tert-butyl 3-cyclopentyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (44.00 mg, 151.00 umol, 1.00 *eq*) in dioxane (2.00 mL) was added HCl/dioxane (4 M, 4.00 mL, 105.96 *eq*) in one portion at 15 °C under N_2. The mixture was stirred at 15 °C for 2 hours. TLC (Ethyl acetate:Petroleum ether=2:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford 3-cyclopentyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (34.39 mg, 151.01 umol, 100.00% yield, HCl) as yellow solid.

Step 4: Preapration of Compound 264

To a mixture of 3-cyclopentyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (34.00 mg, 149.30 umol, 1.00 *eq*, HCl) and TEA (30.22 mg, 298.60 umol, 2.00 *eq*) in DCM (3.00 mL) was added 1-chloro-3-isocyanato-benzene (22.93 mg, 149.30 umol, 1.00 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 15 °C for 0.5 hours. LCMS showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 1 min. The aqueous phase was extracted with DCM (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford N-(3-chlorophenyl)-3-cyclopentyl-1,4,6,7-tetrahydro pyrazolo[4,3-c]pyridine-5-carboxamide (26.00 mg, 73.44 umol, 49.19% yield, 97.4% purity) as white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) □ 7.49-7.56 (m, 1H), 7.27-7.33 (m, 1H), 7.20-7.26 (m, 1H), 6.97-7.04 (m, 1H), 4.55 (s, 2H), 3.80 (s, 2H), 3.00-3.15 (m, 1H), 2.72-2.83 (m, 2H), 1.98-2.16 (m, 2H), 1.70 (br. s., 6H). LCMS: 345 [M+1].

Example 8: Preparation of Compounds 274 and 275



Step 1: Preaparation of Compound 2

To a solution of Compound 1 (400.00 mg, 1.90 mmol, 1.00 *eq*) in H_2O (4 mL) was added a solution of potassium fluoride hydrofluoride (446.12 mg, 5.71 mmol, 3.00 *eq*) in H_2O (4 mL) at 0 °C under N_2, and the mixture was stirred at 18 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to afford the desired product, Compound 2, (847.00 mg, crude) as yellow solid, which was used directly for the next step.

Preparation of Compound 274

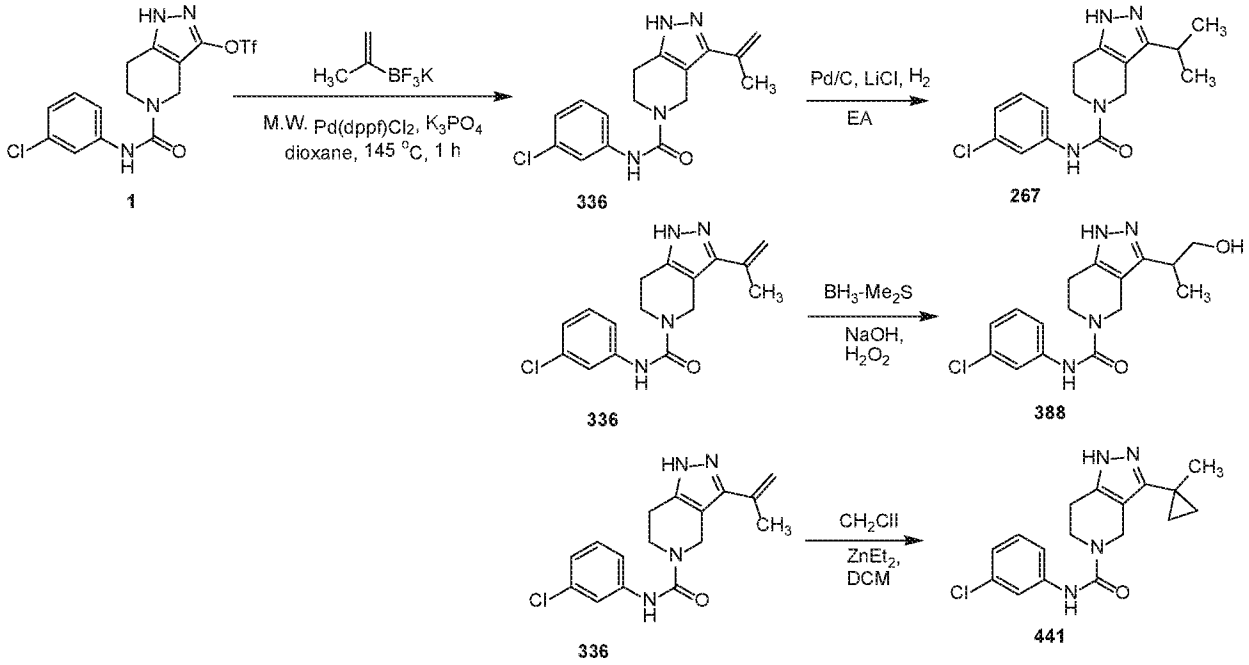
A mixture of Compound 3 (30.00 mg, 70.62 umol, 1.00 *eq*), Compound 2 (20.13 mg, 105.94 umol, 1.50 *eq*), K_3PO_4 (29.98 mg, 141.25 umol, 2.00 *eq*), DPPF (3.92 mg, 7.06 umol, 0.10 *eq*), KBr (840.38 ug, 7.06 umol, 0.10 *eq*) and $Pd(dppf)Cl_2$ (2.58 mg, 3.53 umol, 0.05 *eq*) in dioxane (3.00 mL) was heated to 145 °C in microwave for 1 hr. The reaction mixture was diluted with brine (60 mL), and extracted with EA (80 mL). The organic layer was concentrated under reduced pressure to give a brown residue. The residue was purified by prep-HPLC (FA) to afford desire product (10.00 mg, 27.20 umol, 38.52% yield, 97.6% purity) as yellow solid. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.54 (t, J = 2.01 Hz, 1H), 7.30 - 7.35 (m, 1H), 7.21 - 7.28 (m, 1H), 7.04 (d, J = 0.88 Hz, 1H), 6.07 (s, 1H), 4.66 (s, 2H), 4.35 (q, J = 2.64 Hz, 2H), 3.93 (t, J = 5.52 Hz, 2H), 3.84 (t, J = 5.77 Hz, 2H), 2.84 (s, 2H), 2.56 (d, J = 1.76 Hz, 2H). LCMS: 359/361 [M+1].

Preparation of Compound 275

A mixture of Compound 274 (30.00 mg, 83.61 umol, 1.00 *eq*), LiCl (3.54 mg, 83.61 umol, 1.00 *eq*) and Pd/C (5.00 mg) in EA (8.00 mL) was heated to 50 °C under H_2 (50 Psi) for 16 hrs. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a yellow residue. The residue was purified by prep-HPLC (FA) to give impure

product. The impure product was purified by prep-TLC to afford desire product (5.00 mg, 13.59 umol, 16.26% yield, 98.1% purity) as yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.55 (s, 1H), 7.20 - 7.37 (m, 2H), 7.03 (d, *J* = 7.53 Hz, 1H), 4.61 (s, 2H), 4.05 (d, *J* = 11.17 Hz, 2H), 3.82 (t, *J* = 5.52 Hz, 2H), 3.57 (t, *J* = 11.48 Hz, 2H), 2.98 (s, 1H), 2.81 (t, *J* = 5.52 Hz, 2H), 1.80 - 1.94 (m, 4H). LCMS: 361/363 [M+1].

Example 9: Preparation of Compounds 267, 336, 388, and 441



Step 1: Preparation of Compound 336

A mixture of Compound 1 (100.00 mg, 235.42 umol, 1.00 *eq*), potassium trifluoro(prop-1-en-2-yl)borate (52.26 mg, 353.13 umol, 1.50 *eq*), K_3PO_4 (99.95 mg, 470.84 umol, 2.00 *eq*) and $Pd(dppf)Cl_2$ (17.23 mg, 23.54 umol, 0.10 *eq*) in dioxane (3.00 mL) was heated to 140 °C in microwave for 1 hr. The reaction mixture was diluted with brine (60 mL), and extracted with EA (80 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue. The residue was purified by prep-HPLC (FA) to afford desire product (14.00 mg, 43.63 umol, 18.53% yield, 98.73% purity) as yellow solid. LCMS: 317/319 [M+1]. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.34 - 12.75 (m, 1H), 8.85 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* =8.16 Hz, 1H), 7.26 (t, *J* = 8.09 Hz, 1H), 6.99 (d, *J* = 9.16 Hz, 1H), 5.17 (s, 2H), 4.57 (s, 2H), 3.73 (t, *J* = 5.52 Hz, 2H), 2.71 (s, 2H), 2.09 (s, 3H).

Preparation of Compound 267

A mixture of Compound 1 (40.00 mg, 126.27 umol, 1.00 *eq*), LiCl (5.35 mg, 126.27 umol, 1.00 *eq*) and Pd/C (5.00 mg) in EA (8.00 mL) was heated to 65 °C under H_2 (15 Psi) for 16 hrs. LCMS showed no reaction. The mixture was stirred at 50 °C under H_2 (50 Psi) for 16 hrs. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a yellow residue. The residue was purified by prep-HPLC (FA) to afford the desired product, Compound 267 (15.00 mg, 45.12 umol, 35.73% yield, 95.90% purity) as white solid. LCMS: 319/321 [M+1].

^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.55 (t, *J* = 1.94 Hz, 1H), 7.21 - 7.37 (m, 2H), 7.04 (d, *J* = 8.66 Hz, 1H), 4.62 (s, 2H), 3.85 (t, *J* = 5.96 Hz, 2H), 3.04 - 3.17 (m, 1H), 2.86 (s, 2H), 1.35 (d, *J* = 7.03 Hz, 6H).

Preparation of Compound 388

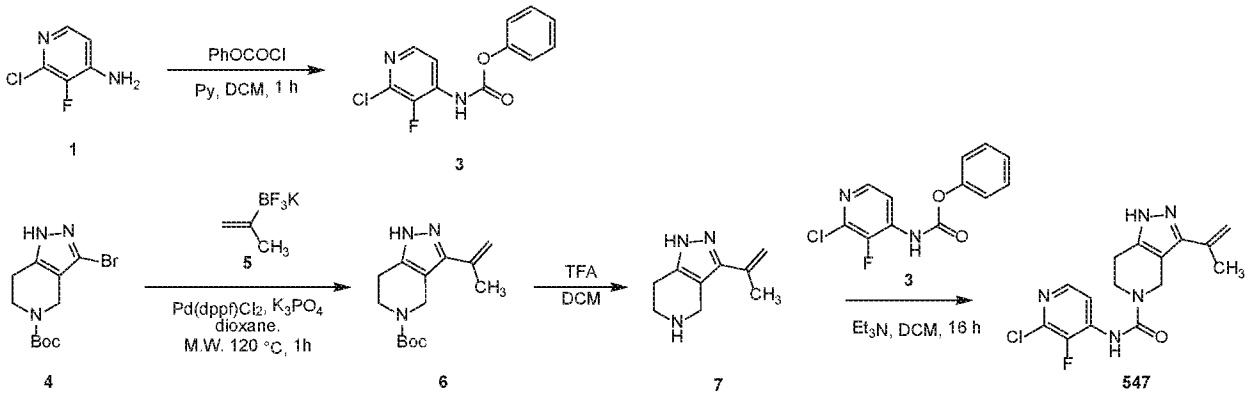
To a solution of Compound 1 (50.00 mg, 157.84 umol, 1.00 *eq*) in THF (3.00 mL) was added BH_3-Me_2S (10 M, 63.14 uL, 4.00 *eq*) at 0 °C under N_2, and the mixture was stirred at 15 °C for 16 hrs. A solution of NaOH (25.25 mg, 631.36 umol, 4.00 *eq*) in H_2O (1.00 mL) and H_2O_2 (81.34 mg, 789.20 umol, 5.00 *eq*) was added into the mixture at 0 °C, and the reaction mixture was stirred at 15 °C for another 2 hrs. The reaction mixture was diluted with Na_2SO_3 (Saturated, 60 mL), and extracted with EA (80 mL). The organic layer was concentrated under reduced pressure to give a yellow residue. The residue was purified by Prep-HPLC(FA) to afford N-(3-chlorophenyl)-3-(2-hydroxy-1-methyl-ethyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (15.00 mg, 43.28 umol, 27.42% yield, 96.6% purity) as white solid. LCMS: 335/337 [M+1]. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.54 (t, *J* = 1.88 Hz, 1H), 7.29 - 7.35 (m, 1H), 7.21 - 7.28 (m, 1H), 7.02 (d, *J* = 7.91 Hz, 1H), 4.60 (d, *J* = 2.64 Hz, 2H), 3.62 - 3.92 (m, 4H), 2.98 - 3.11 (m, 1H), 2.81 (s, 2H), 1.32 (d, *J* = 7.15 Hz, 3H).

Preparation of Compound 441

To a solution of Compound 1 (35.00 mg, 110.49 umol, 1.00 *eq*) in DCM (4.00 mL) was added $ZnEt_2$ (1 M, 552.43 uL, 5.00 *eq*) at 0 °C under N_2, followed by chloro(iodo)methane (116.93 mg, 662.92 umol, 6.00 *eq*) after 0.5 h, and the mixture was stirred at 18 °C for 16 hrs. The mixture was quenched with HCl (2M) to pH = 6 and extracted with EA (60 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give yellow residue. The residue was purified with EW645-416-P1 by prep-HPLC (FA) to afford desired product, Compound 441, (9.00 mg, 26.77 umol, 24.23% yield, 98.4% purity) as yellow solid. LCMS: 331/333 [M+1]. ^{1}H NMR

(400 MHz, METHANOL-d_4) δ = 7.55 (s, 1H), 7.29 - 7.35 (m, 1H), 7.22 - 7.29 (m, 1H), 7.03 (d, *J* = 7.65 Hz, 1H), 4.62 (s, 2H), 3.81 (t, *J* = 5.65 Hz, 2H), 2.79 (t, *J* = 5.52 Hz, 2H), 1.40 (s, 3H), 0.93 (s, 2H), 0.73 (s, 2H).

Example 10: Preparation of Compound 547



Step 1: Preparation of Compound 3

To a solution of 2-chloro-3-fluoro-pyridin-4-amine (100.00 mg, 682.36 umol, 1.00 *eq*) and pyridine (161.92 mg, 2.05 mmol, 3.00 *eq*) in DCM (5.00 mL) was added phenyl carbonochloridate (160.26 mg, 1.02 mmol, 1.50 *eq*) at 0 °C under N_2, and the mixture was stirred at 18 °C for 0.5 hr. The reaction mixture was diluted with DCM (50 mL) and washed with brine (40 mL, three times). The organic layer was concentrated under reduced pressure to afford desired product, Compound 3, (180.00 mg, crude) as yellow oil, which was used directly for the next step.

Step 2: Preparation of Compound 6

A mixture of Compound 4 (1.00 g, 3.31 mmol, 1.00 *eq*), Compound 5 (734.59 mg, 4.97 mmol, 1.50 *eq*), K_3PO_4 (1.41 g, 6.62 mmol, 2.00 *eq*) and $Pd(dppf)Cl_2$ (121.10 mg, 165.50 umol, 0.05 *eq*) in dioxane (20.00 mL) was heated to 120 °C in microwave for 1 hr. The reaction mixture was diluted with brine (80 mL) and extracted with EA (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue. The residue was purified by silicagel column to afford desire product (580.00 mg, 2.20 mmol, 66.47% yield) as yellow solid. LCMS: 264 [M+1].

Step 3: Preparation of Compound 7

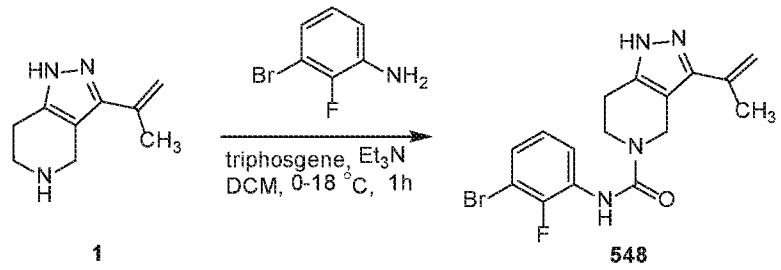
To a solution of Compound 6 (315.00 mg, 1.20 mmol, 1.00 *eq*) in DCM (1.00 mL) was added TFA (1.53 g, 13.42 mmol, 11.18 *eq*) under N_2, and the mixture was stirred at 18 °C under N_2 for 1 hr. The reaction mixture was concentrated under reduced pressure to afford

3-isopropenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (330.00 mg, 1.19 mmol, 99.19% yield, TFA) as yellow oil, which was used directly for the next step.

Step 4: Preparation of Compound 547

To a solution of 3-isopropenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (55.09 mg, 337.50 umol, 2.00 *eq*) and Et_3N (68.30 mg, 675.00 umol, 4.00 *eq*) in DCM (4.00 mL) was added phenyl N-(2-chloro-3-fluoro-4-pyridyl)carbamate (45.00 mg, 168.75 umol, 1.00 *eq*), and the mixture was stirred at 18 °C for 16 hrs. The reaction mixture was diluted with brine (40 mL) and extracted with DCM (50 mL). The organic layer was concentrated under reduced pressure to give a yellow residue. The residue was purified by prep-HPLC (FA) to afford the desired product, Compound 547, (20.00 mg, 57.66 umol, 34.17% yield, 96.8% purity) as yellow solid. LCMS: 336/338 [M+1]. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.22 (s, 1H), 7.12 - 7.19 (m, 2H), 6.84 - 6.91 (m, 1H), 5.26 (s, 2H), 4.66 (s, 2H), 3.84 (t, *J* = 5.77 Hz, 2H), 2.84 (t, *J* = 5.71 Hz, 2H), 2.32 (s, 3H), 2.16 (s, 3H).

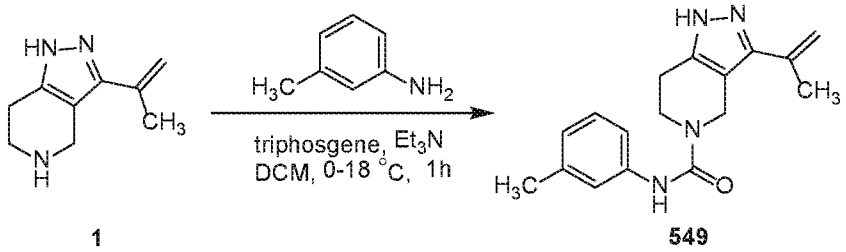
Example 11: Preparation of Compound 548



1 548

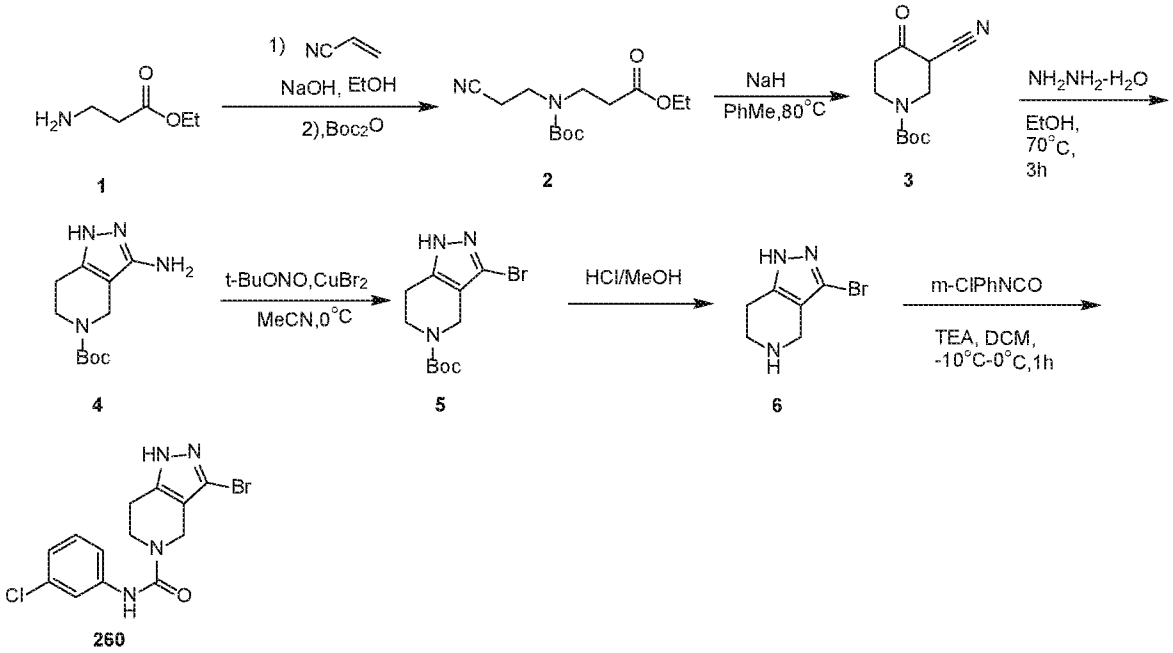
To a solution of 3-bromo-2-fluoro-aniline (25.00 mg, 131.57 umol, 1.00 *eq*) and Et_3N (66.57 mg, 657.85 umol, 5.00 *eq*) in DCM (4.00 mL) was added TRIPHOSGENE (19.52 mg, 65.79 umol, 0.50 *eq*) at 0 °C under N_2, and the mixture was stirred at 18 °C for 0.5 hr. A solution of Compound 1 (42.95 mg, 263.14 umol, 2.00 *eq*) and Et_3N (56.66 mg, 559.95 umol, 3.00 *eq*) in DCM (4.00 mL) was added, and the reaction mixture was stirred at 18 °C for 0.5 h. The reaction mixture was diluted with brine (40 mL) and extracted with DCM (50 mL). The organic layer was concentrated under reduced pressure to give a yellow residue. The residue was purified by prep-HPLC (FA) to afford desire product, Compound 548, (26.00 mg, 67.87 umol, 51.59% yield, 99.00% purity) as yellow solid. LCMS: 379/381 [M+1]. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.32 - 7.51 (m, 2H), 7.07 (dt, *J* = 1.32, 8.13 Hz, 1H), 5.25 (s, 2H), 4.68 (s, 2H), 3.86 (t, *J* = 5.83 Hz, 2H), 2.85 (t, *J* = 5.77 Hz, 2H), 2.16 (s, 3H).

Example 12: Preparation of Compound 549



To a solution of 3-methylaniline (20.00 mg, 186.65 umol, 1.00 *eq*) and Et_3N (94.44 mg, 933.25 umol, 5.00 *eq*) in DCM (4.00 mL) was added TRIPHOSGENE (27.69 mg, 93.33 umol, 0.50 *eq*) at 0 °C under N_2, and the mixture was stirred at 18 °C for 0.5 hr. A solution of 3-isopropenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (54.84 mg, 335.97 umol, 1.80 *eq*) and Et_3N (56.66 mg, 559.95 umol, 3.00 *eq*) in DCM (4.00 mL) was added, and the reaction mixture was stirred at 18 °C for 0.5 h. The reaction mixture was diluted with brine (40 mL), and extracted with DCM (50 mL). The organic layer was concentrated under reduced pressure to give a yellow residue. The residue was purified by prep-HPLC (FA) to afford 3-isopropenyl-N-(m-tolyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (23.00 mg, 76.29 umol, 40.87% yield, 98.30% purity) as yellow solid. LCMS: 297 [M+1]. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.22 (s, 1H), 7.12 - 7.19 (m, 2H), 6.84 - 6.91 (m, 1H), 5.26 (s, 2H), 4.66 (s, 2H), 3.84 (t, J = 5.77 Hz, 2H), 2.84 (t, J = 5.71 Hz, 2H), 2.32 (s, 3H), 2.16 (s, 3H).

Example 13: Preparation of Compounds 260



Step 1: Preparation of Compound 2

To a mixture of ethyl 3-aminopropanoate (50.00 g, 320.55 mmol, 1.00 eq, HCl salt) in MeOH (150.00 mL) was added NaOH (13 g, 320.55 mmol, 1.00 eq). The mixture was heated to 70°C. Acrylonitrile (21.8 g, 410.1 mmol, 1.26 eq) was added dropwise into the above mixture. And the mixture was stirred at 70°C for 4h. It was cooled 25°C, Boc_2O (6.39 g, 29.30 mmol, 0.90 eq) was added. Then the mixture was stirred at 25°C for 16h. TLC showed the reaction completed. The mixture was filtered, the filtrate was wahsed with water (500 mL), extracted with EtOAc (500 mL*3), the filtrate was dried over Na_2SO_4 and concentrated to give Compound 2A (6.70 g, 24.79 mmol, 76.15% yield), which was used directly. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ= 3.71 (s, 3H), 3.50-3.63 (m, 4H), 2.56-2.70 (m, 4H), 1.49 (s, 9H).

Step 2: Preparation of Compound 3

To a mixture of ethyl 3-[tert-butoxycarbonyl(2-cyanoethyl)amino]propanoate (70.00 g, 258.95 mmol, 1.00 eq) in PhMe (150.00 mL) was added NaH (10.46 g, 261.54 mmol, 1.01 eq) in three portions. The mixture was stirred at 110°C for 4h. TLC showed the reaction completed. The reaction was quenched with aqueous saturate NH_4Cl (200 mL), the aqueous was acidified with HCl (2N) to pH=6, then the mixture was extracted with EtOAc (150 mL*3),the organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give Compound 3 which was used directly. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ=4.40 (br. s., 1H), 4.16-4.26 (m, 1H), 3.58 (brs., 2H), 3.41 (d, *J*=7.28 Hz, 1H), 2.67 (d, *J*=14.31 Hz, 1H), 2.53 (dd, *J*=5.77, 9.54 Hz, 1H), 1.52 (s, 9H).

Step 3: Preparation of Compound 4

To a mixture of tert-butyl 3-cyano-4-oxo-piperidine-1-carboxylate (20.00 g, 89.18 mmol, 1.00 eq) in EtOH (200.00 mL) was added $NH_2NH_2.H_2O$ (8.93 g, 178.36 mmol, 2.00 eq) in one portion. The mixture was stirred at 80°C for 2 h. TLC showed the reaction worked well. The mixture was concentrated to give Compound 4 (19.70 g, 82.67 mmol, 92.70% yield).

Step 4: Preparation of Compound 5

To a suspension of Compound 4 (40.00 g, 0.47 mol, 1.00 eq) and $CuBr_2$ (44 g, 0.58 mol, 1.20 eq) in 500 mL of acetonitrile was added t-BuONO (20.2 g, 0.58 mol, 1.20 eq) dropwise at 0°C. The contents were allowed to stir at 50°C for 4 h. TLC showed the reaction completed. Then it was quenched with HCl (1M, 300 mL), extracted with EtOAc (200 mL*3), the organic layer was washed with brine (300 mL), dried over Na_2SO_4 and

concentrated to give Compound 5 (11.00 g, 36.40 mmol, 21.69% yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ= 4.33 (brs, 2H), 3.72 (brs, 2H), 2.83 (t, *J*=5.27 Hz, 2H), 1.50 (s, 9H).

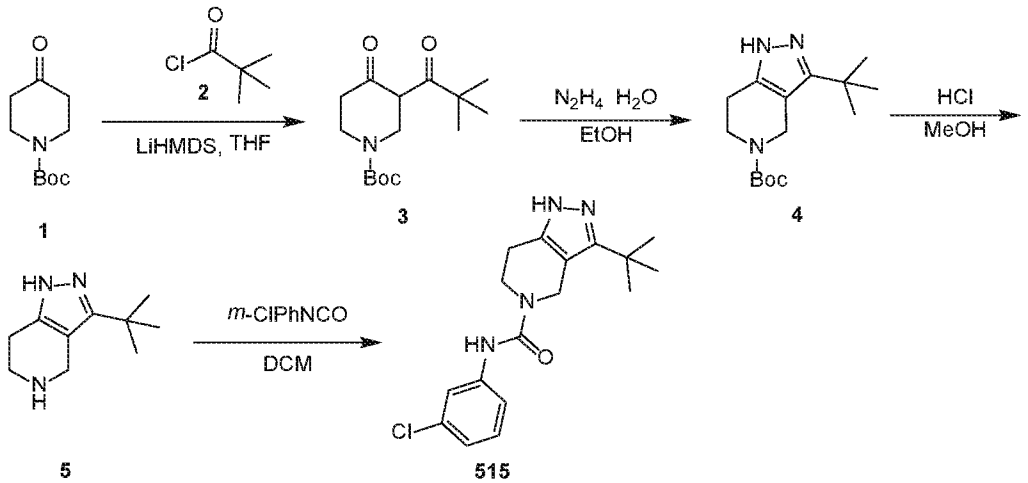
Step 5: Preparation of Compound 6

To a mixture of Compound 5 (11.00 g, 36.40 mmol, 1.00 eq) in DCM (10.00 mL)was added HCl/dioxane (4 M, 20.02 mL) in one portion at 0°C. The mixture was stirred at 0°C for 1 h. The mixture was concentrated to give Compound 5 (HCl).

Preparation of Compound 260

To a mixture of 3-bromo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (10.50 g, 38.19 mmol, 1.00 eq, 2HCl) in MeOH (350.00 mL) was added K_2CO_3 (13.20 g, 95.48 mmol, 2.50 eq). Then the mixture was filtered, the filtrate was used directly. And 1-chloro-3-isocyanato-benzene (5.86 g, 38.19 mmol, 1.00 eq) was added slowly into above filtrate at 25°C. The reaction was stirred at 25°C for 1h. LCMS showed the reaction worked well. The mixture was concentrated. The residue was rinsed with a mixed solution of PE/EA (10/1, 20 mL). The mixture was filtered and the cake was collected to give Compound 260 (11.00 g, 30.93 mmol, 80.99% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ= 12.95 (brs, 1H), 8.88 (s, 1H), 7.64 (s, 1H), 7.41 (d, *J*=8.03 Hz, 1H), 7.26 (t, *J*=8.16 Hz, 1H), 6.99 (d, *J*=7.78 Hz, 1H), 4.34 (s, 2H), 3.72 (brs, 2H), 2.72 (brs, 2H). LCMS: 355 [M+1].

Example 14: Preparation of Compound 515



Step 1: Preparation of Compound 3

To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (1.00 g, 5.02 mmol, 1.00 *eq*) in THF (15.00 mL) was added LiHMDS (1 M, 6.53 mL, 1.30 *eq*) portion-wise at -60 °C under N_2. The mixture was stirred at -60 °C for 30 min, 2,2-dimethylpropanoyl chloride (786.91 mg, 6.53 mmol, 1.30 *eq*) in THF (2.00 mL) was added dropwise at -60 °C. The

mixture was stirred at 10 °C for 2 hr. TLC showed the reaction was completed. The mixture was quenched by saturated NH_4Cl (20 mL) and extrated with EA (50 mL*2). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl 3-(2,2-dimethylpropanoyl)-4-oxo-piperidine-1-carboxylate (1.20 g, crude) as yellow oil.

Step 2: Preparation of Compound 4

To a solution of tert-butyl 3-(2,2-dimethylpropanoyl)-4-oxo-piperidine-1-carboxylate (1.20 g, 4.23 mmol, 1.00 *eq*) in EtOH (10.00 mL) was added $NH_2NH_2.H_2O$ (498.24 mg, 8.46 mmol, 2.00 *eq*) in one portion. The mixture was heated to 110 °C and stirred for 5 hours. LCMS showed the reaction was completed. The mixture was concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford tert-butyl-3-tert-butyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate(300.00 mg, 1.07 mmol, 25.39% yield) as white solid. 1H NMR (400MHz, CHLOROFORM-d) δ= 4.56 (brs, 2 H), 3.69 (brs, 2 H), 2.70 - 2.81 (m, 2 H), 1.50 (s, 10 H), 1.35 (s, 9 H).

Step 3: Preparation of Compound 5

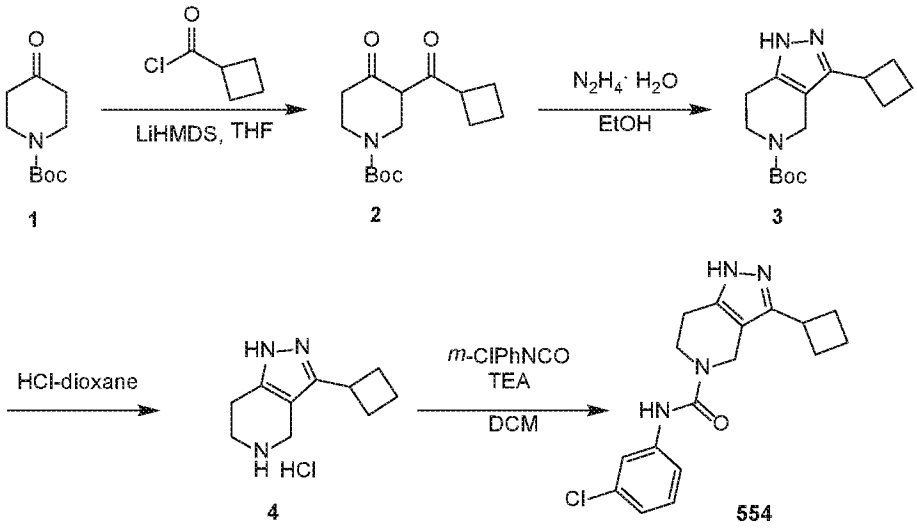
To a solution of tert-butyl 3-tert-butyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine -5-carboxylate (80.00 mg, 286.35 umol, 1.00 *eq*) in dioxane (3.00 mL) was added HCl/dioxane (4 M, 3.00 mL, 41.91 *eq*) in one portion. The mixture was stirred at 10 °C for 30 min. TLC showed the reaction was completed. The mixture was concentrated in vacumm to afford 3-tert-butyl-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine (65.00 mg, 257.75 umol, 90.01% yield, 2HCl) as white solid.

Step 4: Preparation of Compound 515

To a solution of 3-tert-butyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (65.00 mg, 257.75 umol, 1.00 *eq*, 2HCl) in DCM (10.00 mL) was added TEA (52.16 mg, 515.50 umol, 2.00 *eq*) followed by a solution of 1-chloro-3-isocyanato-benzene (39.58 mg, 257.75 umol, 1.00 *eq*) in DCM (1.00 mL) dropwise at -10 °C. The mixture was stirred at -10 °C for 20 min. LCMS showed the reaction was completed. The mixture was quenched with H_2O (10 mL) and extracted with DCM (20 mL*2). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by pre-HPLC (FA) to afford 3-tert-butyl-N-(3-chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (35.00 mg, 102.21 umol, 39.66% yield, 97.2% purity) as yellow solid.

1H NMR (400MHz, METHANOL-d4)δ= 7.54 (t, *J* = 2.0 Hz, 1 H), 7.34 - 7.30 (m, 1H), 7.22 - 7.28 (m, 1 H), 7.01 - 7.05 (m, 1 H), 4.69 (s, 2 H), 3.80 (t, *J* = 5.8 Hz, 2 H), 2.81 (t, *J* = 5.8 Hz, 2 H), 1.38 (s, 9 H).

Example 15: Preparation of Compound 554



Step 1: Preparation of Compound 2

To a solution of LiHMDS (1 M, 7.53 mL, 1.50 *eq*) was added dropwise tert-butyl 4-oxopiperidine-1-carboxylate (1.00 g, 5.02 mmol, 1.00 *eq*) in THF (4.00 mL) at -70 °C for 30 min, then cyclobutanecarbonyl chloride (892.76 mg, 7.53 mmol, 1.50 *eq*) in THF (4.00 mL) was added dropwise at -70 °C. The mixture was stirred at 16 °C for 3 hr. The reaction was quenched with sat. NH_4Cl (20 mL) and then extracted with EA (20 mL*2). The combined organic phase was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give tert-butyl 3-(cyclobutanecarbonyl)-4-oxo-piperidine-1-carboxylate (1.50 g, crude) as a yellow solid. LCMS: 182[M+1-100].

Step 2: Preparation of Compound 3

A solution of tert-butyl 3-(cyclobutanecarbonyl)-4-oxo-piperidine-1-carboxylate (7.50 g, 5.33 mmol, 1.00 *eq*), $N_2H_4.H_2O$ (320.18 mg, 6.40 mmol, 1.20 *eq*) in EtOH (10.00 mL) was heated to 80 °C for 3 hr. The solution was concentrated. The residue was purified by column chromatography (SiO_2, PE/EA=10/1 to 3/1) to give tert-butyl 3-cyclobutyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (700.00 mg, 1.51 mmol, 28.41% yield, 60% purity) as a light yellow solid. LCMS: 278[M+1].

Step 3: Preparation of Compound 4

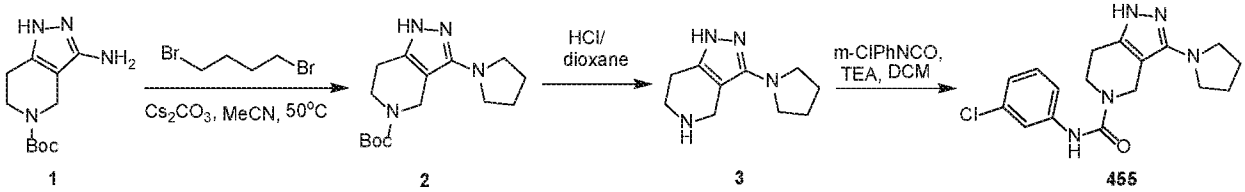
To a solution of tert-butyl 3-cyclobutyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (245.00 mg, 883.33 umol, 1.00 *eq*) in dioxane (3.00 mL) was added HCl/dioxane

(4 M, 3.00 mL, 13.58 *eq*), the solution was stirred at 16 °C for 2 hr. The reaction was concentrated to give 3-cyclobutyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine;hydrochloride (200.00 mg, crude) as a white solid. LCMS: 178[M+1].

Step 4: Preparation of Compound 554

To a solution of 3-cyclobutyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine hydrochloride (90.00 mg, 421.13 umol, 1.00 *eq*), TEA (127.84 mg, 1.26 mmol, 3.00 *eq*) in DCM (8.00 mL) was added dropwise 1-chloro-3-isocyanato-benzene (64.67 mg, 421.13 umol, 1.00 *eq*) in DCM (1mL) at -10 °C and stirred for 30 min. The solution was washed with water (10mL), the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (basic) to give N-(3-chlorophenyl)-3-cyclobutyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine -5-carboxamide (40.00 mg, 120.19 umol, 28.54% yield, 99.4% purity) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 7.52 (t, J = 2.01 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.21 - 7.26 (m, 1 H), 6.99 - 7.03 (m, 1 H), 4.55 (brs, 2 H), 3.79 (t, J = 5.77 Hz, 2 H), 3.58 (brs, 1 H), 2.78 (t, J = 5.65 Hz, 2 H), 2.24 - 2.40 (m, 4 H), 2.03 - 2.15 (m, 1 H), 1.93 (d, J = 7.03 Hz, 1 H). LCMS: 331[M+1].

Example 16: Preparation of Compound 455



Step 1: Preparation of Compound 2

To a mixture of tert-butyl 3-amino-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (150.00 mg, 629.49 umol, 1.00 *eq*) and 1,4-dibromobutane (135.91 mg, 629.49 umol, 1.00 *eq*) in MeCN (10.00 mL) was added Cs_2CO_3 (410.20 mg, 1.26 mmol, 2.00 *eq*). The mixture was stirred at 50 °C for 1 hr. TLC (Petroleum ether/Ethyl acetate=0/1) showed the starting material 1 was consumed completely, and a major new spot detected. The solvent was evaporated, the residue was washed with water (20 mL), extracted with Ethyl acetate (20 mL*2), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated. The residue was purified by chromatography (silica gel, eluting with Petroleum ether/Ethyl acetate=1/1 to 0/1) to afford tert-butyl-3-pyrrolidin-1-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (45.00 mg, 153.91 umol, 24.45% yield) as light yellow oil. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 4.46 (br. s., 2 H), 3.59 (brs, 2 H), 3.28 (t, *J* = 6.27 Hz, 4 H), 2.57 (br. s., 2 H), 1.87 (br. s., 4 H), 1.38 - 1.45 (m, 9 H). LCMS: 293 [M+1].

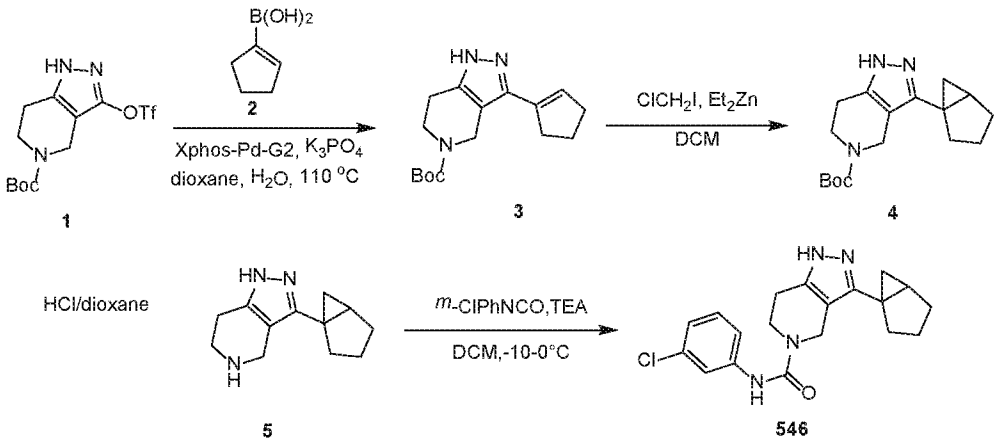
Step 2: Preparation of Compound 3

To a solution of tert-butyl 3-pyrrolidin-1-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine -5-carboxylate (45.00 mg, 153.91 umol, 1.00 *eq*) in dioxane (1.00 mL) was added HCl/dioxane (4 M, 3.00 mL, 77.97 *eq*). The mixture was stirred at 15 °C for 1 hr. Then white solid was formed, the solvent was evaporated to afford 3-pyrrolidin-1-yl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (38.00 mg, crude, HCl) as white solid, which was not purified and used directly in the next step.

Step 3: Preparation of Compound 455

To a solution of 3-pyrrolidin-1-yl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (38.00 mg, 166.14 umol, 1.00 *eq*, HCl) in DCM (3.00 mL) was added TEA (33.62 mg, 332.28 umol, 2.00 *eq*) and 1-chloro-3-isocyanato-benzene (25.51 mg, 166.14 umol, 1.00 *eq*). The mixture was stirred at 15 °C for 1 hr. LCMS showed the material 3 was consumed completely, and a main peak with desired MS detected. The solvent was evaporated, the residue was washed with water (10 mL), extracted with ethyl acetate (10 mL*3), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated to afford a residue. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-pyrrolidin-1-yl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxamide (23.94 mg, 60.77 umol, 36.58% yield, 99.47% purity, FA salt) as white solid. ^1H NMR (400 MHz, MeOD) δ 8.17 (brs, 1 H), 7.54 (brs, 1 H), 7.22 - 7.34 (m, 2 H), 7.03 (d, *J* = 7.53 Hz, 1 H), 4.66 (s, 2 H), 3.80 (t, *J* = 5.27 Hz, 2 H), 3.38 (brs, 4 H), 2.75 (brs, 2 H), 1.99 (brs, 4 H). LCMS: 346/348 [M+1].

Example 17: Preparation of Compound 546



Step 1: Preparation of Compound 3

To a mixture of tert-butyl 3-(trifluoromethylsulfonyloxy)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (300.00 mg, 807.91 umol, 1.00 *eq*) and cyclopenten-1-ylboronic acid (135.64 mg, 1.21 mmol, 1.50 *eq*) in dioxane (2.00 mL) and H_2O (200.00 uL) was added XPHOS-PD-G2 (63.57 mg, 80.79 umol, 0.10 *eq*), K_3PO_4 (342.99 mg, 1.62 mmol, 2.00 *eq*) in one portion under N_2. The mixture was stirred at 110 °C for 10 hour. TLC (Ethyl acetate:Petroleum ether=2:1) showed the reaction was completed and the desired product was detected. The mixture was poured into water (20 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL*2). The combined organic phase was washed with brine (20 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=2/1) to afford tert-butyl 3-(cyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (200.00 mg, 691.16 umol, 85.55% yield) as white solid. LCMS: 290 [M+1].

Step 2: Preparation of Compound 4

To a mixture of tert-butyl 3-(cyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (50.00 mg, 172.79 umol, 1.00 *eq*) in DCM (8.00 mL) was added diethylzinc (1 M, 863.95 uL, 5.00 *eq*) at 0°C under N_2. Then chloro(iodo)methane (182.86 mg, 1.04 mmol, 6.00 *eq*) was added to the mixture and stirred at 20 °C for 12 hours. LCMS showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with DCM (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford tert-butyl 3-(1-bicyclo[3.1.0] hexanyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (20.00 mg, 65.92 umol, 38.15% yield) as yellow solid. LCMS: 304 [M+1].

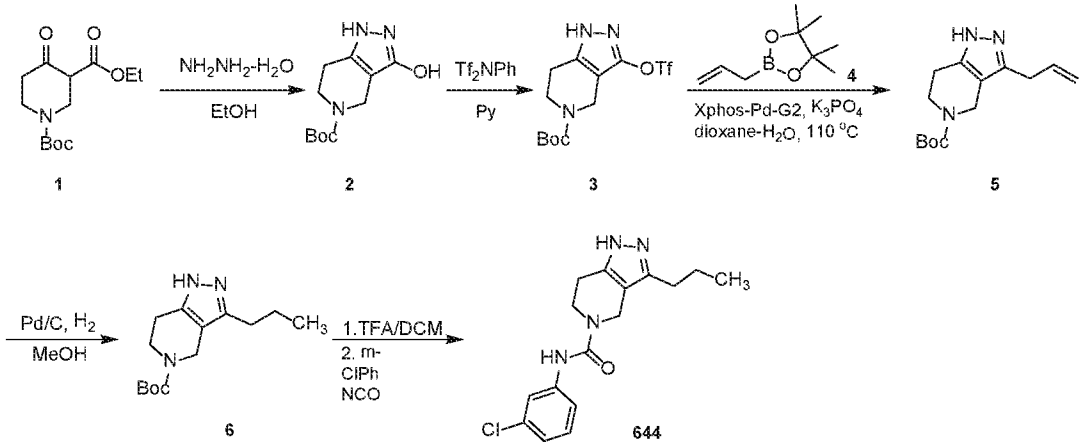
Step 3: Preparation of Compound 5

To a mixture of tert-butyl 3-(1-bicyclo[3.1.0]hexanyl)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (20.00 mg, 65.92 umol, 1.00 *eq*) in dioxane (1.00 mL) was added HCl/dioxane (4 M, 2.00 mL, 121.36 *eq*) in one portion under N_2. The mixture was stirred at 18 °C for 1 hour. TLC (Petroleum ether : Ethyl acetate=2:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford 3-(1-bicyclo[3.1.0]hexanyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (15.80 mg, 65.90 umol, 100.00% yield, HCl) as yellow solid.

Step 4: Preparation of Compound 546

To a mixture of 3-(1-bicyclo[3.1.0]hexanyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (15.80 mg, 65.90 umol, 1.00 *eq*, HCl) and TEA (20.01 mg, 197.70 umol, 3.00 *eq*) in DCM (2.00 mL) was added 1-chloro-3-isocyanato-benzene (9.11 mg, 59.31 umol, 0.90 *eq*) in one portion at 15 °C under N_2. The mixture was stirred at 15 °C for 30 min. LCMS showed the reaction was completed. The mixture was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with DCM (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford 3-(1-bicyclo[3.1.0]hexanyl)-N-(3- chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (10.00 mg, 26.90 umol, 40.82% yield, 96.0% purity) as white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) 7.50-7.54 (m, 1H), 7.27-7.32 (m, 1H), 7.20-7.26 (m, 1H), 6.98-7.04 (m, 1H), 4.57 (s, 2H), 3.78 (t, *J*=5.77 Hz, 2H), 2.77 (t, *J*=5.71 Hz, 2H), 2.05-2.13 (m, 1H), 1.90-2.03 (m, 2H), 1.65-1.87 (m, 3H), 1.28-1.43 (m, 1H), 0.79-0.88 (m, 2H). LCMS: 357 [M+1].

Example 18: Preparation of Compound 644



1 2 3 4 5 6 644

Step 1: Preparation of Compound 2

To a mixture of 1-tert-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (10.00 g, 36.86 mmol, 1.00 *eq*) in EtOH (130.00 mL) was added N_2H_4-H_2O (2.77 g, 44.23 mmol, 1.20 *eq*) in one portion under N_2. The reaction was stirred at 85 °C for 2 hr. TLC (Petroleum ether: ethyl acetate=1:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford tert-butyl 3-hydroxy-1,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (8.82 g, 36.86 mmol, 100.00% yield) as white solid. LCMS: 240 [M+1].

Step 2: Preparation of Compound 3

To a mixture of tert-butyl-3-hydroxy-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (8.82 g, 36.86 mmol, 1.00 *eq*) in Py (100.00 mL) was added 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide at 10 °C. The reaction mixture was stirred at 10 °C for 12 hours. The mixture was concentrated in vacuum. The residue was diluted with ethyl acetate (150 mL) and poured into 0.5N HCl (20 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (100 mL*2). The combined organic phase was washed with brine (100 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=5/1) to afford tert-butyl 3-(trifluoromethylsulfonyloxy)-1,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (9.16 g, 23.19 mmol, 62.91% yield, 94% purity) as yellow solid. LCMS: 372 [M+1].

Step 3: Preparation of Compound 5

To a mixture of tert-butyl 3-(trifluoromethylsulfonyloxy)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (900.00 mg, 2.42 mmol, 1.00 *eq*) and 2-allyl-4,4,5,5 -tetramethyl-1,3,2-dioxaborolane (610.92 mg, 3.64 mmol, 1.50 *eq*) in dioxane (1.00 mL)/H_2O (100.00 uL) was added XPHOS-PD-G2 (190.70 mg, 242.37 umol, 0.10 *eq*) under N_2, followed by K_3PO_4 (1.03 g, 4.85 mmol, 2.00 *eq*). The reaction mixture was stirred at 110 °C for 16 hours. The mixture was extracted with EA (10 mL*3) and water (5 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=10/1 to 1/1) to afford Compound ***5*** (400.00 mg, 1.52 mmol, 62.77% yield) was obtained as yellow oil.

Step 4: Preparation of Compound 6

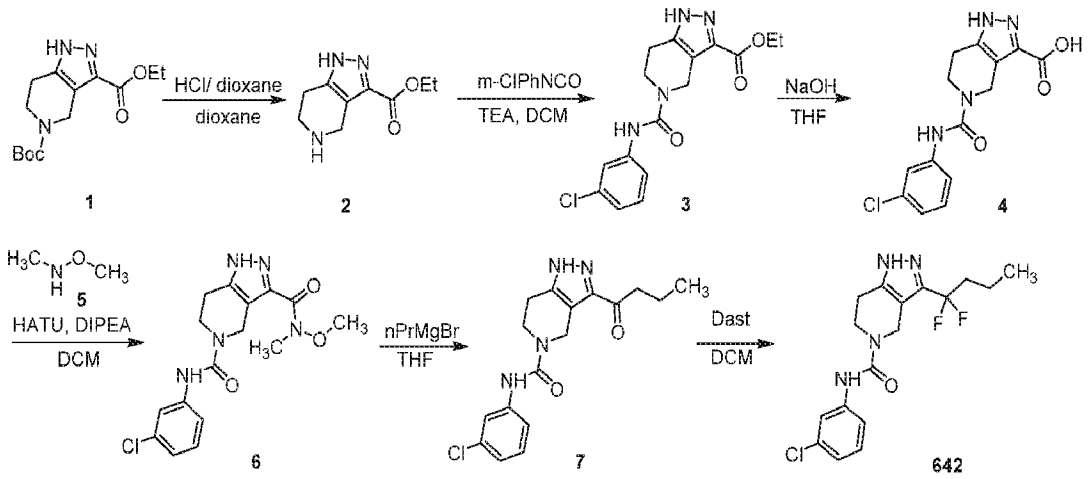
To a solution of tert-butyl-3-allyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (147.06 mg, 189.88 umol, 1.00 *eq*) in MeOH (20.00 mL) was added Pd/C (10%, 0.1 g) under N_2. The suspension was degassed under vacuum and purged with

H_2 several times. The mixture was stirred under H_2 (20 psi) at 15 °C for 16 hours. The mixture was filtrated. The filtrates was concentrated in vacumm to afford tert-butyl 3-propyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5- carboxylate (110.00 mg, crude) as colorless oil.

Preparation of Compound 644

Tert-butyl 3-propyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (80.00 mg, 301.49 umol, 1.00 *eq*) was dissolved in DCM (1.00 mL) and TFA (1.60 g, 14.03 mmol, 46.52 *eq*). The mixture was stirred at 10 °C for 0.5 hr. The mixture was concentrated in vacumm. The residue was dissolved in DCM (5.00 mL) and added TEA (122.03 mg, 1.21 mmol, 4.00 *eq*) followed by a solution of 1-chloro-3-isocyanato-benzene (46.30 mg, 301.49 umol, 1.00 *eq*) in DCM (300.00 uL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The mixture was extracted with DCM (10 mL*2) and H_2O (10 mL). The organic layer was concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-propyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (37.00 mg, 112.69 umol, 37.38% yield, 97.1% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.55 (t, *J* = 1.9 Hz, 1 H), 7.30 - 7.35 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 4.54 (s, 2 H), 3.82 (t, *J* = 5.8 Hz, 2 H), 2.80 (t, *J* = 5.8 Hz, 2 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 1.63 - 1.75 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H). LCMS: 319/321[M+1].

Example 19: Preparation of Compound 642



Step 1: Preparation of Compound 2

To a solution of 5-tert-butyl-3-ethyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-3,5-dicarboxylate (50.00 g, 169.30 mmol, 1.00 eq) in dioxane (200.00 mL) was added HCl/dioxane (4 M, 300.00 mL, 7.09 eq) at 15 °C. The reaction mixture was stirred at 15 °C for one hour. Precipitate formed. Evaporated the solution on a water bath under

reduced pressure using a rotary evaporator to afford ethyl 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (37.00 g, 159.70 mmol, 94.33% yield, HCl) as yellow solid. The crude product was used in next step directly without further purification.

Step 2: Preparation of Compound 3

To a mixture of ethyl 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine-3-carboxylate (37.00 g, 159.70 mmol, 1.00 *eq*, HCl) in DCM (300.00 mL) was added TEA (48.48 g, 479.11 mmol, 3.00 *eq*) at -10 °C, followed by 1-chloro-3-isocyanato-benzene (19.62 g, 127.76 mmol, 0.80 *eq*). The reaction mixture was stirred at -10 °C for another 30 minutes. TLC (Petroleum ether: Ethyl acetate=0:1) indicated 5% of compound 2 was remained, and one major new spot with lower polarity was detected. The mixture was extracted with DCM (800 mL*3) and water (300 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford ethyl-5-[(3-chlorophenyl)carbamoyl]- 1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylate (52.00 g, crude) as yellow solid. The crude product was used in next step directly without further purification.

Step 3: Preparation of Compound 4

To a solution of ethyl 5-[(3-chlorophenyl)carbamoyl]-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-3-carboxylate (30.00 g, 86.01 mmol, 1.00 *eq*) in THF (300.00 mL) was added a solution of NaOH (6.88 g, 172.02 mmol, 2.00 *eq*) in H_2O (60.00 mL) , the reaction mixture was warmed to 40 °C and stirred at 40 °C for 16 hours. TLC (Petroleum ether: Ethyl acetate=0:1) showed the reaction was completed. The pH of the reaction mixture was adjusted to around 5 by adding diluted hydrochloride acid (1 N), then extracted with EA (500 mL*4) and water (300 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford 5-[(3-chlorophenyl)carbamoyl]-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3-carboxylic acid (23.00 g, crude) as light yellow solid. The crude product was used in next step directly without further purification. ^{1}H NMR (400 MHz, METHANOL-d4) 11.48 (t, J =1.94 Hz, 1 H) 11.23 - 11.28 (m, 1 H) 11.14 - 11.21 (m, 1 H) 10.92 - 10.98 (m, 1 H) 8.71 (s, 2 H) 7.78 (t, J = 5.71 Hz, 2 H) 6.80 (t, J = 5.65 Hz, 2 H). LCMS: 321/323 [M+1].

Step 4: Preparation of Compound 6

To a mixture of 5-[(3-chlorophenyl)carbamoyl]-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-3-carboxylic acid (10.00 g, 31.18 mmol, 1.00 *eq*) and HATU (11.86 g, 31.18 mmol, 1.00 *eq*) in DMF (150.00 mL) was added DIPEA (6.04 g, 46.77 mmol, 1.50 *eq*), followed by N-methoxymethanamine (4.56 g, 46.77 mmol, 1.50 *eq*,

HCl), the reaction mixture was stirred at 15 °C for 16hours. TLC (Ethyl acetate: Methanol=20:1) indicated compound 4 was consumed completely, and one major new spot with lower polarity was detected. The mixture was extracted with EA (500 mL*3) and water (300 mL*3), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by silica gel chromatography (100-200 mesh silica gel, Ethyl acetate: Methanol = 100:1 to 20:1) to afford N^5-(3-chlorophenyl)-N^3-methoxy-N^3-methyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-3,5-dicarboxamide (8.00 g, 17.59 mmol, 56.42% yield, 80% purity) as yellow solid. ^{1}H NMR (400 MHz, METHANOL-d4) 11.48 (t, *J* = 1.94 Hz, 1 H) 11.23 - 11.28 (m, 1 H) 11.14 - 11.21 (m, 1 H) 10.92 - 10.98 (m, 1 H) 8.71 (s, 2 H) 7.78 (t, *J* = 5.71 Hz, 2 H) 6.80 (t, *J* = 5.65 Hz, 2 H). LCMS: 364/366 [M+1].

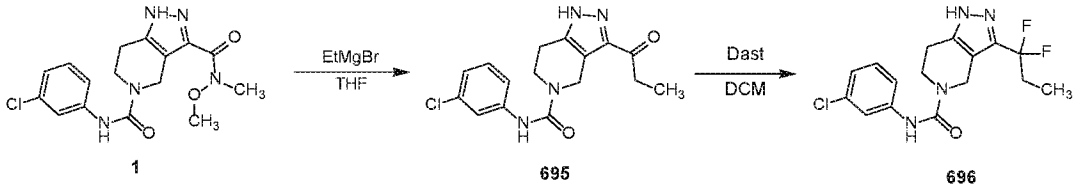
Step 5: Preparation of Compound 7

To a solution of N^5-(3-chlorophenyl)-N^3-methoxy-N^3-methyl-6,7-dihydro-1H- pyrazolo[4,3-c]pyridine-3,5(4H)-dicarboxamide (200.00 mg, 549.75 umol, 1.00 *eq*) in THF (5.00 mL) was added propylmagnesium bromide (1 M, 5.50 mL, 10.00 *eq*) at -10 °C. The reaction mixture was stirred at 10 °C for 3 hr. The mixture was added into saturated NH_4Cl (10 mL) and extracted with EA (10 mL*2). The combined organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by colunm chromatography (PE:EA=30%~60%) to afford 3-butanoyl-N-(3-chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (85.00 mg, 245.09 umol, 44.58% yield) as white solid.

Preparation of Compound 642

To a solution of 3-butanoyl-N-(3-chlorophenyl)-1,4,6,7-tetraHydropyrazolo [4,3-c] pyridine-5-carboxamide (40.00 mg, 115.34 umol, 1.00 *eq*) in DCM (4.00 mL) was added DAST (74.37 mg, 461.36 umol, 4.00 *eq*) at -10 °C. The mixture was stirred at 10 °C for 2 hr. The mixture was extracted with DCM (10 mL*2) and H_2O (10 mL). The combined organic layer was dried over Na_2SO_4, and filtrated and concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(1,1-difluorobutyl)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxamide (11.00 mg, 29.68 umol, 25.73% yield, 99.5% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ 7.54 (t, *J* = 1.9 Hz, 1 H), 7.29 - 7.33 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.03 (d, *J* = 7.9 Hz, 1 H), 4.65 (s, 2 H), 3.83 (t, *J* = 5.7 Hz, 2 H), 2.87 (t, *J* = 5.6 Hz, 2 H), 2.16 - 2.34 (m, 2 H), 1.54 (qd, *J* = 7.5, 15.4 Hz, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H). LCMS: 369/371 [M+1].

Example 20: Preparation of Compound 696



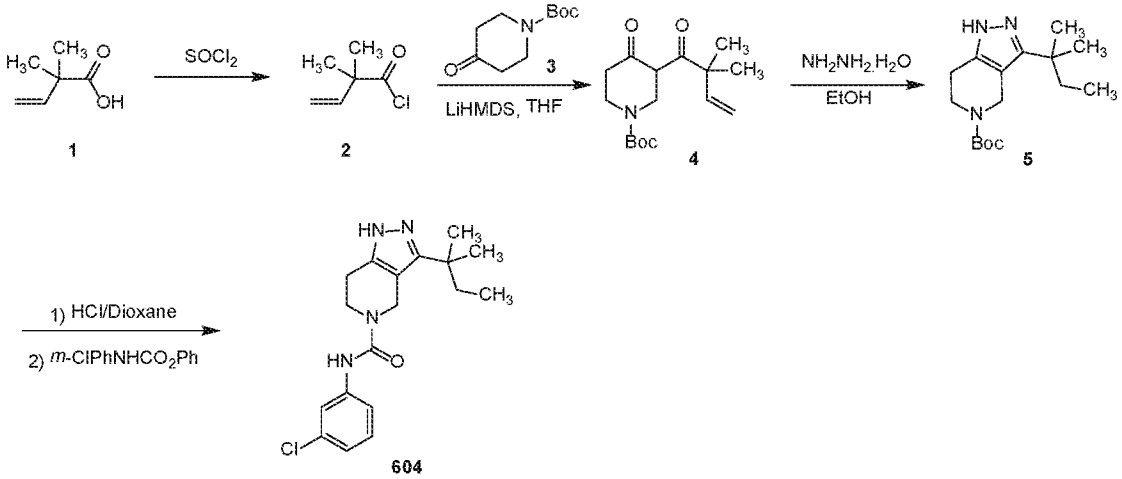
Preparation of Compound 695

To a solution of EtMgBr (1 M, 4.12 mL, 5.00 *eq*) was added a solution of N^5-(3-chlorophenyl)-N^3-methoxy-N^3-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxamide (300.00 mg, 824.63 umol, 1.00 *eq*) in THF (5.00 mL) at -10 °C. The mixture was stirred at 15 °C for 3 hr. TLC (PE:EA = 0:1) showed starting material was remained. EtMgBr (1 M, 4.12 mL, 5.00 *eq*) was added at -10 °C. The mixture was stirred at 15 °C for 2 hr. The mixture was quenched by saturated with NH_4Cl (10 mL) and extracted with EA (20 mL*2). The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacumm. The residue was purified by prep-TLC (PE:EA=0:1) to afford N-(3-chlorophenyl)- 3-propanoyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (100.00 mg, 287.88 umol, 34.91% yield, 95.8% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.54 (t, *J* = 1.9 Hz, 1 H), 7.29 - 7.33 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.02 (d, *J* = 7.9 Hz, 1 H), 4.76 (s, 2 H), 3.82 (t, *J* = 5.6 Hz, 2 H), 3.03 (q, *J* = 7.4 Hz, 2 H), 2.87 (t, *J* = 5.7 Hz, 2 H), 1.12 - 1.23 (m, 3 H). LCMS: 333/335[M+1].

Preparation of Compound 696

To a solution of N-(3-chlorophenyl)-3-propanoyl-1,4,6,7-tetrahydropyrazolo [4,3-c] pyridine-5-carboxamide (60.00 mg, 180.30 umol, 1.00 *eq*) in DCM (3.00 mL) was added DAST (145.31 mg, 901.50 umol, 119.11 uL, 5.00 *eq*) at -40 °C. The mixture was stirred at 15 °C for 2 hr. The mixture was extracted with DCM (10 mL*2). The organic layer was washed with saturated $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtrated, and concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(1,1-difluoropropyl)-1,4,6,7-tetra hydropyrazolo[4,3-c]pyridine-5-carboxamide (23.00 mg, 64.76 umol, 35.92% yield, 99.9% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ= 7.54 (t, *J* = 1.9 Hz, 1 H), 7.29 - 7.33 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.00 - 7.05 (m, 1 H), 4.66 (s, 2 H), 3.83 (t, *J* = 5.7 Hz, 2 H), 2.87 (t, *J* = 5.6 Hz, 2 H), 2.21 - 2.38 (m, 2 H), 1.06 (t, *J* = 7.5 Hz, 3 H). LCMS: 355/357[M+1].

Example 21. Preparation of Compound 604



Steps 1 and 2: Preparation of Compounds 2 and 4

2,2-dimethylbut-3-enoic acid (200.00 mg, 1.75 mmol, 1.00 *eq*) was dissolved in $SOCl_2$ (208.46 mg, 1.75 mmol, 127.11 uL, 1.00 *eq*) and heated to 8 °C for 1 hr. The mixture was concentrated in vacumm to get 2,2-dimethylbut-3-enoyl chloride (190.46 mg), compound 2.

A solution of tert-butyl 4-oxopiperidine-1-carboxylate (278.95 mg, 1.40 mmol, 0.80 *eq*) in THF (3.00 mL) was added into LiHMDS (1 M, 1.75 mL, 1.00 *eq*) dropwise at -70 °C under N_2. The mixture was stirred at -70 °C for 0.5 hr. A solution of 2,2-dimethylbut-3-enoyl chloride (190.46 mg, obtained above) in THF (2.00 mL) was added dropwise at -70 °C. The mixture was stirred at 15 °C for 16 hr. The mixture was quenched by NH_4Cl (10 mL) and extracted with EA (10 mL*2). The combined organic layer was dried over Na_2SO_4, filtrated. The filtrates was concentrated in vacumm to afford tert-butyl 3-(2,2-dimethylbut-3-enoyl)-4-oxo-piperidine-1-carboxylate (450.00 mg, crude) as brown oil.

Step 3: Preparation of Compound 5

To a solution of tert-butyl 3-(2,2-dimethylbut-3-enoyl)-4-oxo-piperidine-1-carboxylate (300.00 mg, 1.02 mmol, 1.00 *eq*) in EtOH (2.00 mL) was added $NH_2NH_2.H_2O$ (204.24 mg, 2.04 mmol, 198.29 uL, 50% purity, 2.00 *eq*). The mixture was heated to 90 °C for 2 hr. The mixture was concentrated. The residue was extracted with EA (10 mL*2) and H_2O (10 mL). The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by prep-HPLC (FA) to afford tert-butyl3-(1,1-dimethylpropyl)-1,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (10.00 mg, 34.08 umol, 3.34% yield) as colorless oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 4.52 (brs, H),

3.69 (brs, H), 2.76 (brs, 2 H), 1.64 (q, *J* = 7.4 Hz, 2 H), 1.45 - 1.53 (m, 16 H), 1.32 (s, 6 H), 0.80 (t, *J* = 7.5 Hz, 3 H).

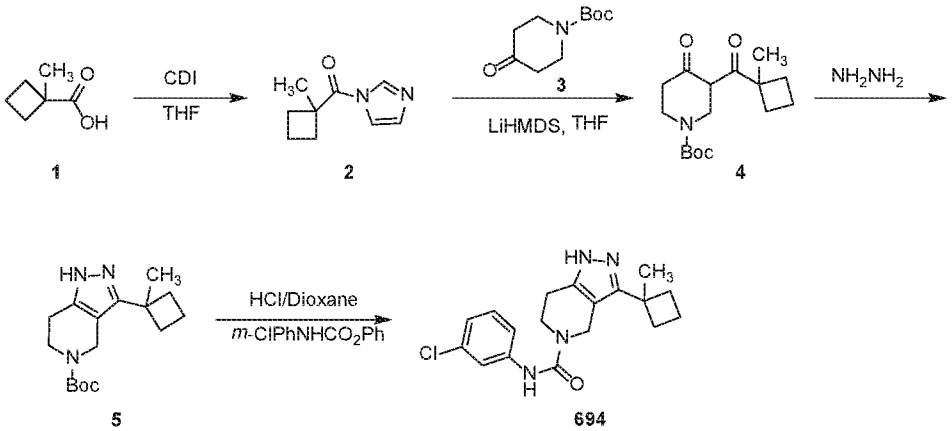
Preparation of Compound 604

Tert-butyl 3-(1,1-dimethylpropyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (10.00 mg, 34.08 umol, 1.00 *eq*) was dissolved in HCl/dioxane (4 M, 3.00 mL, 352.11 *eq*) and stirred at 15 °C for 1 hr. The mixture was concentrated and dissolved in DCM (5.00 mL) added phenyl N-(3-chlorophenyl)carbamate (8.44 mg, 34.08 umol, 1.00 *eq*) followed by TEA (17.24 mg, 170.40 umol, 23.62 uL, 5.00 *eq*). The mixture was stirred at 15 °C for 16 hr. LCMS showed the reaction was completed. The mixture was concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(1,1-dimethylpropyl)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxamide (4.80 mg, 12.90 umol, 37.85% yield, 93.2% purity).

^{1}H NMR (400MHz, METHANOL-d4) δ 7.53 (s, 1 H), 7.29 - 7.34 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.03 (d, *J* = 7.0 Hz, 1 H), 4.65 (s, 2 H), 3.80 (t, *J* = 5.8 Hz, 2 H), 2.82 (t, *J* = 5.7 Hz, 2 H), 1.70 (q, *J* = 7.4 Hz, 2 H), 1.35 (s, 6 H), 0.79 (t, *J* = 7.4 Hz, 3 H).

LCMS: 347/349[M+1].

Example 22. Preparation of Compound 694



Step 1: Preparation of Compound 2

To a solution of 1-methylcyclobutanecarboxylic acid (2.00 g, 17.52 mmol, 1.00 *eq*) in DCM (20.00 mL) was added CDI (3.12 g, 19.27 mmol, 1.10 *eq*) under N_2. The mixture was stirred at 15 °C for 1 hr. The mixture was extracted with EA (20 mL). The organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacumm. The residue was used in the next step directly to afford imidazol-1-yl-(1-methylcyclobutyl)methanone (2.60 g, 15.83 mmol, 90.38% yield) as brown oil.

Step 2: Preparation of Compound 4

To a solution of LiHMDS (1 M, 21.92 mL, 1.20 *eq*) in THF (10.00 mL) was added a solution of tert-butyl 4-oxopiperidine-1-carboxylate (2.55 g, 12.79 mmol, 0.70 *eq*) in THF (15.00 mL) under N_2 at -65 °C. The mixture was stirred at -65 °C for 0.5 hr. A solution of imidazol-1-yl-(1-methylcyclobutyl)methanone (3.00 g, 18.27 mmol, 1.00 *eq*) in THF (15.00 mL) was added at -65 °C dropwise. The solution was stirred at 15 °C for 16 hr. The mixture was quenched by saturated NH_4Cl (20 mL) and extracted with EA (20 mL*2). The combined organic layer was dried over Na_2SO_4 and concentrated to afford tert-butyl 3-(1-methylcyclobutanecarbonyl)-4- oxo-piperidine-1-carboxylate (759.10 mg, 2.57 mmol, 14.07% yield) as colorless oil.

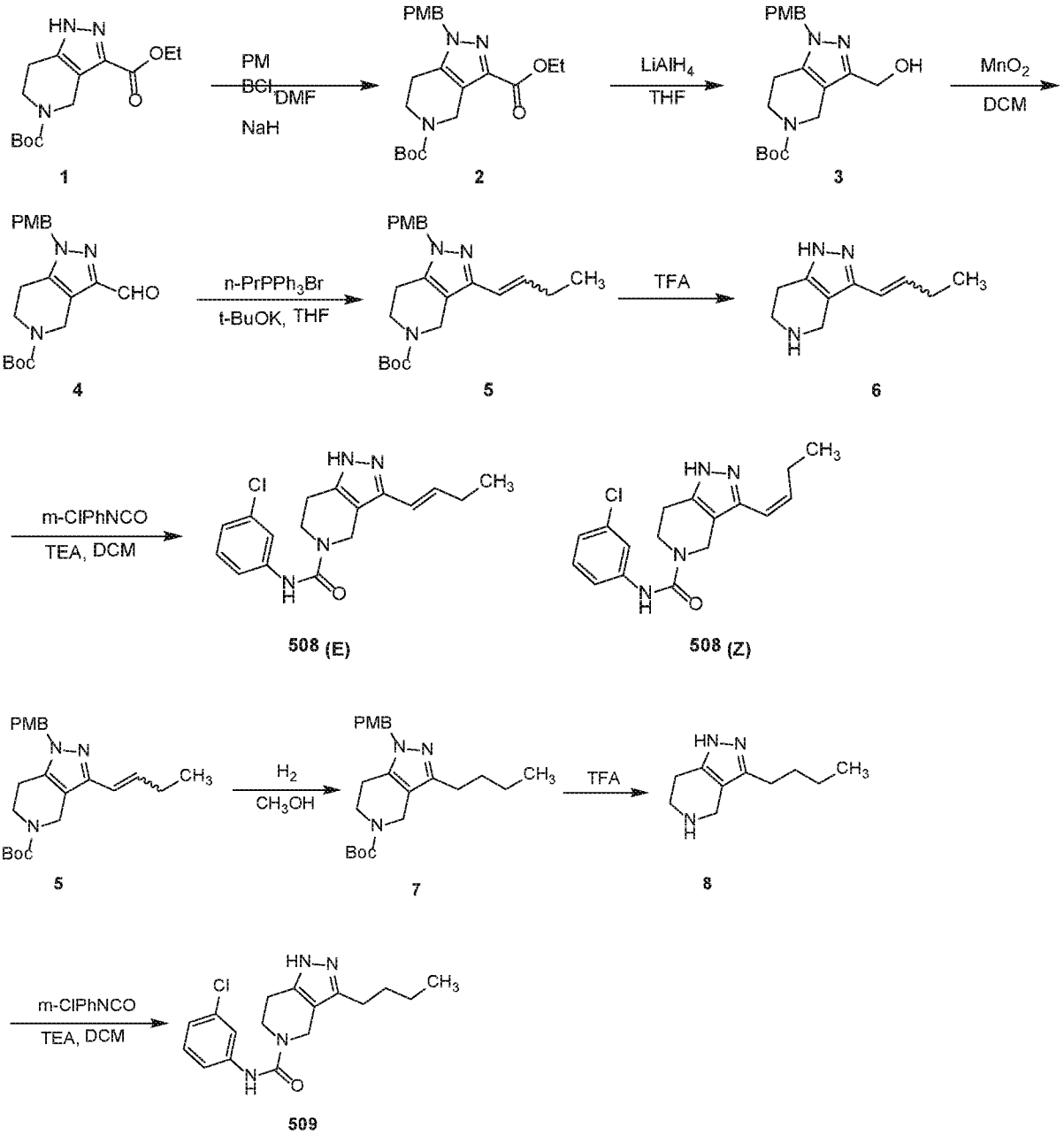
Step 3: Preparation of Compound 5

To a solution of tert-butyl-3-(1-methylcyclobutanecarbonyl)-4-oxo-piperidine-1- carboxylate (760.00 mg, 2.57 mmol, 1.00 *eq*) in EtOH (20.00 mL) was added NH_2NH_2-H_2O (515.23 mg, 5.15 mmol, 500.22 uL, 50% purity, 2.00 *eq*). The mixture was heated to 90 °C for 2 hr. The mixture was concentrated in vacumm. The residue was purified by flash chromatography (PE:EA=50%~100%) to afford tert-butyl 3-(1-methylcyclobutyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (500.00 mg, 1.72 mmol, 66.77% yield) as colorless oil.

Step 4: Preparation of Compound 694

Tert-butyl 3-(1-methylcyclobutyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (60.00 mg, 205.91 umol, 1.00 *eq*) was dissolved in HCl/Dioxane (4 M) and stirred at 15 °C for 1 hr. The mixture was concentrated in vacumm. The residue was dissolved in DCM (3.00 mL), then TEA (62.51 mg, 617.73 umol, 85.63 uL, 3.00 *eq*) and 1-chloro-3-isocyanato-benzene (31.62 mg, 205.91 umol, 24.90 uL, 1.00 *eq*) was added at -10 °C. The mixture was stirred at -10 °C for 30 min. The mixture was concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(1-methylcyclobutyl)-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxamide (42.00 mg, 115.71 umol, 56.19% yield, 95.0% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ 7.53 (t, *J* = 2.0 Hz, 1 H), 7.29 - 7.33 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.00 - 7.05 (m, 1 H), 4.57 (s, 2 H), 3.81 (t, *J* = 5.8 Hz, 2 H), 2.81 (t, *J* = 5.8 Hz, 2 H), 2.46 - 2.56 (m, 2 H), 2.04 - 2.23 (m, 3 H), 1.89 - 2.00 (m, 1 H), 1.52 (s, 3 H). LCMS: 345/347[M+1].

Example 23: Preparation of Compounds 508 (E and Z) and 0509



Step 1: Preparation of Compound 2

To a cooled the three-necked round bottom flask in an ice bath at 0 °C, was added NaH (880.40 mg, 22.01 mmol, 1.30 *eq*) under N_2, then a solution of 5-tert-butyl 3-ethyl 1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-3,5-dicarboxylate (5.00 g, 16.93 mmol, 1.00 *eq*) in DMF (70.00 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 30 minutes. PMBCl (2.92 g, 18.62 mmol, 1.10 *eq*) was added dropwise, the reaction mixture was warmed to 10 °C and stirred at 10 °C for another 16 hours. TLC showed starting material was consumed completed and two major new spots with lower polarity was detected. The reaction was added to water (60 mL) and then extracted with EA (100 mL*3), the

combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford 5-tert-butyl 3-ethyl-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (4.30 g, 7.24 mmol, 42.79% yield, 70% purity) as yellow oil. LCMS: 416 [M+1].

Step 2: Preparation of Compound 3

Cooled the three-necked round bottom flask to -50 °C, $LiAlH_4$ (511.50 mg, 13.48 mmol, 2.00 *eq*) was added under N_2, then a solution of 5-tert-butyl 3-ethyl 1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-3,5-dicarboxylate (4.00 g, 6.74 mmol, 1.00 *eq*) in THF (50.00 mL) was added dropwise, after addition the reaction mixture was warmed to 0 °C and stirred at 0 °C for 2 hours. TLC showed the reaction was completed, two major new spot with larger polarity was detected. The reaction mixture was quenched with water (5 mL) and filtered. The filtrate was washed with DCM (80 mL*3). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Tert-butyl 3-(hydroxymethyl)-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.30 g, crude) was obtained as yellow oil. The crude product was used in the next step directly without further purification. LCMS: 374 [M+1].

Step 3: Preparation of Compound 4

To a solution of tert-butyl-3-(hydroxymethyl)-1-[(4-methoxyphenyl) methyl]-6,7- dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.40 g, 3.75 mmol, 1.00 *eq*) in DCM (25.00 mL) was added MnO_2 (6.52 g, 75.00 mmol, 20.00 *eq*) in three portions. The reaction mixture was warmed to 60 °C and stirred at 60 °C for 16 hours. LCMS showed starting material was consumed completely and one main peak with desired MS was detected. The mixture was filtered to remove MnO_2. The filtrate was extracted with DCM (30 mL*3) and water (20 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford tert-butyl-3-formyl-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (750.00 mg, 2.02 mmol, 53.85% yield) as yellow oil.

LCMS: 372 [M+1].

Step 4: Preparation of Compound 5

To a mixture of triphenyl(propyl)phosphonium;bromide (1.24 g, 3.23 mmol, 4.00 *eq*) in THF (1.00 mL) was added t-BuOK (362.52 mg, 3.23 mmol, 4.00 *eq*) under N_2 at 0 °C, the reaction mixture was stirred at 0 °C for one hour, then a solution of tertbutyl-3-formyl-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridine-5-carboxylate (300.00 mg,

807.69 umol, 1.00 *eq*) in THF (2.00 mL) was added dropwise under N_2, the mixture was warmed to 10 °C and stirred at 10 °C for 16 hours. LCMS showed compound 4 was consumed completely and one main peak with desired MS was detected. The mixture was extracted with EtOAc (10 mL*3) and water (5 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford tert-butyl-3-[but-1-enyl]-1- [(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (200.00 mg, 503.13 umol, 62.29% yield) as yellow oil. LCMS: 398 [M+1].

Step 5: Preparation of Compound 6

Tert-butyl-3-[but-1-enyl]-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo [4,3- c]pyridine-5-carboxylate (50.00 mg, 125.78 umol, 1.00 *eq*) was dissolved in TFA (2.00 mL). The mixture was heated to 80 °C for 16 hours. LCMS showed the reaction was completed. The mixture was concentrated in vacuum to afford 3-[but-1-enyl]-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (20.00 mg, 112.83 umol, 89.71% yield) as brown oil. The residue was used in the next step directly. LCMS: 178 [M+1].

Preparation of Compound 508 (E and Z)

To a solution of 3-[but-1-enyl]-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (20.00 mg, 112.83 umol, 1.00 *eq*) in DCM (3.00 mL) was added TEA (34.25 mg, 338.49 umol, 3.00 *eq*) at 0 °C, followed by 1-chloro-3-isocyanato-benzene (17.33 mg, 112.83 umol, 1.00 *eq*), the reaction mixture was stirred at 0 °C for 30 minutes. LCMS showed compound 6 was consumed completely and one main peak with desired MS was detected. The mixture was extracted with DCM (10 mL*3) and water (5 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Purification by prep-HPLC (FA) gave both E-isomer and Z-isomer.

3-[(E)-but-1-enyl]-N-(3-chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (2.00 mg, 5.92 umol, 5.25% yield, 98.0% purity) was obtained as white solid. ^{1}H NMR (400 MHz, METHANOL-d4) 7.52 (brs, 1 H), 7.29 (brs, 1 H), 7.23 - 7.25 (d, 1 H), 7.00 - 7.02 (d, 1 H), 6.33 - 6.37 (m, J = 16 Hz, 1 H), 6.17 - 6.21 (m, 1 H), 4.61 (brs, 2 H), 3.81 (brs, 2 H), 2.79 (brs, 2 H), 2.27 (brs, 2 H), 1.12 (brs, 3 H). LCMS: 331/333 [M+1].

3-[(Z)-but-1-enyl]-N-(3-chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (16.00 mg, 47.83 umol, 42.39% yield, 98.9% purity) was obtained as white solid. ^{1}H NMR (400 MHz, METHANOL-d4) 7.52 (brs, 1 H), 7.28 - 7.30 (m, 1 H), 7.20 - 7.24 (m, 1 H), 6.99 - 7.00 (d, 1 H), 6.15 - 6.18 (d, J = 12 Hz, 1 H), 5.79 - 5.80 (d, 1 H), 4.49

(brs, 2 H), 3.81 (brs, 2 H), 2.81 (brs, 2 H), 2.32 (brs, 2 H), 1.03 - 1.05 (m, 3 H). LCMS: 331/333 [M+1].

Step 7: Preparation of Compound 7

To a solution of tert-butyl-3-[but-1-enyl]-1-[(4-methoxyphenyl) methyl]-6,7-dihydro -4H-pyrazolo[4,3-c]pyridine-5-carboxylate (50.00 mg, 125.78 umol, 1.00 *eq*) in CH_3OH (10.00 mL) was added Pd/C (10.00 mg) under N_2, the suspension was degassed under vacuum and purged with H_2 three times, the mixture was stirred under H_2 (15 psi) at 15 °C for 16 hours. LCMS showed starting material was consumed completely and one main peak with desired MS was detected. The reaction mixture was filtered and the filter was concentrated. Compound tert-butyl-3-butyl-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (45.00 mg, 112.63 umol, 89.54% yield) was obtained as yellow oil. The crude product was used in the next step directly without further purification. LCMS: 400 [M+1].

Step 8: Preparation of Compound 8

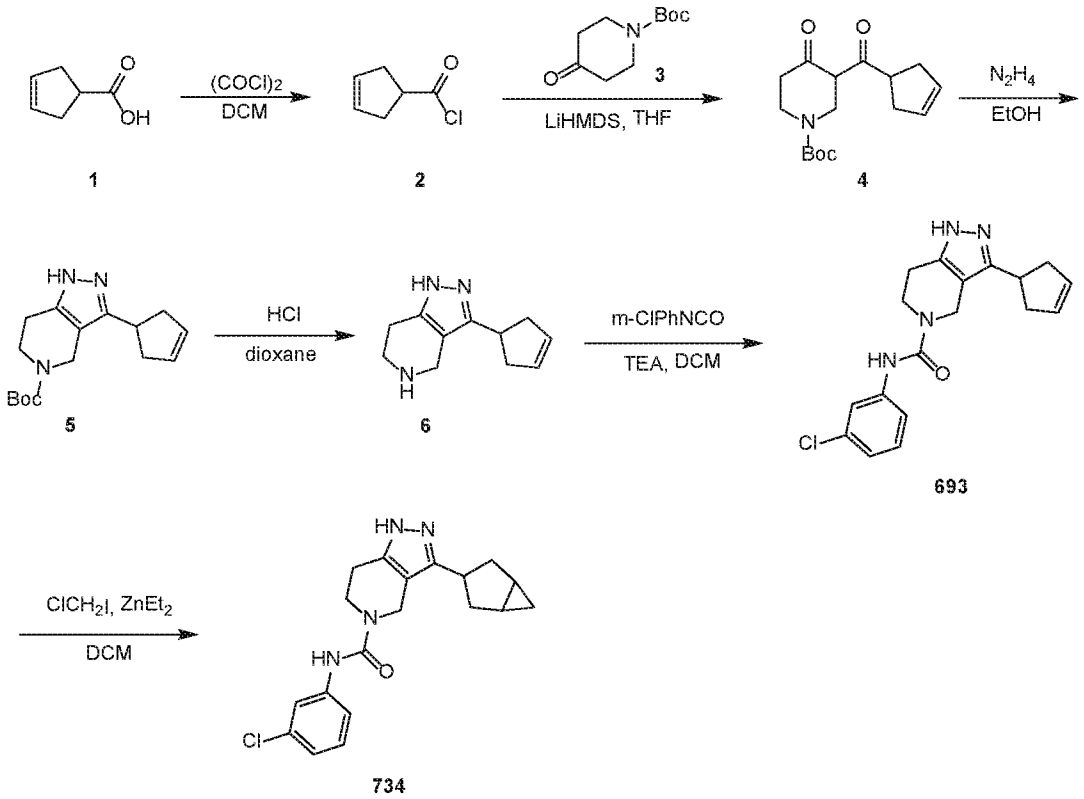
Tert-butyl-3-butyl-1-[(4-methoxyphenyl)methyl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridine-5-carboxylate (45.00 mg, 112.63 umol, 1.00 *eq*) was dissolved in TFA (3.00 mL), the reaction mixture was warmed to 75 °C and stirred at 75 °C for 16 hours. LCMS showed that the Boc was removed and the PMB preserved. The reaction mixture was warmed to 80 °C and stirred at 80 °C for another 16 hours. Several new peaks were shown on LCMS and 50% of desired compound was detected. Removed the solvent on a rotary evaporator to afford 3-butyl-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine(18.00 mg, crude) as black brown oil. The crude product was used in the next step without further purification. LCMS: 180 [M+1].

Preparation of Compound 509

To a solution of 3-butyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (18.00 mg, 100.41 umol, 1.00 *eq*) in DCM (5.00 mL) was added TEA (30.48 mg, 301.23 umol, 3.00 *eq*) at 0 °C, followed by 1-chloro-3-isocyanato-benzene (15.42 mg, 100.41 umol, 1.00 *eq*). The reaction mixture was stirred at 0 °C for 30 minutes. LCMS showed compound 8 was consumed completely and one main peak with desired MS was detected. The mixture was extracted with DCM (10 mL*3) and water (10 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Further purification by prep-HPLC(FA) afforded Compound 509 (20.00 mg, 58.89 umol, 58.65% yield, 98% purity) as white solid. ^1H NMR (400MHz, METHANOL-d_4) 7.52 - 7.53 (t, J = 1.94 Hz, 1 H), 7.29 (m, 1 H), 7.21 - 7.25 (m, 1 H), 6.99 - 7.01 (m, 1 H), 4.51 (s, 2 H), 3.78 - 3.81 (t, J = 5.83 Hz, 2

H), 2.76 - 2.79 (t, *J* = 5.77 Hz, 2 H), 2.60 - 2.64 (t, *J* = 7.65 Hz, 2 H), 1.59 - 1.65 (q, *J* = 7.65 Hz, 2 H), 1.34 - 1.40 (dq, *J* = 14.98, 7.39 Hz, 2 H), 0.93 - 0.97 (t, *J* = 7.34 Hz, 3 H). LCMS: 333/335 [M+1].

Example 24: Preparation of Compounds 693 and 734



Step 1: Preparation of Compound 2

To a solution of cyclopent-3-ene-1-carboxylic acid (6.00 g, 53.51 mmol, 1.00 *eq*) in DCM (20.00 mL) was added catalytic amount of DMF. $(COCl)_2$ (10.19 g, 80.26 mmol, 1.50 *eq*) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for one hour. TLC monitored that starting material was consumed completely by quenching with MeOH. The reaction mixture was concerntrated in vacuo on a rotary evaporator. The residue was purified by distillation (bp 120-125°C 50 mm Hg) to give cyclopent-3-ene-1-carbonyl chloride (4.10 g, 31.40 mmol, 58.68% yield) as colorless oil.

Step 2: Preparation of Compound 4

A three-necked round bottom flask was cooled to -78 °C, a solution of tert-butyl 4-oxopiperidine-1-carboxylate (3.82 g, 19.15 mmol, 1.00 *eq*) in THF (15.00 mL) was added dropwise to LiHMDS (1 M, 22.98 mL, 1.20 *eq*) under N_2. The reaction mixture was stirred at -78 °C for one hour under N_2. Then, cyclopent-3-ene-1-carbonyl chloride (2.50 g, 19.15 mmol, 1.00 *eq*) was added dropwise. After addition the reaction mixture was warmed to 25

°C and stirred at 25 °C for another 2 hours. TLC showed starting material was consumed completely. Several new peaks were shown on LCMS and 20% of desired compound was detected. The reaction mixture was added to saturated aqueous NH_4Cl (40 mL) and then extracted with EA (80 mL*3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl 3-(cyclopent-3-ene-1-carbonyl)-4-oxo-piperidine-1-carboxylate (4.20 g, crude) as yellow oil. The crude product was used in the next step directly without further purification. LCMS: 294 [M+1].

Step 3: Preparation of Compound 5

To a solution of tert-butyl-3-(cyclopent-3-ene-1-carbonyl)-4-oxo-piperidine-1-carboxylate (7.00 g, 23.86 mmol, 1.00 *eq*) in EtOH (15.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (2.11 g, 35.79 mmol, 1.50 *eq*). The reaction mixture was warmed to 60 °C and stirred at 60 °C for 2 hours. TLC indicated starting material was consumed completely and many new spots formed. The mixture was extracted with EA (50 mL*3) and water (20 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give tert-butyl 3-cyclopent-3-en-1-yl-1,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (4.50 g, 12.44 mmol, 52.14% yield, 80% purity) as yellow solid. LCMS: 290 [M+1].

Step 4: Preparation of Compound 6

To a solution of tert-butyl-3-cyclopent-3-en-1-yl-1,4,6,7-tetrahydropyrazolo [4,3-c] pyridine-5-carboxylate (500.00 mg, 1.73 mmol, 1.00 *eq*) in dioxane (3.00 mL) was added HCl/dioxane (4 M, 10.00 mL, 23.12 *eq*). The reaction mixture was stirred at 25 °C for 30 minutes. TLC showed starting material was consumed completely. The reaction mixture was filtered and the filtrate was washed with dioxane (15 mL*3) to give 3-cyclopent-3-en-1-yl-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine (320.00 mg, 1.42 mmol, 81.95% yield,HCl) as light yellow solid. The crude product was used in the next step directly without further purification.

^1H NMR (400MHz, METHANOL-d_4) 5.82 - 5.86 (s, 2 H), 4.30 (s, 2 H), 3.72 - 3.75 (tt, J = 9.22, 6.02 Hz, 1 H), 3.60 - 3.63 (t, J = 6.34 Hz, 2 H), 3.18 - 3.20 (t, J = 6.27 Hz, 2 H), 2.90 - 2.96 (m, 2 H), 2.50 - 2.55 (m, 2 H).

Preparation of Compound 693

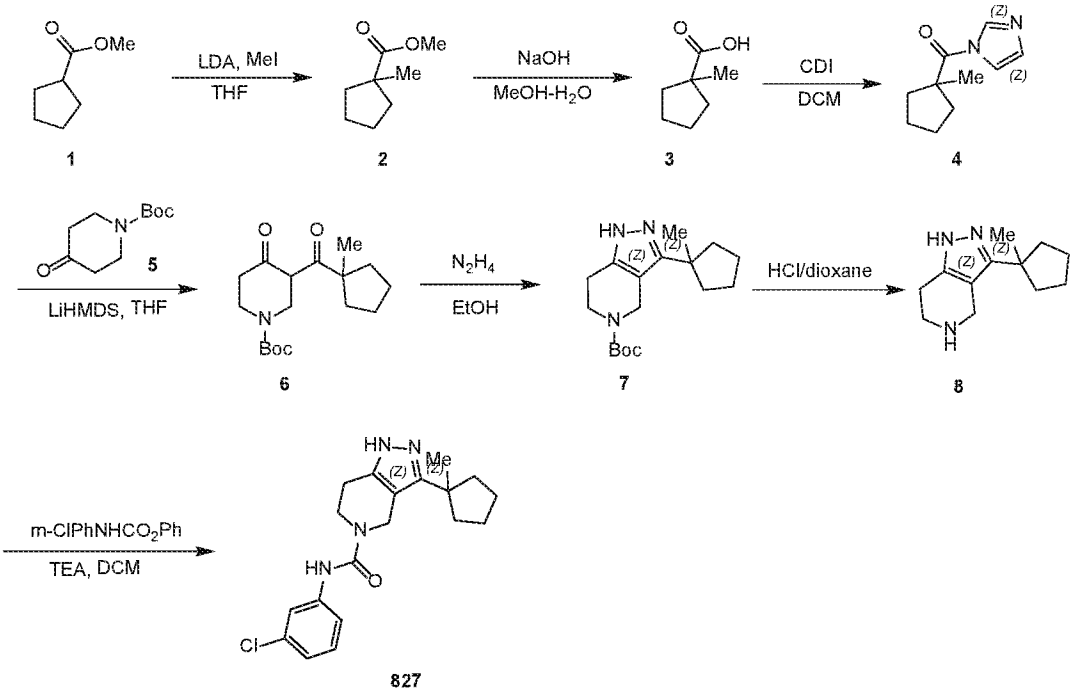
To a mixture of 3-cyclopent-3-en-1-yl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (120.00 mg, 531.63 umol, 1.00 *eq*, HCl) in DCM (2.00 mL) was added TEA (161.39 mg, 1.59 mmol, 3.00 *eq*) at 0 °C, followed by 1-chloro-3-isocyanato-benzene (48.99 mg, 318.98 umol, 0.60 *eq*), the reaction mixture was stirred at 0 °C for 30 minutes. LCMS showed

compound 6 was consumed completely and one main peak with desired MS was detected. The mixture was extracted with DCM (10 mL*3) and water (10 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (FA) to afford Compound 693 (35.00 mg, 97.70 umol, 18.38% yield, 95.7% purity) as white solid. ^{1}H NMR (400 MHz, METHANOL-d4) 7.51 - 7.52 (t, J = 1.94 Hz, 1 H), 7.28 - 7.30 (m, 1 H), 7.20 - 7.25 (m, 1 H), 6.99 - 7.01 (d, J = 7.78 Hz, 1 H), 5.78 - 5.82 (m, 2 H), 4.51 (s, 2 H), 3.77 - 3.80 (t, J = 5.77 Hz, 2 H), 3.51 - 3.57 (m, 1 H), 2.76 - 2.81 (dt, J = 11.51, 5.85 Hz, 4 H), 2.50 - 2.54 (dd, J = 14.12, 7.47 Hz, 2 H). LCMS: 343/345 [M+1].

Preparation of Compound 734

To a solution of N-(3-chlorophenyl)-3-cyclopent-3-en-1-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (80.00 mg, 233.36 umol, 1.00 *eq*) in DCM (2.00 mL) was added Et_2Zn (1 M, 1.17 mL, 5.00 *eq*) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min. A solution of $ClCH_2I$ (246.99 mg, 1.40 mmol, 6.00 *eq*) in DCM (500.00 uL) was added dropwise at 0 °C. The mixture was stirred at 1 °C for 1 hr. LCMS showed the reaction was completed. The mixture was quenched by saturted NH_4Cl (10 mL) and extracted with EA (10 mL*2). The combined organic layer was dried over Na_2SO_4, filtrated and concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford 3-(3-bicyclo[3.1.0]hexanyl)-N-(3-chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (12.00 mg, 31.07 umol, 13.31% yield, 92.4% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.54 (t, J = 1.9 Hz, 1 H), 7.30 - 7.34 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.00 - 7.05 (m, 1 H), 4.54 (s, 2 H), 3.77 - 3.83 (m, 2 H), 3.47 - 3.58 (m, 1 H), 2.78 (t, J = 5.7 Hz, 2 H), 2.10 - 2.42 (m, 2 H), 1.93 (dd, J = 5.2, 13.5 Hz, 2 H), 1.38 - 1.47 (m, 2 H), 0.58 - 0.66 (m, 1 H), 0.16 - 0.46 (m, 1 H). LCMS: 357/359[M+1].

Example 25: Preparation of Compound 827



Step 1: Preparation of Compound 2

To a solution of methyl cyclopentanecarboxylate (6.40 g, 49.93 mmol, 1.00 *eq*) in THF (40.00 mL) was added LDA (2 M, 29.96 mL, 1.20 *eq*) at 0 °C under N_2, followed by MeI (8.50 g, 59.92 mmol, 3.73 mL, 1.20 *eq*) after 0.5 h. The mixture was stirred at 25 °C for 1.5 h. TLC showed two major new spots. The mixture was quenched with NH_4Cl (saturated, 120 mL) and extracted with EA (120 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford methyl 1-methylcyclopentanecarboxylate (7.20 g, crude), which was used directly for the next step.

Step 2: Preparation of Compound 3

To a solution of methyl 1-methylcyclopentanecarboxylate (3.60 g, 25.32 mmol, 1.00 *eq*) in MeOH (30.00 mL)/H_2O (6.00 mL) was added NaOH (1.52 g, 37.98 mmol, 1.50 *eq*). The reaction mixture was warmed to 70 °C and stirred at 70 °C for 2 hours. TLC indicated starting material was consumed completely. The reaction mixture was extracted with DCM (20 mL) and water (10 mL*2). The pH of the aqueous phase was adjusted to around 6 by adding diluted hydrochloride acid (1 N, 5 mL), then extracted with DCM (20 mL*4). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford 1-methylcyclopentanecarboxylic acid (2.10 g, 16.38 mmol, 64.71% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) 11.92 (brs, 1 H), 1.97 - 2.01 (m, 2 H), 1.58 - 1.61 (m, 4 H), 1.34 - 1.38 (m, 2 H), 1.14 (s, 3 H).

Step 3: Preparation of Compound 4

To a solution of 1-methylcyclopentanecarboxylic acid (400.00 mg, 3.12 mmol, 1.00 *eq*) in DCM (10.00 mL) was added CDI (556.65 mg, 3.43 mmol, 1.10 *eq*) at 0 °C under N_2, the reaction mixture was warmed to 30 °C and stirred at 30 °C for one hour. TLC showed the reaction was completed. The mixture was extracted with DCM (10 mL*3) and water (10 mL*2). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford imidazol-1-yl-(1-methyl cyclopentyl)methanone (510.00 mg, crude) as yellow oil. The crude product was used in the next step without further purification.

Step 4: Preparation of Compound 6

At -78 °C, to LiHMDS (1 M, 4.01 mL, 1.40 *eq*) was added a solution of tert-butyl 4-oxopiperidine-1-carboxylate (456.12 mg, 2.29 mmol, 0.80 *eq*) in THF (10.00 mL) dropwise under N_2. The reaction mixture was stirred at -78 °C for one hour under N_2. A solution of imidazol-1-yl-(1-methylcyclopentyl)methanone (510.00 mg, 2.86 mmol, 1.00 *eq*) in THF (10.00 mL) was added dropwise. After addition, the reaction mixture was warmed to 30 °C and stirred at 30 °C for another 2 hours. TLC showed compound 5 was consumed completely. The reaction mixture was added to saturated aqueous of NH_4Cl (30 mL) and then extracted with EA (50 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl 3-(1-methylcyclopentanecarbonyl) -4-oxo-piperidine-1-carboxylate (730.00 mg, crude) as yellow oil. The crude product was used in the next step directly without purification.

Step 5: Preparation of Compound 7

To a solution of tert-butyl 3-(1-methylcyclopentanecarbonyl)-4-oxo-piperidine-1- carboxylate (500.00 mg, 1.62 mmol, 1.00 *eq*) in EtOH (10.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (124.03 mg, 2.11 mmol, 120.42 uL, 85% purity, 1.30 *eq*), the reaction mixture was warmed to 60 °C and stirred at 60 °C for 30 minutes. Several new peaks were shown on LCMS and 25% of the desired compound was detected. The mixture was extracted with EA (20 mL*3) and water (20 mL), the organic phase was washed with water (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography, further purification by prep-TLC to afford tert-butyl-3-(1-methylcyclopentyl) -1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (31.00 mg, 101.50 umol, 6.27% yield) as yellow oil. LCMS: 306 [M+1].

Step 6: Preparation of Compound 8

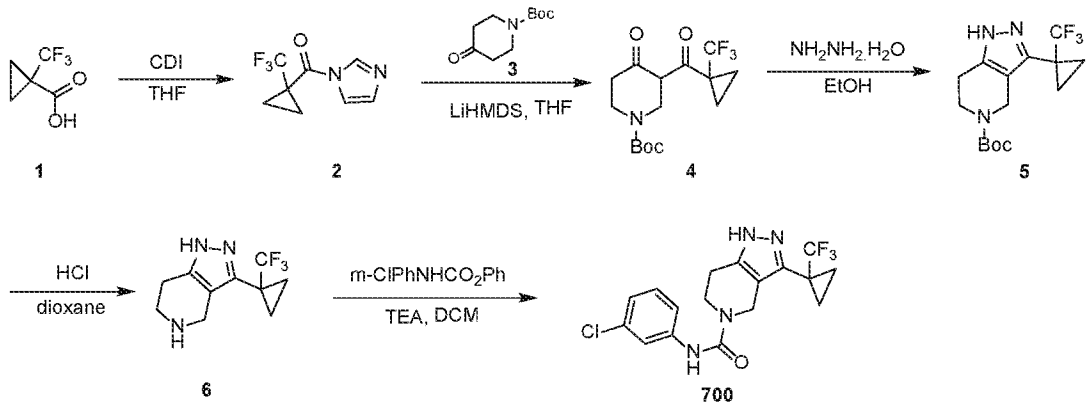
To a solution of tert-butyl 3-(1-methylcyclopentyl)-1,4,6,7-

tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (31.00 mg, 81.20 umol, 1.00 *eq*) in dioxane (1.00 mL) was added HCl/dioxane (4 M, 1.00 mL, 49.26 *eq*). The reaction mixture was stirred at 30 °C for 3 hours. TLC showed starting material was consumed completely. Evaporated the solution on a water bath under reduced pressure using a rotary evaporator to afford 3-(1-methylcyclopentyl)- 4,5,6,7-tetrahydro-1H-pyrazol o[4,3-c] pyridine (13.00 mg, 53.77 umol, 66.22% yield, HCl) as yellow oil. The crude product was used in the next step directly without further purification.

Preparation of Compound 827

To a mixture of 3-(1-methylcyclopentyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (13.00 mg, 43.02 umol, 1.00 *eq*, HCl) in DCM (5.00 mL) was added TEA (13.06 mg, 129.05 umol, 17.89 uL, 3.00 *eq*), followed by phenyl N-(3-chlorophenyl)carbamate (10.65 mg, 43.02 umol, 1.00 *eq*). The reaction mixture was stirred at 30 °C for 5 hours. LCMS showed the starting material was consumed completely and one main peak with desired MS was detected. The mixture was extracted with DCM (15 mL*3) and water (10 mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (FA) to afford Compound 827 (5.16 mg, 14.14 umol, 32.86% yield, 98.32% purity) as white solid. ^{1}H NMR (400 MHz, METHANOL-d4) 7.51 - 7.52 (t, J = 2.01 Hz, 1 H), 7.28 (m, 1 H), 7.21 - 7.25 (m, 1 H), 7.00 - 7.02 (m, 1 H), 4.62 (s, 2 H), 3.77 - 3.80 (t, J = 5.83 Hz, 2 H), 2.77 - 2.80 (t, J = 5.77 Hz, 2 H), 2.01 - 2.03 (t, J = 7.09 Hz, 2 H), 1.73 - 1.81 (m, 6 H), 1.29 (s, 3 H). LCMS: 359/361 [M+1].

Example 26: Preparation of Compound 700



Steps 1 and 2: Preparation of Compounds 2 and 4

To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (2.59 g, 12.98 mmol, 1.00 *eq*) in THF (20.00 mL) was added CDI (2.32 g, 14.28 mmol, 1.10 *eq*) under N_2. The mixture was stirred at 15 °C for 1 hr. The mixture was extracted with DCM (20 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4, filtrated and concentrated in vacumm to gave a crude (1H-imidazol-1-yl) (1-(trifluoromethyl)cyclopropyl)methanone.

A solution of tert-butyl 4-oxopiperidine-1-carboxylate (2.59 g, 12.98 mmol, 1.00 *eq*) in THF (15.00 mL) was added to LiHMDS (1 M, 16.87 mL, 1.30 *eq*) dropwise at -70 °C under N_2. The mixture was stirred at -70 °C for 0.5 hr. (1H-imidazol-1-yl)(1-(trifluoromethyl)cyclopropyl)methanone prepared above was dissolved in THF (5.00 mL) and added to reaction mixture at -70 °C. Then the resulting mixture was stirred at 15 °C for 16 hr. The mixture was quenched by saturated NH_4Cl (20 mL) and extracted with EA (50 mL*2). The combined organic layer was dried over Na_2SO_4, filtrated. The filtrates was concentrated in vacumm to afford tert-butyl 4-oxo-3-[1-(trifluoromethyl)cyclopropanecarbonyl]piperidine-1- carboxylate (3.30 g, crude) as brown oil.

Step 3: Preparation of Compound 5

To a solution of tert-butyl 4-oxo-3-[1-(trifluoromethyl)cyclopropanecarbonyl] piperidine-1-carboxylate (3.30 g, 9.84 mmol, 1.00 *eq*) in EtOH (30.00 mL) was added $NH_2NH_2•H_2O$ (985.18 mg, 19.68 mmol, 956.49 uL, 2.00 *eq*). The solution was heated at 90 °C for 16 hr. The mixture was concentrated in vacumm and extracted with EA (20 mL*2). The combined organic layer was dried over Na_2SO_4. The residue was purified by prep-HPLC (FA) to afford tert-butyl 3-[1-(trifluoromethyl)cyclopropyl]-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (200.00 mg, 603.63 umol, 6.13% yield) as brown oil.

Step 4: Preparation of Compound 6

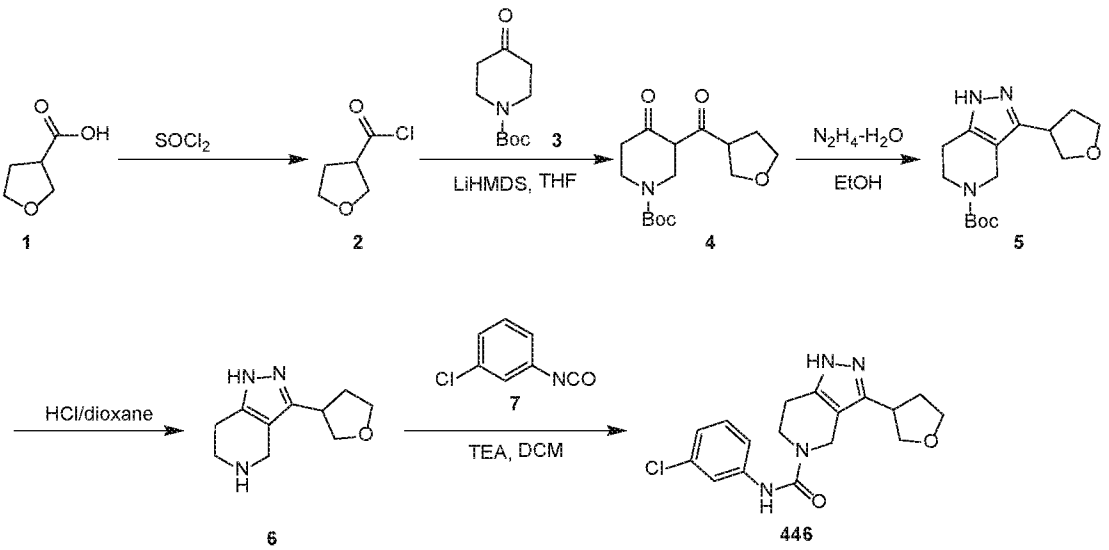
Tert-butyl3-[1-(trifluoromethyl)cyclopropyl]-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (50.00 mg, 150.91 umol, 1.00 *eq*) was treated with HCl/dioxane (4 M, 37.73 uL, 1.00 *eq*). The mixture was stirred at 15 °C for 1 hr. TLC (PE:EA=0:1) showed the reaction was completed. The mixture was concentrated in vacumm to afford 3-[1-(trifluoromethyl)cyclopropyl]-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine (45.00 mg, 147.96 umol, 98.04% yield, 2HCl) as brown solid.

Preparation of Compound 700

To a solution of 3-[1-(trifluoromethyl)cyclopropyl]-4,5,6,7-tetrahydro-

1H-pyrazolo [4,3-c]pyridine (45.90 mg, 150.92 umol, 1.00 *eq*, 2HCl) in DCM (8.00 mL) was added phenyl N-(3-chlorophenyl)carbamate (37.38 mg, 150.92 umol, 1.00 *eq*) and TEA (61.09 mg, 603.68 umol, 83.68 uL, 4.00 *eq*). The mixture was stirred at 15 °C for 16 hr. The mixture was concentrated in vacumm. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-[1-(trifluoromethyl) cyclopropyl] -1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (25.00 mg, 63.93 umol, 42.36% yield, 98.4% purity) as white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ 7.54 (t, *J* = 2.0 Hz, 1 H), 7.29 - 7.34 (m, 1 H), 7.22 - 7.28 (m, 1 H), 7.00 - 7.05 (m, 1 H), 4.61 (brs, 3 H), 3.83 (t, *J* = 5.8 Hz, 2 H), 2.84 (t, *J* = 5.5 Hz, 2 H), 1.37 (brs, 2 H), 1.18 (brs, 2 H). LCMS: 385/387[M+1]

Example 27: Preparation of Compound 446



Step 1: Preparation of Compound 2

A mixture of tetrahydrofuran-3-carboxylic acid (8.00 g, 68.90 mmol, 1.00 *eq*) in $SOCl_2$ (80.00 mL) was stirred at 60 °C for 1 hour. TLC showed the reaction was completed. The mixture was concentrated in vacuum to give tetrahydrofuran-3- carbonyl chloride (8.90 g, 66.14 mmol, 96.00% yield) as light yellow oil, which was used directly for next step.

Step 2: Preparation of Compound 4

To a mixture of LiHMDS (1 M, 65.25 mL, 1.30 *eq*) in THF (100 mL) at -60°C under N_2, then tert-butyl 4-oxopiperidine-1-carboxylate (10.00 g, 50.19 mmol, 1.00 *eq*) in THF (25 mL) was added portion-wise at -60°C under N_2. The mixture was stirred at -60°C for 30 min. Then tetrahydrofuran-3-carbonyl chloride (8.78 g, 65.25 mmol, 1.30 *eq*) in THF (25 mL) was

added dropwise at -60°C. The mixture was stirred at 15°C for 2.5 hr under N_2 atmosphere. TLC and LCMS showed the reaction was completed. The mixture was quenched by saturated NH_4Cl (200 mL) and extracted with EA (50 mL*3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give tert-butyl4-oxo-3-(tetrahydrofuran-3-carbonyl)piperidine-1-carboxylate (15.60 g, crude) as a yellow oil. LCMS: 298 [M+1].

Step 3: Preparation of Compound 5

A mixture of tert-butyl 4-oxo-3-(tetrahydrofuran-3-carbonyl)piperidine-1- carboxylate (15.50 g, 52.13 mmol, 1.00 *eq*) , $NH_2NH_2•H_2O$ (6.14 g, 104.25 mmol, 2.00 *eq*) in EtOH (150.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 3 hour under N_2 atmosphere. LCMS and TLC showed the reaction was completed. The mixture was poured into HCl (0.5N 200 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (100 mL*3). The combined organic phase was washed with brine (200 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=100/1 to 1/1) to give tert-butyl 3-tetrahydrofuran-3-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (6.00 g, 20.45 mmol, 39.23% yield) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) ppm 4.42 (brs, 2 H), 4.03 (dt, J = 5.46, 8.19 Hz, 2 H), 3.82 - 3.94 (m, 2 H), 3.69 (brs, 2 H), 3.39 - 3.48 (m, 1 H), 2.73 (t, J = 5.71 Hz, 2 H), 2.27 - 2.39 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.45 - 1.53 (m, 11 H). LCMS: 294 [M+1].

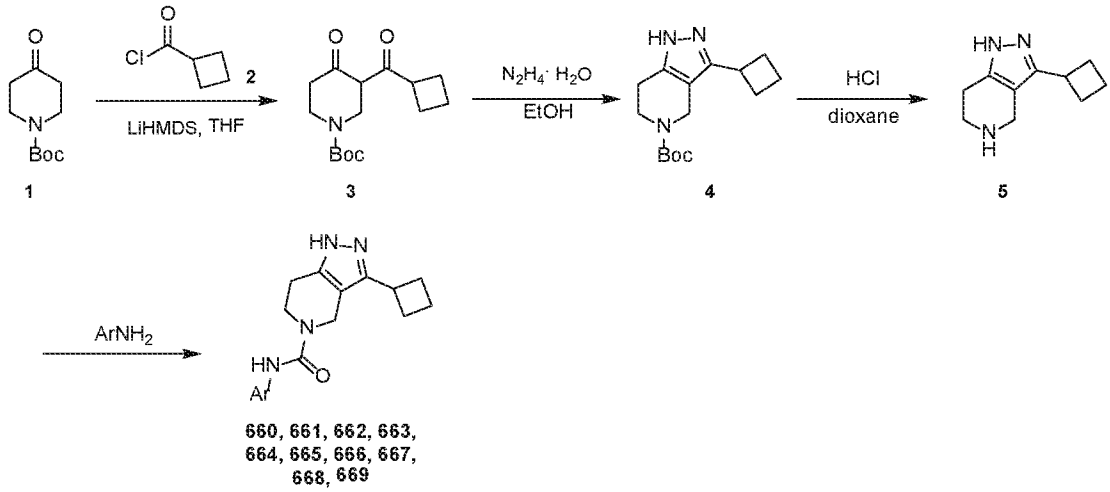
Step 4: Preparation of Compound 6

A mixture of tert-butyl-3-tetrahydrofuran-3-yl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (6.00 g, 20.45 mmol, 1.00 *eq*) in dioxane (20.00 mL) was added HCl/dioxane (4 M, 40.00 mL, 7.82 *eq*) , and then the mixture was stirred at 15 °C for 1 hour. TLC showed the reaction was completed. The mixture was concentrated in vacuum to give 3-tetrahydrofuran-3-yl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (4.50 g, 19.59 mmol, 95.79% yield, HCl) as a yellow solid. ^{1}H NMR (300 MHz, METHANOL-d_4) ppm 4.38 (s, 1 H), 4.09 (dt, J = 4.62, 8.52 Hz, 1 H), 3.96 - 4.03 (m, 1 H), 3.86 - 3.94 (m, 1 H), 3.78 - 3.85 (m, 1 H), 3.70 (d, J = 2.07 Hz, 1 H), 3.58 - 3.64 (m, 2 H), 3.31 (td, J = 1.67, 3.25 Hz, 1 H), 3.20 (t, J = 6.31 Hz, 2 H), 2.48 (dd, J = 4.14, 8.48 Hz, 1 H), 2.06 (dd, J = 5.46, 7.54 Hz, 1 H).

Preparation of Compound 446

A mixture of 3-tetrahydrofuran-3-yl-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine (80.00 mg, 348.27 umol, 1.00 *eq*, HCl), TEA (70.48 mg, 696.53 umol, 2.00 *eq*), 1-chloro-3-isocyanato-benzene (48.13 mg, 313.44 umol, 0.90 *eq*) in DCM (5.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 15 °C for 1 hour under N_2 atmosphere. LCMS showed the reaction was completed. The mixture was poured into water (10 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (5 mL*3). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (FA) to give N-(3-chlorophenyl)-3-tetrahydrofuran-3-yl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxamide (30.00 mg, 85.38 umol, 24.51% yield, 98.7% purity) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 7.52 (t, J = 1.94 Hz, 1 H), 7.27 - 7.32 (m, 1 H), 7.20 - 7.26 (m, 1 H), 7.00 (td, J = 0.93, 7.81 Hz, 1 H), 4.56 (s, 2 H), 4.00 - 4.11 (m, 2 H), 3.87 (q, J = 7.95 Hz, 1 H), 3.75 - 3.82 (m, 3 H), 3.50 (t, J = 7.91 Hz, 1 H), 2.79 (t, J = 5.71 Hz, 2 H), 2.30 - 2.40 (m, 1 H), 2.04 - 2.17 (m, 1 H). LCMS: 347/349 [M+1].

Example 28: Procedure for preparation of Compounds 660, 661, 662, 663, 664, 665, 666, 667, 668, and 669



Step 1: Preparation of Compound 3

At -78 °C, to LiHMDS (1 M, 24.10 mL, 1.20 *eq*) was added a solution of tert-butyl 4-oxopiperidine-1-carboxylate (4.00 g, 20.08 mmol, 1.00 *eq*) in THF (50.00 mL) dropwise under N_2. The reaction mixture was stirred at -78 °C for one hour under N_2. Cyclobutanecarbonyl chloride (2.38 g, 20.08 mmol, 1.00 *eq*) was added dropwise. After addition, the reaction mixture was warmed to 20 °C and stirred at 20 °C for another 2 hours.

Several new peaks were shown on LCMS and 20% of desired compound was detected. The reaction mixture was added to aqueous solution of NH_4Cl (100 mL) and then neutralised by dilute hydrochloric acid (1 N), the aqueous layer was extracted with EA (200 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl 3-(cyclobutanecarbonyl)-4-oxo-piperidine-1-carboxylate (5.00 g, crude) as yellow oil. The crude product was used in the next step directly without purification.

Step 2: Preparation of Compound 4

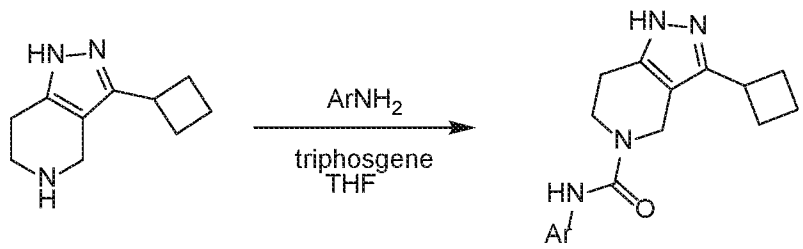
To a solution of tert-butyl 3-(cyclobutanecarbonyl)-4-oxo-piperidine-1-carboxylate (5.00 g, 17.77 mmol, 1.00 *eq*) in EtOH (50.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (2.09 g, 35.54 mmol, 2.00 *eq*) dropwise, the reaction mixture was warmed to 60 °C and stirred at 60 °C for 2 hours. LCMS showed starting material was consumed completely. Several new peaks were shown on LCMS and 50% of desired compound was detected. Removed the solvent on a rotary evaporator, the mixture was extracted with EA (80 mL*3) and water (50 mL*2). The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford tert-butyl 3-cyclobutyl- 1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (3.20 g, 9.23 mmol, 51.94% yield, 80% purity) as yellow oil.

Step 3: Preparation of Compound 5

To a solution of tert-butyl-3-cyclobutyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (2.70 g, 9.73 mmol, 1.00 *eq*) in dioxane (10.00 mL) was added HCl/dioxane (4 M, 25.00 mL, 10.28 *eq*) at 30 °C. The reaction mixture was stirred at 30 °C for one hour. Precipitate formed. TLC showed starting material was consumed completely. The reaction mixture was filtered and the filtrate cake was washed with dioxane (15 mL*2) to afford 3-cyclobutyl-4,5,6,7-tetrahydro -1H-pyrazolo[4,3-c] pyridine (2.00 g, 9.36 mmol, 96.18% yield, HCl) as light yellow solid. The crude product was used in the next step directly without further purification. ^{1}H NMR (400 MHz, METHANOL-d_4) 4.35 (s, 2 H), 3.78 (m, J = 9.03 Hz, 1 H), 3.62 - 3.66 (m, 2 H), 3.16 - 3.28 (m, 2 H), 2.39 - 2.53 (m, 2 H), 2.28 - 2.39 (m, 2 H), 2.12 - 2.26 (m, 1 H), 1.93 - 2.06 (m, 1 H).

General procedure for preparation of Compounds 660 through 669

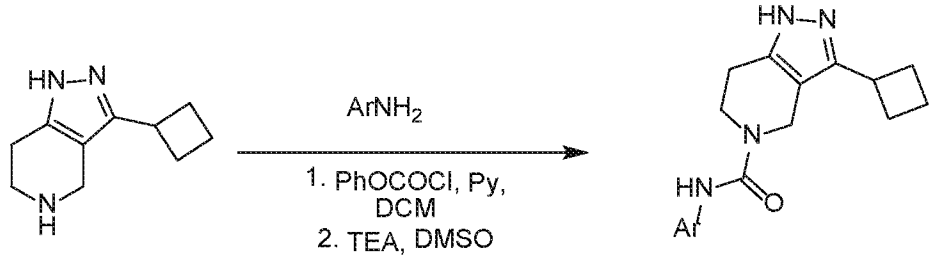
General procedure I:



5 660 - 669

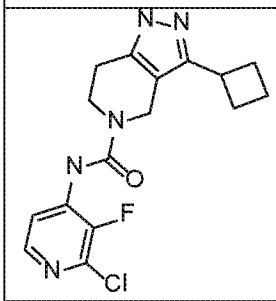
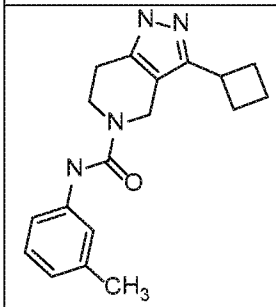
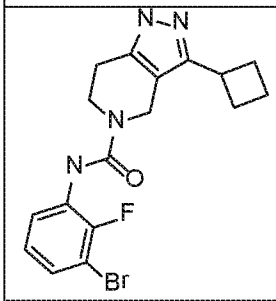
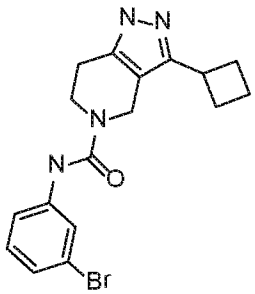
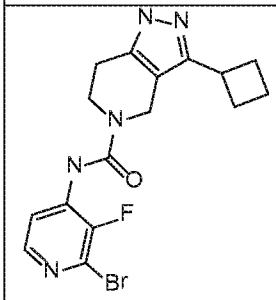
To a solution of amine (1 eq) and TEA (10 eq.) in 1.5 mL of dry THF, a solution of triphosgene (0.45 eq) in 0.5 mL dry THF was added. The resulting mixture was stirred at 0°C for 4 hr and TLC showed amine was consumed completely. Then a mixture of compound 5 (1 eq) in 1 mL of dry THF was added. The reaction mixture was allowed to warm to 30°C for 8 hr. LC-MS showed the reaction was completed. The solution was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (FA or Base) to afford the desired products.

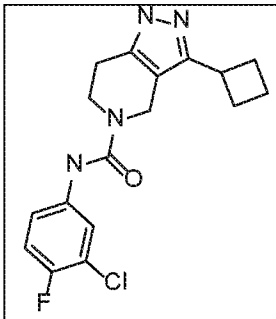
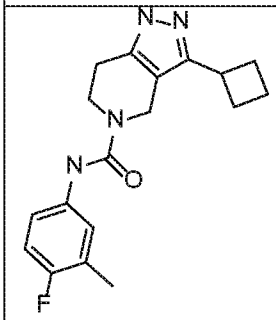
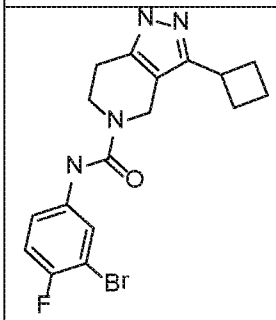
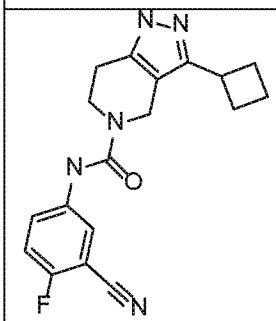
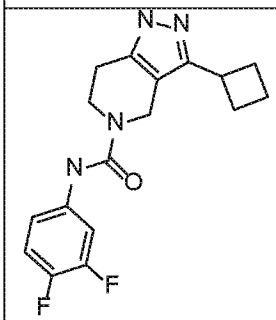
General procedure II:



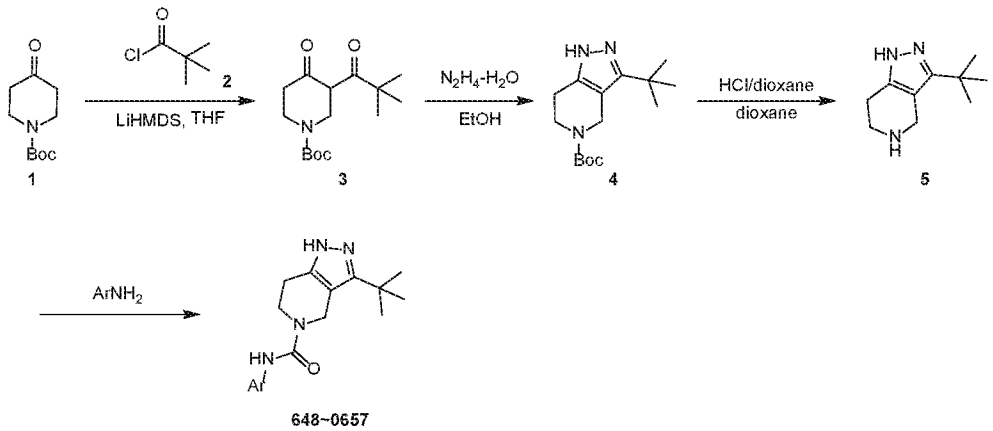
5 660~669

To a stirred solution of amine (1.2 eq) and phenyl carbonochloridate (1.2 eq) in 2 mL of dry DCM was added a solution of Py (3 eq). The mixture was stirred at 0 °C for 4 hr and TLC showed amine was consumed completely. The mixture was quenched with water (15 mL) and extracted with DCM (15mL). The combined organic phase was dried with Na_2SO_4 and concentrated in vacuum. The residue was dissolved in DMSO (3mL). Compound 5 (1 eq), TEA (3 eq.) was added and stirred at 40°C for 8 hr. LC-MS showed reaction was completed. The solution was purified by pre-HPLC (FA or Base) to afford the desired product.

Structure	Comp. ID (Prepared Method)	Analytical Data
	660 (II)	LCMS (M+1) : 350/352
	661 (II)	LCMS (M+1) : 311
	662 (I)	LCMS (M+1) : 393/395
	0663 (II)	LCMS (M+1) : 375/377
	664 (II)	LCMS (M+1) : 394/396 1H NMR (400MHz, METHANOL-d4) δ = 8.03 (d, J = 5.5 Hz, 1 H), 7.83 (t, J = 5.6 Hz, 1 H), 4.61 (brs, 2 H), 3.84 (t, J = 5.8 Hz, 2 H), 3.60 (quin, J = 8.9 Hz, 1 H), 2.82 (t, J = 5.7 Hz, 2 H), 2.34 (td, J = 8.7, 17.6 Hz, 4 H), 2.05 - 2.19 (m, 1 H), 1.86 - 2.01 (m, 1 H).

	665 (II)	LCMS (M+1) : 349/351 1HNMR(400MHz,DMSO-d6) 12.30(s, 1H), 8.79 (s, 1H), 7.76-7.74 (m,1H), 7.43-7.41 (m,1H), 7.32-7.30 (d, J=9.2 Hz, 1H), 4.46 (s, 2H), 3.71-3.68 (m, 2H), 3.45-3.42 (m, 1H), 2.65-2.53 (m, 2H), 2.26-2.21 (m, 4H), 1.96-1.94(m, 1H), 1.90-1.83 (m, 1H).
	666 (II)	LCMS (M+1) : 329
	667 (II)	LCMS (M+1) : 393/395
	668 (I)	LCMS (M+1) : 340
	669 (II)	LCMS (M+1) : 333 1HNMR(400MHz,DMSO-d6) 12.34(s, 1H), 8.80 (s, 1H), 7.65-7.61(m,1H), 7.32-7.35 (m,1H), 4.45 (s, 2H), 3.71-3.47 (m, 1H), 2.68-2.64 (m, 1H), 2.26-2.24 (m, 4H), 2.21-1.98 (m, 1H), 1.95-1.94(m, 1H).

Example 29: Procedure for Preparation of Compounds 648, 649, 650, 651, 652, 653, 654, 655, 656, and 657



Step 1: Preparation of Compound 3

A mixture of tert-butyl 4-oxopiperidine-1-carboxylate (20.00 g, 100.38 mmol, 1.00 *eq*), (15.73 g, 130.49 mmol, 1.30 *eq*) in THF (20 mL) was added to LiHMDS (1 M, 130.49 mL, 1.30 *eq*) portion-wise at -60 °C under N_2. The mixture was stirred at -60 °C for 30 min. 2,2-dimethylpropanoyl chloride (15.73 g, 130.49 mmol, 1.30 *eq*) in THF (20 mL) was added dropwise at -60°C. The mixture was stirred at 15 °C for 2.5 hr. TLC showed the reaction was completed. The mixture was quenched by saturated NH_4Cl (80 mL) and extracted with EA (50 mL*3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give tert-butyl3-(2,2-dimethylpropanoyl)- 4-oxo-piperidine-1-carboxylat e (33.29 g, crude) as a yellow oil, which was used directly for next step.

Step 2: Preparation of Compound 4

A mixture of tert-butyl 3-(2,2-dimethylpropanoyl)-4-oxo-piperidine-1-carboxylate (33.29 g, 117.48 mmol, 1.00 *eq*), N_2H_4•H_2O (11.76 g, 234.96 mmol, 2.00 *eq*) in EtOH (350.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 16 hour under N_2 atmosphere. LCMS showed the reaction was completed. The mixture was poured into HCl (0.5 N, 500 mL) and stirred at 5 min. The aqueous phase was extracted with ethyl acetate (200 mL*3). The combined organic phase was washed with brine (500 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 1/1) and checked by LCMS and HPLC, the desired product was impurity. The impure desired product was purified by Prep-HPLC (FA) to give tert-butyl 3-tert-butyl-1,4,6,7-tetrahydropyr azolo[4,3-c]pyridine-5-carboxylate (4.00 g, 14.32 mmol,

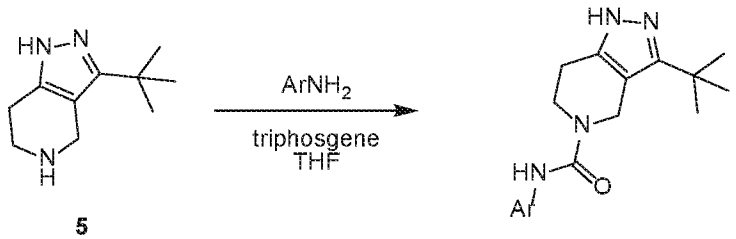
12.19% yield) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 4.54 (s, 2 H), 3.66 (s, 2 H), 2.68 (s, 2 H), 1.46 - 1.50 (m, 9 H), 1.32 (s, 9 H). LCMS: 280 [M+1].

Step 3: Preparation of Compound 5

A mixture of tert-butyl3-tert-butyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridinee-5- carboxylate (4.00 g, 14.32 mmol, 1.00 *eq*) in dioxane (30.00 mL) was added HCl/dioxane (4 M, 30.00 mL, 8.38 *eq*), and then the mixture was stirred at 15 °C for 2 hour. TLC showed the reaction was completed. The mixture was concentrated in vacuum to give 3-tert-butyl-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c]pyridine (2.60 g, 12.05 mmol, 84.17% yield, HCl) as a yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 4.50 (s, 2 H), 3.59 - 3.65 (m, 2 H), 3.21 (s, 2 H), 1.43 (s, 9 H).

General procedure for preparation of Compounds 648 through 0657

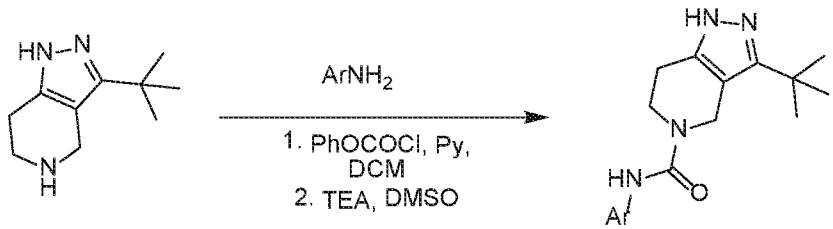
General procedure I:



5 648 - 0657

To a solution of amine (1 eq) and TEA (10 eq) in 1.5 mL of dry THF, a solution of triphosgene (0.45 eq) in 0.5 mL dry THF was added. The resulting mixture was stirred at 0°C for 4 hr and TLC showed amine was consumed completely. Then Compound 5 (1 eq) in 1 mL of dry THF was added. The reaction mixture was allowed to warm to 30°C for 8 hr. LC-MS showed the reaction was completed. The solution was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (FA or Base) to afford the desired products.

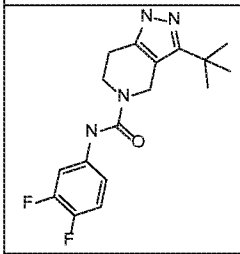
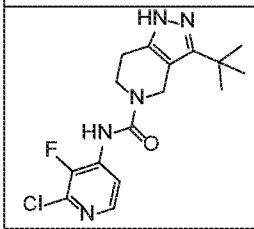
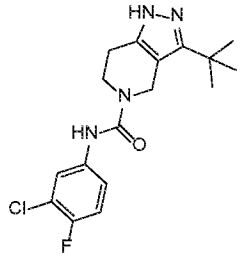
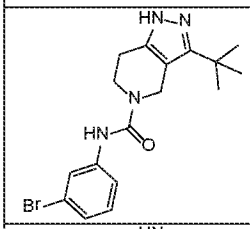
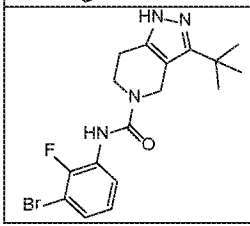
General procedure II:

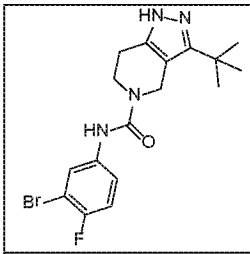
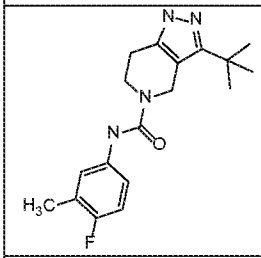
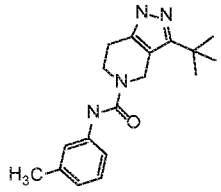
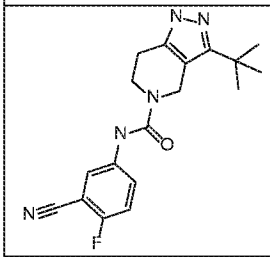
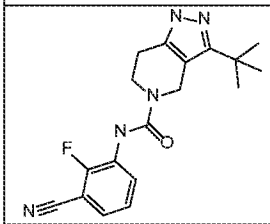


5 648 - 0657

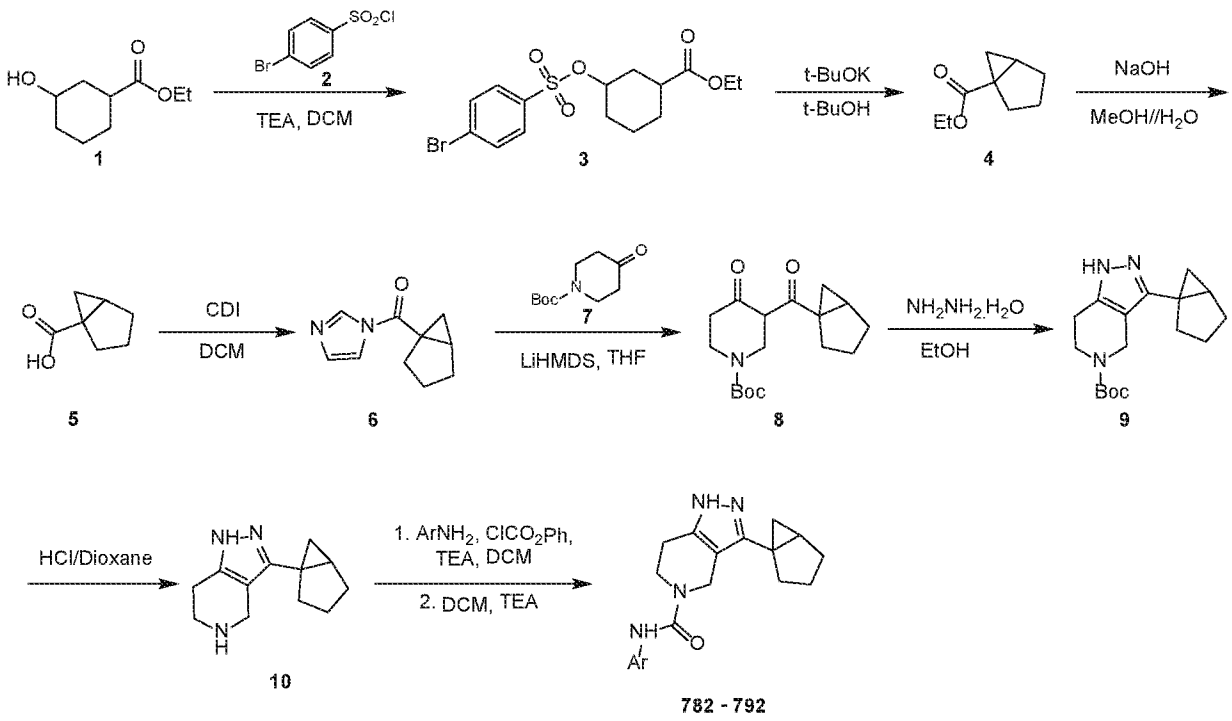
To a stirred solution of amine (1.2 eq) and phenyl carbonochloridate (1.2 eq) in 2 mL of dry DCM was added a solution of Py (3 eq.). The mixture was stirred at 0°C for 4 hr and TLC showed amine was consumed completely. The mixture was quenched with water (15

mL) and extracted with DCM (15mL). The combined organic phase was dried with Na_2SO_4 and concentrated in vacuum. The residue was dissolved in DMSO (3mL). Compound 5 (1 eq), TEA (3 eq) was added and stirred at 40°C for 8 hr. LC-MS showed reaction was completed. The solution was purified by pre-HPLC (FA or Base) to afford the desired product.

Structure	Comp. ID (Prepared Method)	Analytical Data
	648 (II)	LCMS (M+1) : 335
	649 (II)	LCMS (M+1) : 352/354
	650 (II)	LCMS (M+1) : 351/353 ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (s, 1 H) 7.73 (dd, *J*=6.96, 2.57 Hz, 1 H) 7.37 - 7.46 (m, 1 H) 7.23 - 7.33 (m, 1 H) 4.54 (s, 2 H) 3.67 (t, *J*=5.46 Hz, 2 H) 2.66 - 2.68 (m, 2 H) 2.30 - 2.34 (m, 2 H) 1.27 (s, 9 H)
	651 (II)	LCMS (M+1) : 377/379
	652 (I)	LCMS (M+1) : 395/397

	653 (II)	LCMS (M+1) : 395/397
	654 (II)	LCMS (M+1) : 331
	655 (II)	LCMS (M+1) : 313 1H NMR (400 MHz, DMSO-d6) δ 12.1 (s, 1H), 8.55 (s, 1H),7.28 (s, 1H), 7.26-7.24 (d,J=8.3Hz,1H), 7.13-7.09(t,J=7.8Hz ,1H),6.78-6.76 (d,J=7.4Hz,1H),4.55 (s,2H), 3.70-3.67 (t, J= 5.8 Hz, 2H), 2.68-2.65 (m, 2H), 2.26 (s, 3H),1.28 (s,9H).
	656 (II)	LCMS (M+1) : 342
	657 (II)	LCMS (M+1) : 342

Example 30: Preparation of Compounds 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, and 792



Step 1: Preparation of Compound 3

To a solution of ethyl 3-hydroxycyclohexanecarboxylate (10.00 g, 58.07 mmol, 1.00 *eq*) in DCM (100.00 mL) was added 4-bromobenzenesulfonyl chloride (22.26 g, 87.11 mmol, 1.50 *eq*) under N_2. The mixture was stirred at 15 °C for 16 hr. TLC (PE:EA =3:1) showed the reaction was nearly completed. The mixture was extracted wih DCM (200 mL) and saturated $NaHCO_3$ (80 mL). The organic layer was washed with 1N HCl (50 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash chromatography (PE:EA= 0%~10%) to afford ethyl 3-(4-bromophenyl)sulfonyloxycyclohexanecarboxylate (20.00 g, 51.11 mmol, 88.02% yield) as colorless oil.

Step 2: Preparation of Compound 4

To a solution of ethyl 3-(4-bromophenyl)sulfonyloxycyclohexane carboxylate (20.00 g, 51.11 mmol, 1.00 *eq*) in t-BuOH (200.00 mL) was added a solution of t-BuOK (7.46 g, 66.44 mmol, 1.30 *eq*) in t-BuOH (60.00 mL) dropwise under N_2. The mixture was stirred at 90 °C for 1.0 hr. TLC (PE:EA = 20:1) showed the reaction was completed. The mixture was extracted with DCM (200 mL*3) and H_2O (100 mL). The combined organic layer was washed saturated NaCl (80 mL), dried over Na_2SO_4, filtated, and concentrated in vacumm. The residue was purified by colunm chromatography (PE:EA

0%~1%) to afford ethyl bicyclo[3.1.0] hexane-1-carboxylate (4.80 g, 31.13 mmol, 60.90% yield) as colorless oil.

Step 3: Preparation of Compound 5

To a solution of ethyl bicyclo[3.1.0]hexane-1-carboxylate (2.00 g, 12.97 mmol, 1.00 *eq*) in MeOH (20.00 mL) was added a solution of NaOH (778.16 mg, 19.45 mmol, 1.50 *eq*) in H_2O (8.00 mL). The mixture was stirred at 70 °C for 3 hr. The mixture was concentrated in vacumm. pH of the residue was adjusted to 6 and the mixture was extracted with DCM (50 mL*3). The organic layer was dried over Na_2SO_4, filtrated and concentrated. The residue was used in the next step directly to afford bicyclo[3.1.0]hexane-1-carboxylic acid (1.40 g, crude) as brown oil.

Step 4: Preparation of Compound 6

To a solution of bicyclo[3.1.0]hexane-1-carboxylic acid (2.40 g, 19.02 mmol, 1.00 *eq*) in DCM (24.00 mL) was added di(imidazol-1-yl)methanone (3.39 g, 20.92 mmol, 1.10 *eq*). The mixture was stirred at 15 °C for 3 hr. The mixture was extracted with DCM (80 mL*2) and H_2O (50 mL). The combined organic layer was dried over Na_2SO_4, filtrated and concentrated. The residue was used in the next step directly to afford 1-bicyclo[3.1.0]hexanyl(imidazol-1-yl)-methanone (2.40 g, 13.62 mmol, 71.61% yield) as brown oil.

Step 5: Preparation of Compound 8

To a solution of LiHMDS (1 M, 16.34 mL, 1.20 *eq*) in THF (5.00 mL) was added a solution of tert-butyl 4-oxopiperidine-1-carboxylate (2.71 g, 13.62 mmol, 1.00 *eq*) in THF (20.00 mL) under N_2 at -65°C. The mixture was stirred at -65 °C for 0.5 hr. A solution of 1-bicyclo[3.1.0]hexanyl(imidazol-1-yl)methanone (2.40 g, 13.62 mmol, 1.00 *eq*) in THF (20.00 mL) was added at -65 °C dropwise. The solution was stirred at 15 °C for 16 hr. The reaction was quenched by saturated NH_4Cl (30 mL) and extracted with EA (50 mL*3). The combined organic layer was dried over Na_2SO_4, filtrated and concentrated in vacumm. The residue was purified by colunm chromatography (PE:EA:10%~100%) to afford tert-butyl 3-(bicyclo[3.1.0]hexane-1-carbonyl)-4-oxo-piperidine-1-carboxylate (2.30 g, 4.94 mmol, 36.26% yield, 66% purity) as colorless oil.

Step 6: Preparation of Compound 9

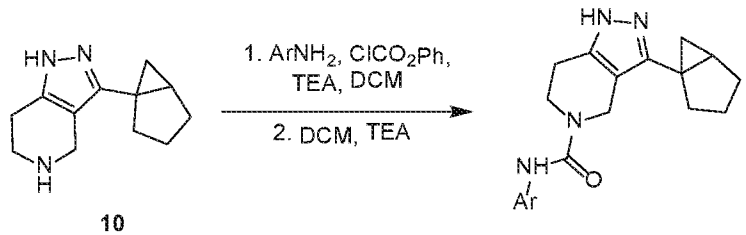
To a solution of tert-butyl-3-(bicyclo[3.1.0]hexane-1-carbonyl)-4-oxo-piperidine-1- carboxylate (2.30 g, 7.48 mmol, 1.00 *eq*) in EtOH (15.00 mL) was added $NH_2NH_2 \cdot H_2O$ (1.50 g, 14.97 mmol, 1.45 mL, 50% purity, 2.00 *eq*). The mixture was heated to 90 °C for 3 hr. The mixture was concentrated in vacumm. The residue was extracted with

EtOAc (50 mL*3) and H_2O (50 mL). The organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacumm. The residue was purified by colunm chromatography (PE:EA=20%~100%) to afford tert-butyl-3-(1-bicyclo[3.1.0]hexanyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5- carboxylate (1.90 g, 6.26 mmol, 83.69% yield) as brown oil.

Step 7: Preparation of Compound 10

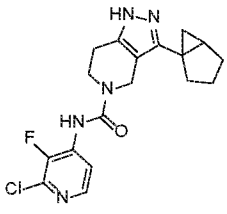
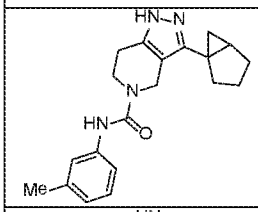
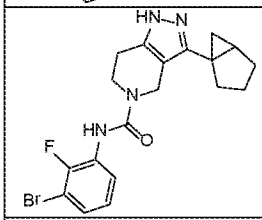
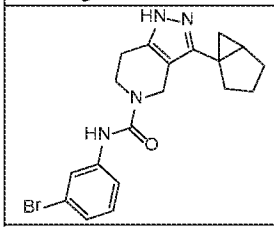
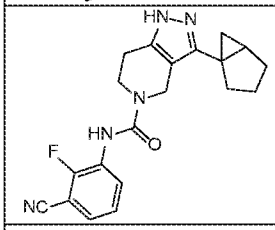
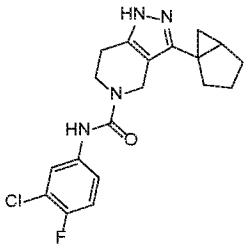
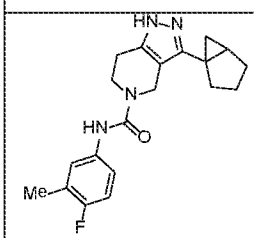
Tert-butyl-3-(1-bicyclo[3.1.0]hexanyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (1.30 g, 4.28 mmol, 1.00 *eq*) was dissolved in HCl/dioxane (4 M, 20.00 mL, 18.69 *eq*) and stirred at 15 °C for 1 hr. The mixture was filtrated. The solid was collected and dried to afford 3-(1-bicyclo[3.1.0]hexanyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (950.00 mg, crude, 2HCl) as yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ 4.40 (brs, 2 H), 3.53 - 3.69 (m, 1 H), 3.21 (brs, 1 H), 2.12 - 2.21 (m, 1 H), 1.87 - 2.08 (m, 4 H), 1.76 - 1.86 (m, 1 H), 1.43 (d, *J* = 11.2 Hz, 1 H), 1.13 (brs, 1 H), 1.03 (brs, 1 H).

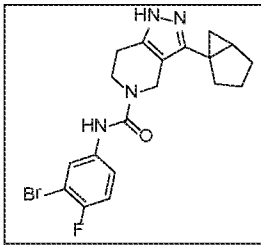
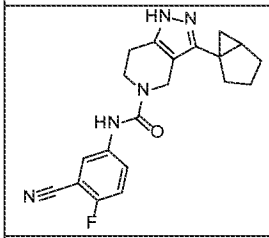
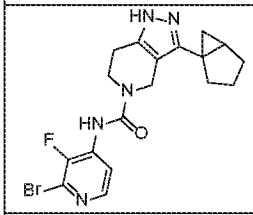
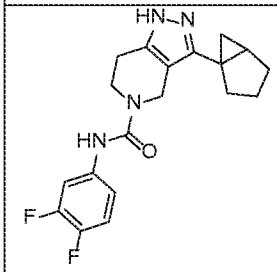
General procedure for preparation of Compounds 648 through 657



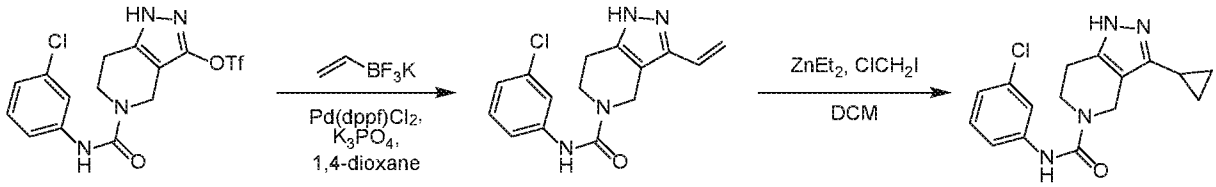
10 782 - 792

To a solution of amine (1.00 *eq*) in DCM (2.00 mL) were added TEA (2.00 *eq*) and phenyl carbonochloridate (1.00 *eq*). The mixture was stirred at 25°C for 2 hr. To a solution of compound 10 (60.00 mg, 1.00 *eq*, HCl) and TEA (2.00 *eq*) in DCM (2.00 mL) were added above reaction mixture. The mixture was stirred at 25 °C for 20 hr. LC-MS showed the reaction was completed. The reaction mixture was concentrated in vacuo. The resiude was purified by prep-HPLC (FA) to afford the desired product.

Structure	Comp. ID	Analytical Data
	782	LCMS (M+1) : 376/378 ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.02 (d, J = 5.52 Hz, 1 H), 7.80 (t, J = 5.65 Hz, 1 H), 4.56 - 4.65 (m, 2 H), 3.82 (t, J = 5.90 Hz, 2 H), 2.80 (t, J = 5.77 Hz, 2 H), 2.04 - 2.14 (m, 1 H), 1.90 - 2.02 (m, 2 H), 1.83 (dd, J = 12.42, 7.91 Hz, 1 H), 1.64 - 1.78 (m, 2 H), 1.27 - 1.43 (m, 1 H), 0.77 - 0.90 (m, 2 H).
	783	LCMS (M+1) : 337
	784	LCMS (M+1) :419/421
	785	LCMS (M+1) : 401/403
	786	LCMS (M+1) : 366
	787	LCMS (M+1) : 375/377 ^{1}H NMR (400 MHz, METHANOL-d_4) ppm 7.58 (dd, J = 6.53, 2.51 Hz, 1 H), 7.25 - 7.36 (m, 1 H), 7.14 (t, J = 8.91 Hz, 1 H), 4.56 (s, 2 H), 3.78 (t, J = 5.77 Hz, 2 H), 2.76 (t, J = 5.65 Hz, 2 H), 2.04 - 2.15 (m, 1 H), 1.90 - 2.03 (m, 2 H), 1.83 (dd, J = 12.17, 7.91 Hz, 1 H), 1.64 - 1.77 (m, 2 H), 1.33 (m, 1 H), 0.77 - 0.90 (m, 2 H).
	788	LCMS (M+1) : 355

	789	LCMS (M+1) : 419/421
	790	LCMS (M+1) : 366
	791	LCMS (M+1) : 420/422
	792	LCMS (M+1) : 359

Example 31: Preparation of Compound 440



Step 1: Preparation of Compound 2

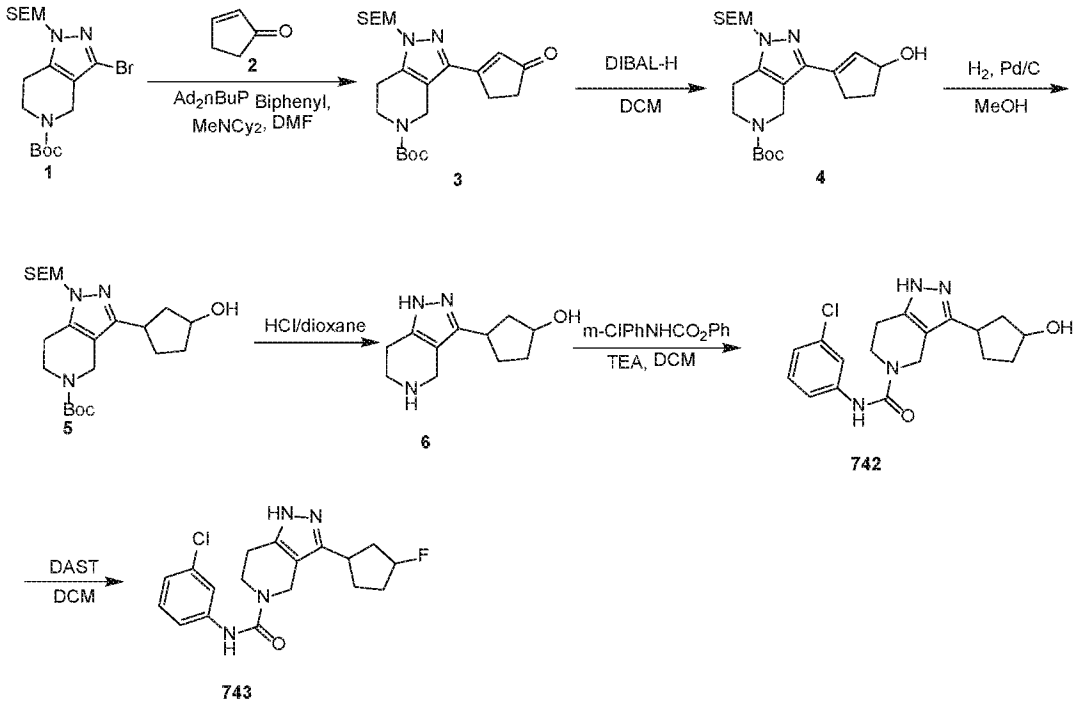
A mixture of 3-bromo-N-(3-chlorophenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxamide (1.07 g, 3.00 mmol, 1.00 *eq*), potassium trifluoro(vinyl)borate (602.78 mg, 4.50 mmol, 1.50 *eq*), $Pd_2(dba)_3$ (137.36 mg, 150.00 umol, 0.05 *eq*), XPhos (143.02 mg, 300.00 umol, 0.10 *eq*) and Na_2CO_3 (699.53 mg, 6.60 mmol, 2.20 *eq*) in dioxane (40.00 mL) and H_2O (6.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 8 hours under N_2 atmosphere. TLC indicated the reactant was consumed, and a major new spot formed. The reaction mixture was concentrated, extracted with EA (30 mL) and water (10 mL). The aqueous layer was extracted with EA (20

mL*2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=3/1 to 1:1, then DCM: MeOH 50:1 to 20:1) to afford N-(3-chlorophenyl)-3-vinyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5- carboxamide (435.97 mg, 1.44 mmol, 48.00% yield) as yellow solid.

Preparation of Compound 440

A mixture of N-(3-chlorophenyl)-3-vinyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine -5-carboxamide (100.00 mg, 330.29 umol, 1.00 eq) in DCM (2.00 mL) was degassed and purged with N_2 for 3 times, and then $ZnEt_2$ (1 M, 1.65 mL, 5.00 eq) was added dropwise at 0 °C. The mixture was stirred for 30 min. Chloro(iodo)methane (291.28 mg, 1.65 mmol, 5.00 eq) was added. The mixture was stirred at 15°C for 1 hr under N_2 atmosphere. LCMS showed material was consumed completely. The mixture was poured into saturated NH_4Cl (10 mL), extracted with ethyl acetate (15 mL*2), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-cyclopropyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine- 5-carboxamide (7.87 mg, 24.40 umol, 7.39% yield, 98.21% purity) as white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 1 H), 7.20 - 7.35 (m, 2 H), 7.02 (d, J = 7.72 Hz, 1 H), 4.57 (s, 2 H), 3.80 (s, 2 H), 2.77 (t, J = 5.65 Hz, 2 H), 1.84 (brs, 1 H), 0.94 (d, J = 6.59 Hz, 2 H), 0.81 (d, J=3.77 Hz, 2 H). LCMS: 317/319 [M+1].

Example 32: Preparation of Compounds 742 and 743



Step 1: Preparation of Compound 3

To a solution of tert-butyl 3-bromo-1-(2-trimethylsilylethoxymethyl)-6,7-dihydro -4H-pyrazolo[4,3-c]pyridine-5-carboxylate (200.00 mg, 462.50 umol, 1.00 *eq*) and cyclopent-2-en-1-one (56.96 mg, 693.75 umol, 1.50 *eq*) in DMF (2.00 mL) were added N-cyclohexyl-N-methylcyclohexanamine (135.52 mg, 693.75 umol, 1.50 *eq*) and Ad_2nBuP Biphenyl (9.28 mg, 13.88 umol, 0.03 *eq*). The mixture was stirred at 100 °C for 16 hr under N_2 protection. LCMS showed starting material remained and desired product and multiply peaks were detected. The mixture was poured into water (10 mL), extracted with ethyl acetate (10 mL*3), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated. The residue was purified by chromatography (silica gel, eluting with Petroleum ether/Ethyl acetate=50:1, 10:1) to afford tert-butyl 3-(3-oxocyclopenten-1-yl)-1-(2-trimethyl silylethoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (55.00 mg, 126.84 umol, 27.42% yield) as colorless oil. LCMS: 434 [M+1].

Step 2: Preparation of Compound 4

To a solution of tert-butyl 3-(3-oxocyclopenten-1-yl)-1-(2-trimethylsilylethoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (300.00 mg, 691.85 umol, 1.00 *eq*) in DCM (4.00 mL) was added DIBAL-H (146.54 mg, 1.04 mmol, 1.50 *eq*) at -78 °C under N_2 protection. The mixture was stirred at 25 °C for 16 hr. TLC (Petroleum ether/ethyl acetate=3:1) showed material was consumed completely, and

a major new spot detected. The mixture was poured into water (10 mL), extracted with ethyl acetate 10 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated. The residue was purified by chromatography (silica gel, eluting with Petroleum ether/ethyl acetate=10:1, 5:1, 3:1) to afford tert-butyl 3-(3-hydroxycyclopenten-1-yl)-1-(2-trimethylsilylethoxy methyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (180.00 mg, 413.19 umol, 59.72% yield) as colorless oil.

Step 3: Preparation of Compound 5

To a solution of tert-butyl 3-(3-hydroxycyclopenten-1-yl)-1-(2-trimethylsilylethoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (120.00 mg, 275.46 umol, 1.00 *eq*) in MeOH (10.00 mL) was added Pd-C (10%, 25 mg) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (45 psi) at 50°C for 16 hours. LCMS showed the material was consumed completely, and major desired MS detected. The reaction mixture was filtered and the filtrate was concentrated to afford tert-butyl 3-(3-hydroxycyclopentyl)-1-(2-trimethylsilylethoxymethyl)- 6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (100.00 mg, 228.49 umol, 82.95% yield) as colorless oil, which was used directly in the next step. LCMS: 438 [M+1].

Step 4: Preparation of Compound 6

A mixture of tert-butyl 3-(3-hydroxycyclopentyl)-1-(2-trimethylsilylethoxy methyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (180.00 mg, 411.29 umol, 1.00 *eq*) in HCl/dioxane (4 M, 5.00 mL, 48.63 *eq*) was stirred at 25 °C for 2 hr. Precipitate was formed. The mixture was evaporated to afford 3-(4,5,6,7- tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopentanol (100.00 mg, 410.29 umol, 99.76% yield, HCl) as white solid,without further purification and used directly in the next step.

Preparation of Compound 742

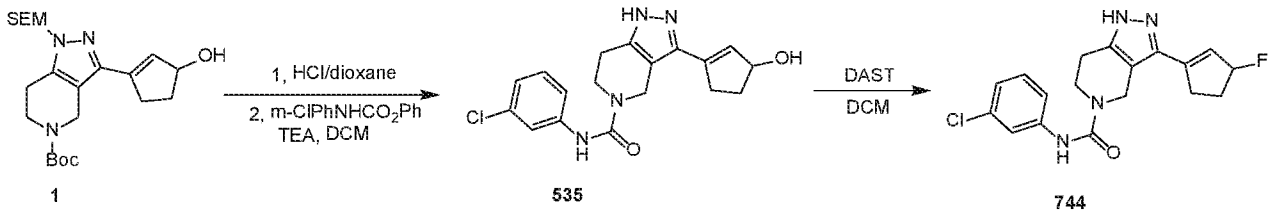
To a solution of 3-(4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopentanol (100.00 mg, 410.29 umol, 1.00 *eq*, HCl) in DCM (5.00 mL) were added TEA (83.03 mg, 820.58 umol, 113.74 uL, 2.00 *eq*) and phenyl N-(3-chlorophenyl)carbamate (101.62 mg, 410.29 umol, 1.00 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed material was consumed completely, and major desired MS detected. The solvent was evaporated. The residue was purified by prep-HPLC(FA) to afford N-(3-chlorophenyl)-3-(3-hydroxycyclopentyl)-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxamide (57.00 mg, 155.04 umol, 37.79% yield, 98.15% purity) as white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 1 H), 7.31 (s, 1 H), 7.20 - 7.28 (m, 1 H), 7.02 (d, J = 7.78 Hz, 1 H), 4.54 - 4.71 (m, 2

H), 4.39 (brs, 1 H), 3.72 - 3.93 (m, 3 H), 3.03 (ddd, *J* = 11.67, 7.65, 4.27 Hz, 1 H), 2.81 (t, *J* = 5.65 Hz, 2 H), 1.91 - 2.22 (m, 4 H), 1.69 - 1.87 (m, 2 H). LCMS: 361/363 [M+1].

Preparation of Compound 743

To a solution of N-(3-chlorophenyl)-3-(3-hydroxycyclopentyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (50.00 mg, 138.57 umol, 1.00 *eq*) in DCM (3.00 mL) was added DAST (33.50 mg, 207.86 umol, 27.46 uL, 1.50 *eq*) at -78°C. The mixture was stirred at 25 °C for 16 hr. LCMS showed the material was consumed completely, and major desired MS detected. The reaction was quenched by water (10 mL), extracted with DCM (10 mL*2). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, the residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(3-fluorocyclopentyl) -1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (6.02 mg, 16.06 umol, 11.59% yield, 96.8% purity) as white solid. LCMS: 363/365 [M+1].

Example 33: Preparation of Compounds535 and 744



Preparation of Compound 535

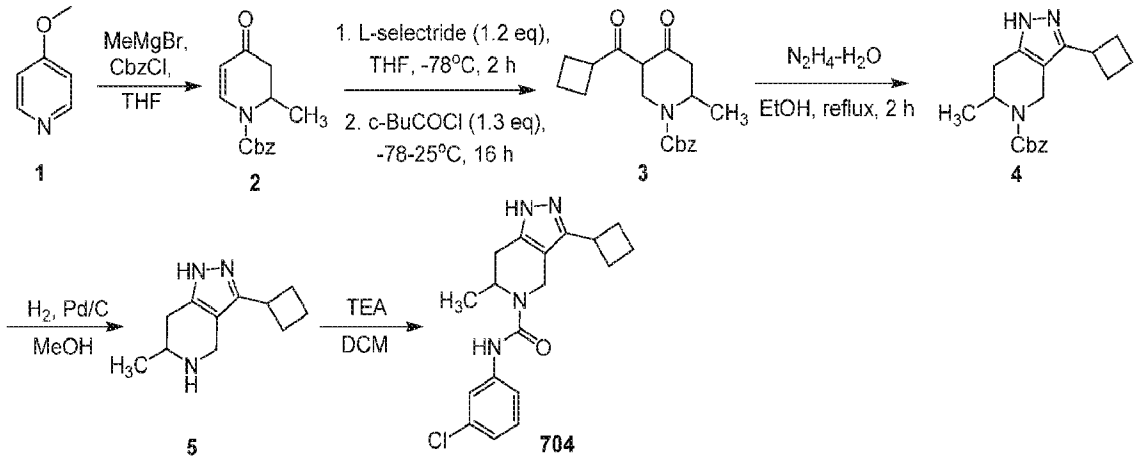
A mixture of tert-butyl 3-(3-hydroxycyclopenten-1-yl)-1-(2-trimethylsilylethoxymethyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (60.00 mg, 137.73 umol, 1.00 *eq*) in HCl/dioxane (4 M, 4.00 mL, 116.17 *eq*) was stirred at 25 °C for 2 hr. The the solvent was evaporated, and diluted in DCM (3.00 mL), TEA (27.87 mg, 275.46 umol, 38.18 uL, 2.00 *eq*) and phenyl N-(3-chlorophenyl)carbamate (34.11 mg, 137.73 umol, 1.00 *eq*) were added, the mixture was stirred at 25 °C for 16 hr. LCMS showed the material was consumed completely, and major desired MS detected. The solvent was evaporated. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(3-hydroxycyclopenten-1-yl) -1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (7.44 mg, 20.21 umol, 14.67% yield, 97.46% purity) as white solid. LCMS: 359/361 [M+1].

Preparation of Compound 744

To a solution of N-(3-chlorophenyl)-3-(3-hydroxycyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (50.00 mg, 139.35 umol, 1.00 *eq*) in DCM (5.00 mL) was added DAST (44.92 mg, 278.70 umol, 36.82 uL, 2.00 *eq*) at - 78 °C under N_2

protection. The mixture was stirred at 25 °C for 16 hr. LCMS showed the material was consumed completely, and major desired MS detected. The mixture was poured into water (10 mL), extracted with ethyl acetate (10 mL*2), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-(3-fluorocyclopenten-1-yl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (15.00 mg, 41.03 umol, 29.45% yield, 98.7% purity) as white solid. LCMS: 361/363 [M+1].

Example 34: Preparation of Compound 704



Step 1: Preparation of Compound 2

To a solution of 4-methoxypyridine (16.10 g, 147.53 mmol, 1.00 *eq*) in THF (200.00 mL) was added CH_3MgBr (3 M, 59.50 mL, 1.21 *eq*) at -10 °C over a period of 20 min under N_2, during which the temperature was maintained below 5 °C. The reaction mixture was warmed to 25 °C for 30 min. A solution of CbzCl (30.20 g, 177.04 mmol, 1.20 *eq*) in THF (80.00 mL) was added dropwise at -10 °C under N2, during which the temperature was maintained below 25°C. The reaction mixture was stirred at 25 °C for 3hr. TLC (PE:EA=3:1) showed the starting material was dissapeared. A HCl solution (3N, 300 mL) was added into the reaction dropwise at -10 °C. The mixtire was extracted with EA (200 mL*2). The combined organic layer was washed 5 % $NaHCO_3$ (500 mL) and dried over Na_2SO_4, filtrated. The filtrate was concentrated in vacuum. The residue was purified by column chromatography (PE:EA=10:1,5:1) to afford benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate (14.50 g, 59.12 mmol, 40.07% yield) as brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 1 H), 7.35 - 7.27 (m, 5 H), 5.28 - 5.22 (m, 1 H), 5.20 (d, *J* = 4.0 Hz, 2H), 4.70 - 4.61 (m, 1 H), 2.78 (dd, *J* = 6.8, 16.4 Hz, 1H), 2.24 (d, *J* = 16.4 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H).

Step 2: Preparation of Compound 3

To a solution of benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate (1.00 g, 4.08 mmol, 1.00 *eq*) in THF (10.00 mL) was added lithium trisec-butylboranuide (1 M, 4.90 mL, 1.20 *eq*) at -78 °C under N_2 protection. The reaction mixture was stirred for 1 hr. Then a solution of cyclobutanecarbonyl chloride (628.84 mg, 5.30 mmol, 604.65 uL, 1.30 *eq*) in THF (1 mL) was added at -78 °C. The mixture was stirred 20 °C for 16 hr. LCMS showed material was consumed completely, and several new peaks were detected. The mixture was poured into saturated NH_4Cl (20 mL), extracted with ethyl acetate (15 mL*2), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated to afford benzyl 5-(cyclobutanecarbonyl)-2-methyl-4-oxo-piperidine-1-carboxylate (1.30 g, crude) as light yellow oil, which was not purified and used directly in the next step. LCMS: 352 [M+23].

Step 3: Preparation of Compound 4

To a solution of benzyl 5-(cyclobutanecarbonyl)-2-methyl-4-oxo-piperidine-1-carboxylate (1.00 g, 3.04 mmol, 1.00 *eq*) in EtOH (10.00 mL) was added N_2H_4-H_2O (1.22 g, 6.08 mmol, 1.18 mL, 2.00 *eq*). The mixture was stirred at 80 °C for 1 hr. TLC (petroleum ether/ethyl acetate=1:1) showed a major new spot. The mixture was concentrated. The residue was extracted with ethyl acetate (10 mL*2). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography (silical gel, eluting with petroleum ether/ethyl acetate=10:1,1:1) to afford impure product (230 mg with 30 % purity, colorless oil) which was purified by prep-HPLC (FA) to afford benzyl 3-cyclobutyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (30.00 mg, 92.19 umol, 3.03% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=3.96 Hz, 5 H), 5.19 (s, 2 H), 4.58 - 4.65 (m, 1 H), 4.14 (brs, 1 H), 3.56 (s, 1 H), 2.90 (dd, *J* = 15.82, 5.84 Hz, 1 H), 2.56 (d, *J* = 15.82 Hz, 1 H), 2.32 (brs, 4 H), 2.02 - 2.15 (m, 1 H), 1.84 - 1.99 (m, 1 H), 1.15 (d, *J* = 6.97 Hz, 3 H). LCMS: 326 [M+1].

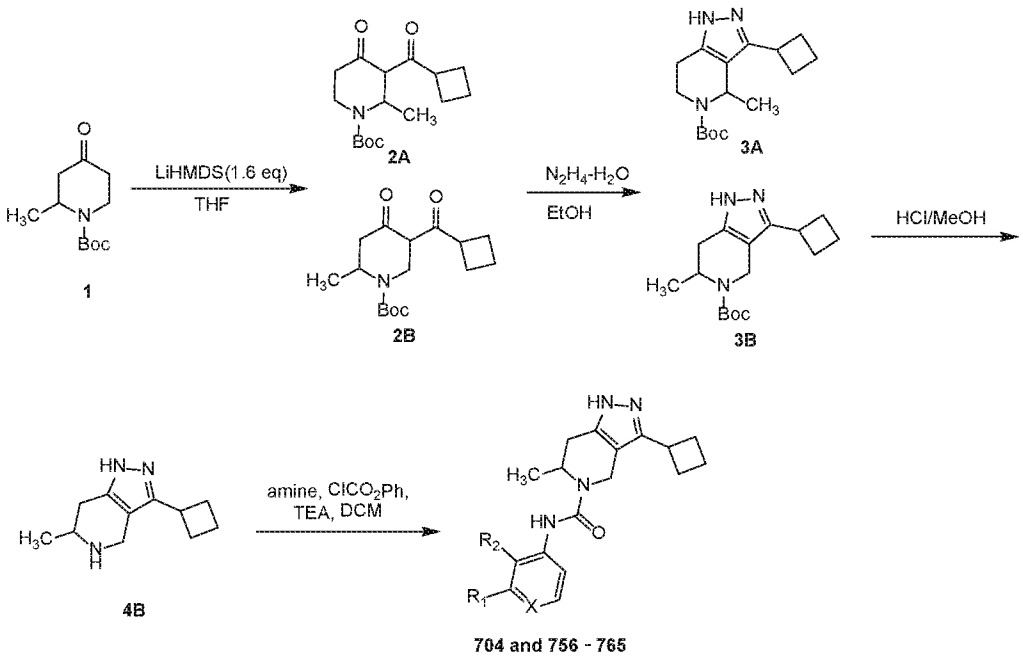
Step 4: Preparation of Compound 5

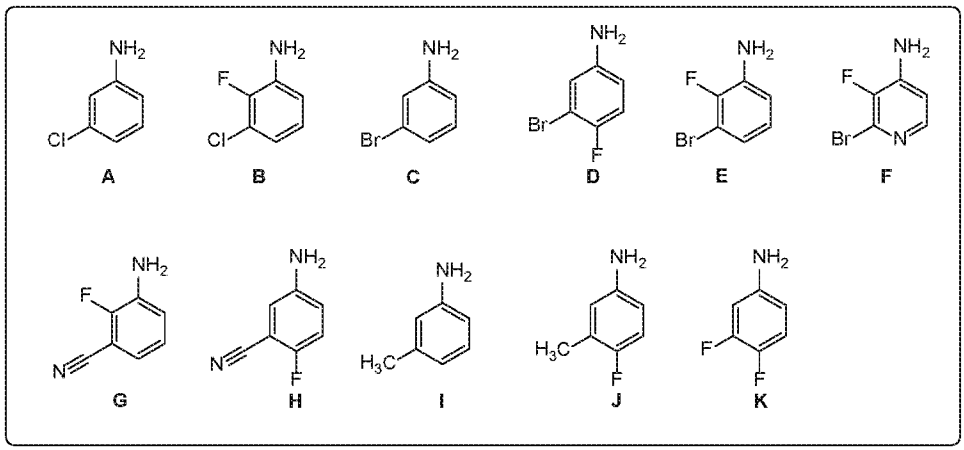
To a solution of benzyl 3-cyclobutyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (60.00 mg, 184.39 umol, 1.00 *eq*) in MeOH (5.00 mL) was added Pd/C (6.00 mg,10%) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50psi) at 25 °C for 16 hours. TLC (Petroleum ether/ethyl acetate=1:1) showed the material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated to afford 3-cyclobutyl-6-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (18.00 mg, 94.11 umol, 51.04% yield) as colorless oil.

Preparation of Compound 704

To a solution of 3-cyclobutyl-6-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (18.00 mg, 94.11 umol, 1.00 *eq*) and phenyl N-(3-chlorophenyl)carbamate (27.97 mg, 112.93 umol, 1.20 *eq*) in DCM (4.00 mL) was added TEA (19.05 mg, 188.22 umol, 26.10 uL, 2.00 *eq*). The mixture was stirred at 25 °C for 4 hr. LCMS showed the material was consumed completely, major was desired MS detected. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (FA) to afford N-(3-chlorophenyl)-3-cyclobutyl-6-methyl-1,4,6,7- tetrahydropyrazolo[4,3-c]pyridine-5-carboxamide (29.98 mg, 81.35 umol, 86.44% yield, 93.57% purity) as white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 1 H), 7.19 - 7.36 (m, 2 H), 7.03 (d, *J* = 7.78 Hz, 1 H), 4.91 (brs, 2 H), 4.21 (d, *J* = 15.31 Hz, 1 H), 3.61 (s, 1 H), 2.98 (d, *J* = 5.77 Hz, 1 H), 2.62 (d, *J* = 15.81 Hz, 1 H), 2.28 - 2.43 (m, 4 H), 2.04 - 2.16 (m, 1 H), 1.97 (brs, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H). LCMS: 345/347 [M+1].

Example 35: Preparation of Compounds704 and 756, 757, 758, 759, 760, 761, 762, 763, 764, and 765

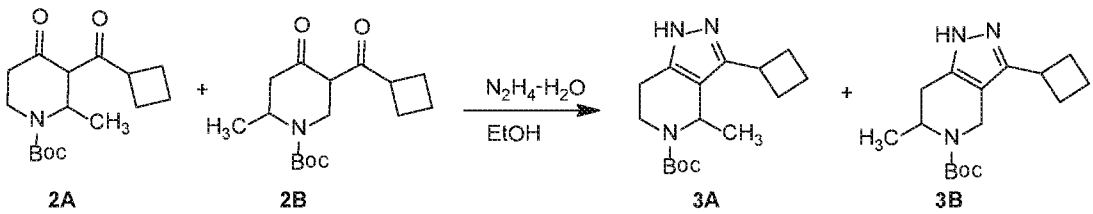




Step 1: Preparation of Compounds 2A and 2B

To a solution of tert-butyl 2-methyl-4-oxo-piperidine-1-carboxylate (1.00 g, 4.69 mmol, 1.00 *eq*) in THF (10.00 mL) was added LiHMDS (1 M, 9.38 mL, 2.00 *eq*) at -78 °C. The mixture was stirred for 1 hr. Then cyclobutanecarbonyl chloride (834.07 mg, 7.04 mmol, 801.99 uL, 1.50 *eq*) was added, and the mixture was stirred at 25 °C for 15 hr. TLC (Petroleum ether/ethyl acetate=5:1) showed material was consumed completely and a major new spot detected. The mixture was poured into saturated NH_4Cl (20 mL), extracted with ethyl acetate (20 mL*2). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to afford a mixture of tert-butyl3-(cyclobutanecarbonyl)-2-methyl-4-oxo-piperidine-1- carboxylate and tert-butyl5-(cyclobutanecarbonyl)-2-methyl-4-oxo-piperidine-1-carboxylate (1.10 g, crude) as light yellow oil.

Step 2: Preparation of Compounds 3A and 3B



To a mixture of tert-butyl 3-(cyclobutanecarbonyl)-2-methyl-4-oxo-piperidine-1- carboxylate (1.10 g, 3.72 mmol, 1.00 *eq*) and tert-butyl 5-(cyclobutanecarbonyl)-2-methyl-4-oxo-piperidine-1-carboxylate (1.10 g, 3.72 mmol, 1.00 *eq*) in EtOH (15.00 mL) was added hydrazine (238.45 mg, 7.44 mmol, 267.92 uL, 2.00 *eq*). The mixture was stirred at 80 °C for 1 hr. TLC (Petroleum ether/ethyl acetate=1:1) showed material was consumed completely, and a major new spot detected. The solvent was evaporated. The residue was washed with water (20 mL), extracted with ethyl acetate (30 mL*2). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography (silical gel, eluting with Petroleum ether/ethyl

acetate=10:1, 3:1, 1:1) to afford a mixture of tert-butyl 3-cyclobutyl-4-methyl-1,4,6,7-tetrahydro pyrazolo[4,3-c]pyridine-5-carboxylate and tert-butyl 3-cyclobutyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (680.00 mg, 2.33 mmol, 62.63% yield) as white solid. The mixture (200 mg) was purified by chiral SFC to afford two fractions, **fraction 1** (86 mg, white solid, Rt = 1.855,1.922 min) and **fraction 2** (82 mg, white solid, Rt = 2.251,2.357 min).

The separation method:

Instrument: SFC 80

Column: AD-10um.

Mobile phase: A for CO_2 and B for Ethanol (0.1%Ammonia)

Gradient: B 40%

Flow rate: 70mL /min

Back pressure: 100bar

Column temperature: 35°C

Wavelength: 220nm

The **fraction 1** (2.5 g) was further purified by chiral SFC to afford the first enantiomer of tert-butyl3-cyclobutyl-4-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate **3A_E1** (:.10 g, 3.78 mmol, 44.06% yield, Rt = 1.128 min) as white solid and the first enantiomer of tert-butyl 3- cyclobutyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate **3B_E1** (1.20 g, 4.12 mmol, 48.02% yield, Rt = 1.536 min) as white solid.

3A_E1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 - 5.20 (m, 1 H), 4.09 - 4.40 (m, 1 H), 3.43 (q, J = 8.72 Hz, 1 H), 2.98 (brs, 1 H), 2.51 - 2.74 (m, 2 H), 2.08 - 2.34 (m, 4 H), 1.95 - 2.04 (m, 1 H), 1.85 (d, J = 7.28 Hz, 1 H), 1.41 (s, 9 H), 1.18 - 1.26 (m, 3 H). **3B_E1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (brs, 2 H), 3.90 (d, J = 15.56 Hz, 1 H), 3.39 - 3.51 (m, 1 H), 2.86 (dd, J = 15.69, 5.90 Hz, 1 H), 2.46 (d, J = 15.56 Hz, 1 H), 2.11 - 2.33 (m, 4 H), 1.93 - 2.07 (m, 1 H), 1.78 - 1.90 (m, 1 H), 1.37 - 1.49 (m, 9 H), 1.05 (d, J = 7.03 Hz, 3 H).

The separation method:

Instrument: SFC 80

Column: AS-10um.

Mobile phase: A for CO_2 and B for Ethanol (0.1%Ammonia)

Gradient: B 40%

Flow rate: 70mL /min

Back pressure: 100bar

Column temperature: 35°C

Wavelength: 220nm

The **fraction 2** (2.5 g) was further purified by chiral SFC to afford the second enantiomer of tert-butyl3-cyclobutyl-4-methyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate **3A_E2** (1.10 g, 3.78 mmol, 44.06% yield, Rt = 1.587) as white solid and the second enantiomer of tert-butyl 3-cyclobutyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate **3B_E2** (1.20 g, 4.12 mmol, 48.02% yield, Rt = 1.841 min) as white solid. **3A_E2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 - 5.22 (m, 1 H), 4.06 - 4.39 (m, 1 H), 3.36 - 3.50 (m, 1 H), 2.98 (brs, 1 H), 2.59 (brs, 2 H), 2.09 - 2.34 (m, 4 H), 1.93 - 2.06 (m, 1 H), 1.85 (d, *J* = 7.28 Hz, 1 H), 1.31 - 1.46 (m, 9 H), 1.22 (d, *J* = 6.53 Hz, 3 H). **3B_E2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (brs, 2 H), 3.90 (d, *J* = 15.56 Hz, 1 H), 3.45 (t, *J* = 8.78 Hz, 1 H), 2.86 (dd, *J* = 15.69, 5.90 Hz, 1 H), 2.46 (d, *J* = 15.81 Hz, 1 H), 2.12 - 2.34 (m, 4 H), 1.96 - 2.04 (m, 1 H), 1.78 - 1.90 (m, 1 H), 1.42 (s, 9 H), 1.05 (d, *J*=6.78 Hz, 3 H).

The separation method:

Instrument: SFC 80

Column: AD-10um.

Mobile phase: A for CO_2 and B for Ethanol (0.1%Ammonia)

Gradient: B 40%

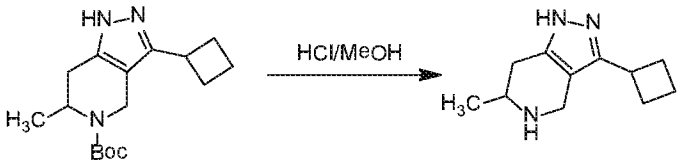
Flow rate: 70mL /min

Back pressure: 100bar

Column temperature: 35°C

Wavelength: 220nm.

Step 3: Preparation of Compound 4B_E1/E2

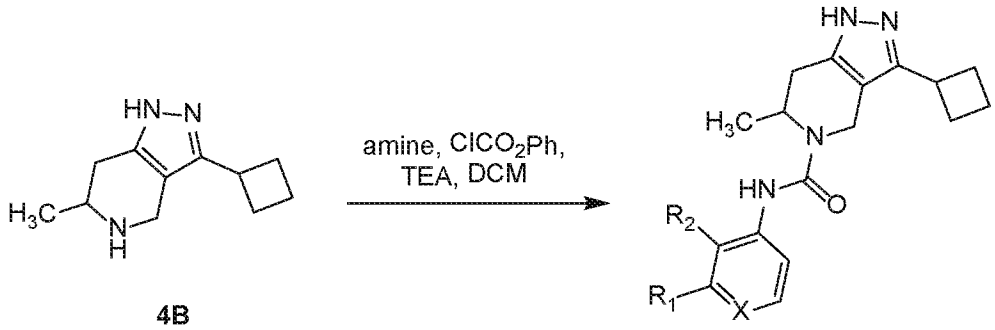


3B_E1
3B_E2

4B_E1
4B_E2

A mixture of tert-butyl 3-cyclobutyl-6-methyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate **3B_E1** (1.20 g, 4.12 mmol, 1.00 *eq*) in HCl/dioxane (4 M, 10.00 mL, 9.71 *eq*) was stirred at 25 °C for 2 hr. White solid was formed. The solvent was evaporated to afford 3-cyclobutyl-6-methyl-4,5,6,7-tetrahydro -1H-pyrazolo[4,3-c]pyridine **4B_E1** (930.00 mg, 4.08 mmol, 99.12% yield, HCl) as white solid.

Preparation of Compounds 704, and 757 through 765

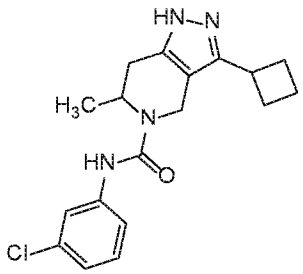
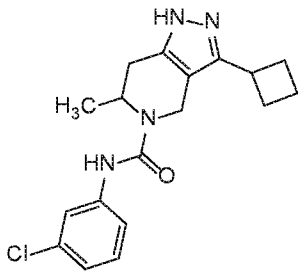


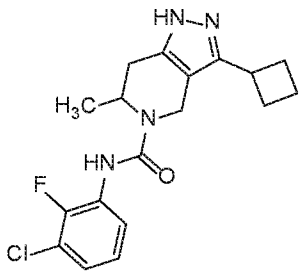
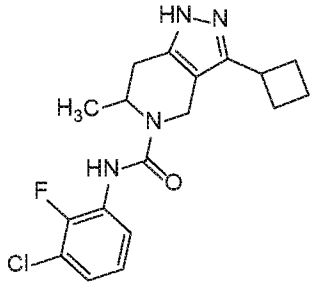
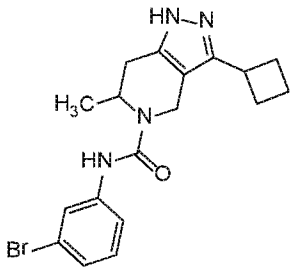
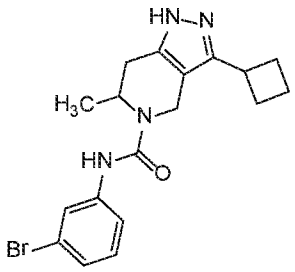
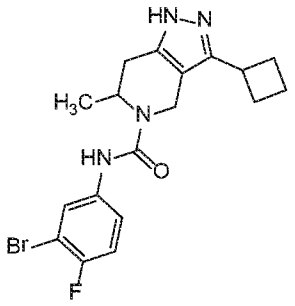
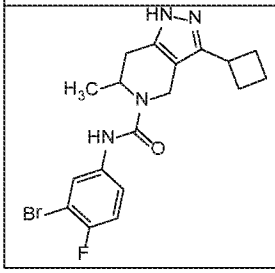
4B

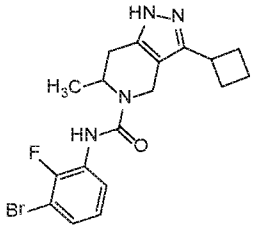
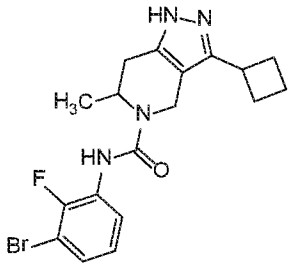
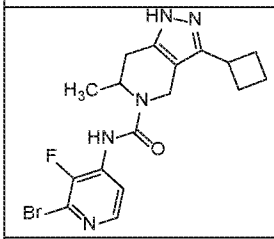
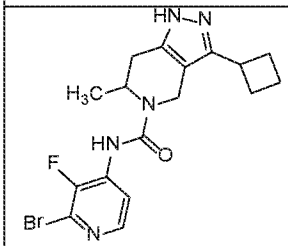
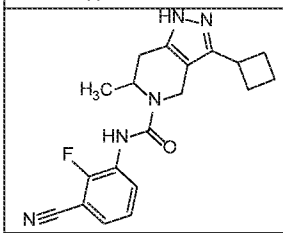
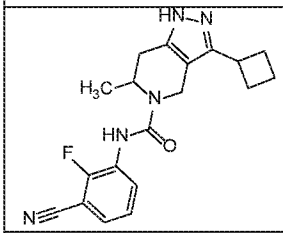
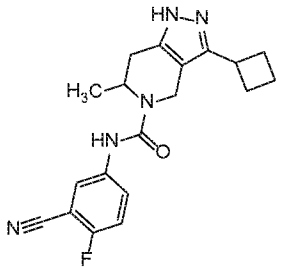
704 and 757 - 765

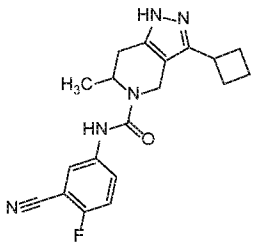
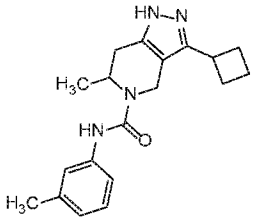
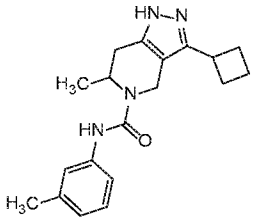
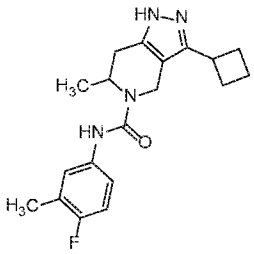
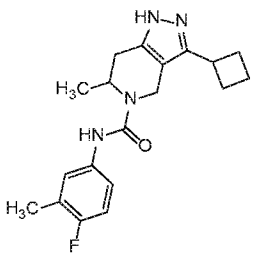
General Procedure

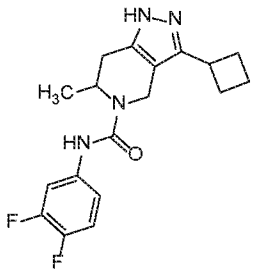
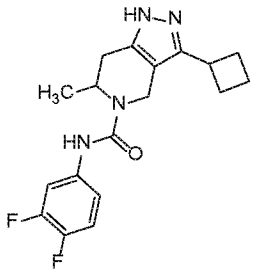
To a solution of amine (1.0 eq) and phenyl carbonochloridate (1.0 eq) in DCM (1.00 mL) was added TEA (3 *eq*), the reaction mixture was stirred at 30 °C for 30 minutes. TLC indicated amine was consumed completely. The mixture was added to a mixture of compound 4B (1.00 *eq*, HCl salt) in DCM (1.00 mL) and TEA (3 eq). The reaction mixture was stirred at 30 °C for 16 hours. LCMS showed reaction was completed. The mixture was extracted with DCM (10 mL*3) and water (10 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (FA) to give the desired product as white solid.

Structure	Comp. ID	Analytical Data
	704 (E1)	LCMS(M+1):345/347; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.54 (t, *J* = 1.88 Hz, 1 H), 7.31 (s, 1 H), 7.22 - 7.28 (m, 1 H), 7.03 (d, *J* = 7.78 Hz, 1 H), 4.84 (brs, 2 H), 4.21 (d, *J* = 15.06 Hz, 1 H), 3.61 (t, *J* = 8.78 Hz, 1 H), 3.00 (dd, *J* = 15.69, 5.90 Hz, 1 H), 2.62 (d, *J* = 15.81 Hz, 1 H), 2.27 - 2.43 (m, 4 H), 2.10 (d, *J* = 9.03 Hz, 1 H), 1.95 (dd, *J* = 7.53, 3.26 Hz, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).
	704 (E2)	LCMS(M+1):345/347; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.54 (t, *J* = 1.88 Hz, 1 H), 7.21 - 7.37 (m, 2 H), 7.03 (d, *J* = 7.78 Hz, 1 H), 4.84 (brs, 2 H), 4.21 (d, *J* = 15.06 Hz, 1 H), 3.61 (t, *J* = 8.91 Hz, 1 H), 3.00 (dd, *J* = 15.81, 5.77 Hz, 1 H), 2.62 (d, *J* = 15.81 Hz, 1 H), 2.26 - 2.46 (m, 4 H), 2.10 (d, *J* = 9.29 Hz, 1 H), 1.95 (dd, *J* = 7.53, 3.51 Hz, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).

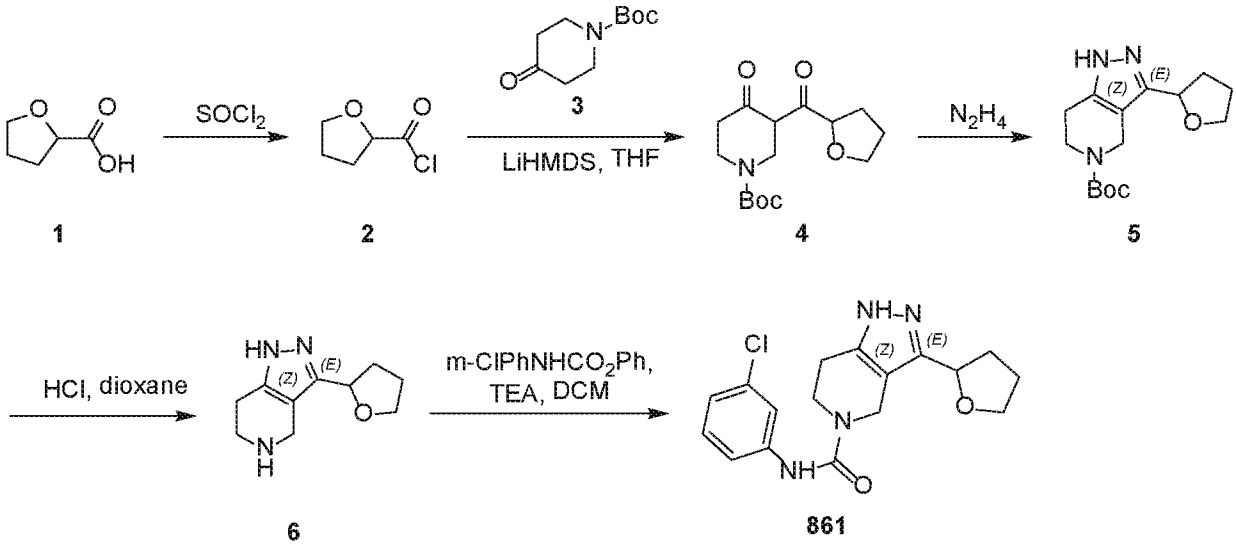
	756 (E1)	LCMS(M+1):363/365; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.34 - 7.41 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.08 - 7.14 (m, 1 H), 4.83 (brs, 2 H), 4.19 - 4.26 (m, 1 H), 3.59 (m, *J* = 8.97 Hz, 1 H), 2.99 (dd, *J* = 15.81, 5.90 Hz, 1 H), 2.61 (d, *J* = 15.81 Hz, 1 H), 2.28 - 2.39 (m, 4 H), 2.02 - 2.15 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).
	756 (E2)	LCMS(M+1):363/365; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.34 - 7.40 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.11 (td, *J* = 8.12, 1.44 Hz, 1 H), 4.83 (s, 2 H), 4.22 (d, *J* = 15.31 Hz, 1 H), 3.59 (m, *J* = 8.82 Hz, 1 H), 2.99 (dd, *J* = 15.81, 5.90 Hz, 1 H), 2.61 (d, *J* = 15.69 Hz, 1 H), 2.29 - 2.38 (m, 4 H), 2.02 - 2.15 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.20 (d, *J* = 6.90 Hz, 3 H).
	757 (E1)	LCMS(M+1):389/391; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.66 - 7.68 (m, 1 H), 7.34 (dt, *J* = 6.87, 2.15 Hz, 1 H), 7.14 - 7.21 (m, 2 H), 4.82 (s, 2 H), 4.19 (d, *J* = 15.18 Hz, 1 H), 3.58 (m, *J* = 8.75 Hz, 1 H), 2.97 (dd, *J* = 15.81, 5.77 Hz, 1 H), 2.60 (d, *J* = 15.81 Hz, 1 H), 2.27 - 2.38 (m, 4 H), 2.03 - 2.14 (m, 1 H), 1.88 - 1.99 (m, 1 H), 1.18 (d, *J* = 6.78 Hz, 3 H).
	757 (E2)	LCMS(M+1):389/391; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.69 (s, 1 H), 7.36 (brs, 1 H), 7.16 - 7.24 (m, 2 H), 4.84 (brs, 2 H), 4.21 (d, *J* = 15.06 Hz, 1 H), 3.61 (t, *J* = 8.91 Hz, 1 H), 3.00 (dd, *J* = 15.81, 5.77 Hz, 1 H), 2.36 (t, *J* = 8.66 Hz, 4 H), 2.05 - 2.19 (m, 1 H), 1.89 - 2.00 (m, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).
	758 (E1)	LCMS(M+1):407/409; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.73 (dd, *J* = 6.15, 2.64 Hz, 1 H), 7.35 (ddd, *J* = 8.97, 4.20, 2.64 Hz, 1 H), 7.13 (t, *J* = 8.72 Hz, 1 H), 4.82 (s, 2 H), 4.19 (d, *J* = 14.93 Hz, 1 H), 3.59 (m, J = 8.69 Hz, 1 H), 2.97 (dd, *J* = 15.69, 5.65 Hz, 1 H), 2.61 (d, *J* = 15.94 Hz, 1 H), 2.28 - 2.39 (m, 4 H), 2.03 - 2.16 (m, 1 H), 1.88 - 1.99 (m, 1 H), 1.18 (d, *J* = 6.90 Hz, 3 H).
	758 (E2)	LCMS(M+1):407/409; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.71 - 7.76 (m, 1 H), 7.33 - 7.41 (m, 1 H), 7.14 (t, *J* = 8.66 Hz, 1 H), 4.83 (brs, 2 H), 4.21 (d, *J* = 15.06 Hz, 1 H), 3.61 (s, 1 H), 2.94 - 3.03 (m, 1 H), 2.62 (d, *J* = 15.81 Hz, 1 H), 2.36 (t, *J* = 8.53 Hz, 4 H), 2.05 - 2.18 (m, 1 H), 1.89 - 2.00 (m, 1 H),

		1.19 (d, *J* = 6.78 Hz, 3 H).
	759 (E1)	LCMS(M+1):407/409; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.35 - 7.44 (m, 2 H), 7.05 (td, J = 8.09, 1.25 Hz, 1 H), 4.83 (s, 2 H), 4.22 (d, *J* = 14.81 Hz, 1 H), 3.58 (m, *J* = 8.85 Hz, 1 H), 2.99 (dd, *J* = 15.75, 6.09 Hz, 1 H), 2.61 (d, *J* = 15.81 Hz, 1 H), 2.27 - 2.38 (m, 4 H), 2.01 - 2.15 (m, 1 H), 1.87 - 1.98 (m, 1 H), 1.19 (d, *J* = 6.78 Hz, 3 H).
	759 (E2)	LCMS(M+1):407/409; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.37 - 7.48 (m, 2 H), 7.07 (t, *J* = 8.16 Hz, 1 H), 4.85 (brs, 2 H), 4.24 (d, *J* = 15.06 Hz, 1 H), 3.61 (q, *J* = 8.85 Hz, 1 H), 3.01 (dd, *J* = 15.81, 5.77 Hz, 1 H), 2.63 (d, *J* = 15.81 Hz, 1 H), 2.27 - 2.42 (m, 4 H), 2.10 (d, *J* = 10.04 Hz, 1 H), 1.90 - 2.01 (m, 1 H), 1.21 (d, *J* = 6.78 Hz, 3 H).
	760 (S)	LCMS(M+1):408/410
	760 (R)	LCMS(M+1):408/410
	761 (S)	LCMS(M+1):354
	761 (R)	LCMS(M+1):354
	762 (E1)	LCMS(M+1):354; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.80 (dd, *J* = 5.71, 2.70 Hz, 1 H), 7.67 - 7.73 (m, 1 H), 7.28 (t, *J* = 8.97 Hz, 1 H), 4.83 (brs, 2 H), 4.20 (d, *J* = 15.18 Hz, 1 H), 3.59 (t, *J* = 8.60 Hz, 1 H), 2.97 (dd, *J* = 15.62, 5.58 Hz, 1 H), 2.61 (d, *J* = 15.94 Hz, 1 H), 2.27 - 2.39 (m, 4 H), 2.04 - 2.14 (m, 1 H), 1.94 (d, *J* = 8.03 Hz, 1 H),

		1.19 (d, *J* = 6.78 Hz, 3 H).
	762 (E2)	LCMS(M+1):354; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.82 (dd, *J* = 5.77, 2.76 Hz, 1 H), 7.72 (ddd, *J* = 9.10, 4.71, 3.01 Hz, 1 H), 7.29 (t, *J* = 8.91 Hz, 1 H), 4.85 (brs, 2 H), 4.22 (d, *J* = 15.06 Hz, 1 H), 3.61 (t, *J* = 8.91 Hz, 1 H), 2.99 (dd, *J* = 15.69, 5.65 Hz, 1 H), 2.63 (d, *J* = 15.56 Hz, 1 H), 2.29 - 2.43 (m, 4 H), 2.05 - 2.16 (m, 1 H), 1.89 - 2.01 (m, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).
	763 (E1)	LCMS(M+1):325; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.20 (s, 1 H), 7.15 (d, *J* = 5.02 Hz, 2 H), 6.86 (t, *J* = 3.45 Hz, 1 H), 4.82 (s, 2 H), 4.19 (d, *J* = 15.18 Hz, 1 H), 3.59 (m, *J* = 8.94 Hz, 1 H), 2.98 (dd, *J* = 16.00, 5.58 Hz, 1 H), 2.60 (d, *J* = 15.56 Hz, 1 H), 2.26 - 2.39 (m, 7 H), 2.04 - 2.14 (m, 1 H), 1.88 - 1.99 (m, 1 H), 1.18 (d, *J* = 6.78 Hz, 3 H).
	763 (E2)	LCMS(M+1):325; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.15 - 7.24 (m, 2 H), 6.88 (brs, 1 H), 4.84 (brs, 2 H), 4.21 (d, *J* = 15.06 Hz, 1 H), 3.61 (t, *J* = 8.91 Hz, 1 H), 3.00 (dd, *J* = 15.81, 5.77 Hz, 1 H), 2.62 (d, *J* = 15.81 Hz, 1 H), 2.31 - 2.40 (m, 7 H), 2.05 - 2.15 (m, 1 H), 1.95 (dd, *J* = 7.28, 3.51 Hz, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).
	764 (E1)	LCMS(M+1):343; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.22 (dd, *J* = 6.65, 2.51 Hz, 1 H), 7.12 - 7.18 (m, 1 H), 6.93 (t, *J* = 9.10 Hz, 1 H), 4.81 - 4.85 (m, 2 H), 4.18 (d, *J* = 15.06 Hz, 1 H), 3.59 (q, *J* = 8.88 Hz, 1 H), 2.97 (dd, *J* = 16.00, 5.96 Hz, 1 H), 2.60 (d, *J* = 15.81 Hz, 1 H), 2.28 - 2.39 (m, 4 H), 2.24 (d, *J* = 1.88 Hz, 3 H), 2.03 - 2.15 (m, 1 H), 1.88 - 1.98 (m, 1 H), 1.17 (d, *J* = 6.90 Hz, 3 H).
	764 (E2)	LCMS(M+1):343; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.21 - 7.27 (m, 1 H), 7.13 - 7.19 (m, 1 H), 6.95 (t, *J* = 9.03 Hz, 1 H), 4.83 (brs, 2 H), 4.20 (d, *J* = 15.06 Hz, 1 H), 3.60 (s, 1 H), 2.94 - 3.03 (m, 1 H), 2.61 (d, *J* = 15.81 Hz, 1 H), 2.30 - 2.42 (m, 4 H), 2.26 (s, 3 H), 2.10 (d, *J* = 10.04 Hz, 1 H), 1.96 (d, *J* = 7.78 Hz, 1 H), 1.19 (d, *J* = 6.78 Hz, 3 H).

	765 (E1)	LCMS(M+1):347; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 1.18 (d, *J* = 6.78 Hz, 3 H), 1.90 - 1.98 (m, 1 H), 2.04 - 2.14 (m, 1 H), 2.28 - 2.39 (m, 4 H), 2.60 (d, *J* = 15.81 Hz, 1 H), 2.97 (dd, *J* = 15.50, 6.21 Hz, 1 H), 3.53 - 3.64 (m, 1 H), 4.18 (d, *J* = 14.68 Hz, 1 H), 4.81 (s, 2 H), 7.09 - 7.20 (m, 2 H), 7.39 - 7.46 (m, 1 H).
	765 (E2)	LCMS(M+1):347; ^{1}H NMR (400 MHz, METHANOL-d4) d ppm 7.41 - 7.49 (m, 1 H), 7.11 - 7.21 (m, 2 H), 4.79 - 4.85 (m, 2 H), 4.20 (d, *J* = 15.06 Hz, 1 H), 3.61 (t, *J* = 8.91 Hz, 1 H), 2.99 (dd, *J* = 15.81, 5.77 Hz, 1 H), 2.62 (d, *J* = 15.81 Hz, 1 H), 2.36 (t, *J* = 8.53 Hz, 4 H), 2.06 - 2.16 (m, 1 H), 1.95 (dd, *J* = 7.53, 3.51 Hz, 1 H), 1.20 (d, *J* = 6.78 Hz, 3 H).

Example 36: Preparation of Compound 861



Step 1: Preparation of Compound 2

A mixture of tetrahydrofuran-2-carboxylic acid (2.00 g, 17.23 mmol, 1.65 mL, 1.00 *eq*) in $SOCl_2$ (10.25 g, 86.13 mmol, 6.25 mL, 5.00 *eq*) was stirred at 90 °C for 3 hours. The mixture was concentrated in reduced pressure to afford tetrahydrofuran-2-carbonyl chloride (2.32 g, 17.24 mmol, 100.00% yield) as yellow oil.

Step 2: Preparation of Compound 4

To a mixture of tert-butyl 4-oxopiperidine-1-carboxylate (3.44 g, 17.24 mmol, 1.00 *eq*) in THF (20 mL) was added LiHMDS (1 M, 25.86 mL, 1.50 *eq*) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 30 min, then tetrahydrofuran-2-carbonyl

chloride (2.32 g, 17.24 mmol, 1.00 *eq*) in THF (20 mL) was added to the mixture. The mixture was heated to 25 °C and stirred for 2.5 hours. LCMS showed the reaction was completed. The mixture was quenched with aq. NH_4Cl (30 mL). The aqueous phase was extracted with ethyl acetate (40 mL*2). The combined organic phase was washed with brine (40 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl 4-oxo-3-(tetrahydrofuran-2-carbonyl)piperidine-1-carboxylate (6.00 g, crude) as yellow oil. LCMS: 298 [M+1].

Step 3: Preparation of Compound 5

To a mixture of tert-butyl 4-oxo-3-(tetrahydrofuran-2-carbonyl)piperidine-1-carboxylate (6.00 g, 20.18 mmol, 1.00 *eq*) in MeOH (100.00 mL) was added $N_2H_4·H_2O$ (1.19 g, 20.18 mmol, 1.15 mL, 85% purity, 1.00 *eq*) in one portion under N_2. The mixture was stirred at 30 °C for 12 hours. LCMS showed the reaction was completed, and desired product was detected. The mixture was concentrated in reduced pressure. The residue was poured into water (50 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (50 mL*2). The combined organic phase was washed with brine (50 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=1/1) to afford tert-butyl 3-tetrahydrofuran-2-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5- carboxylate (1.80 g, 3.31 mmol, 16.42% yield, 54% purity) as yellow solid.

LCMS: 294 [M+1].

Step 4: Preparation of Compound 6

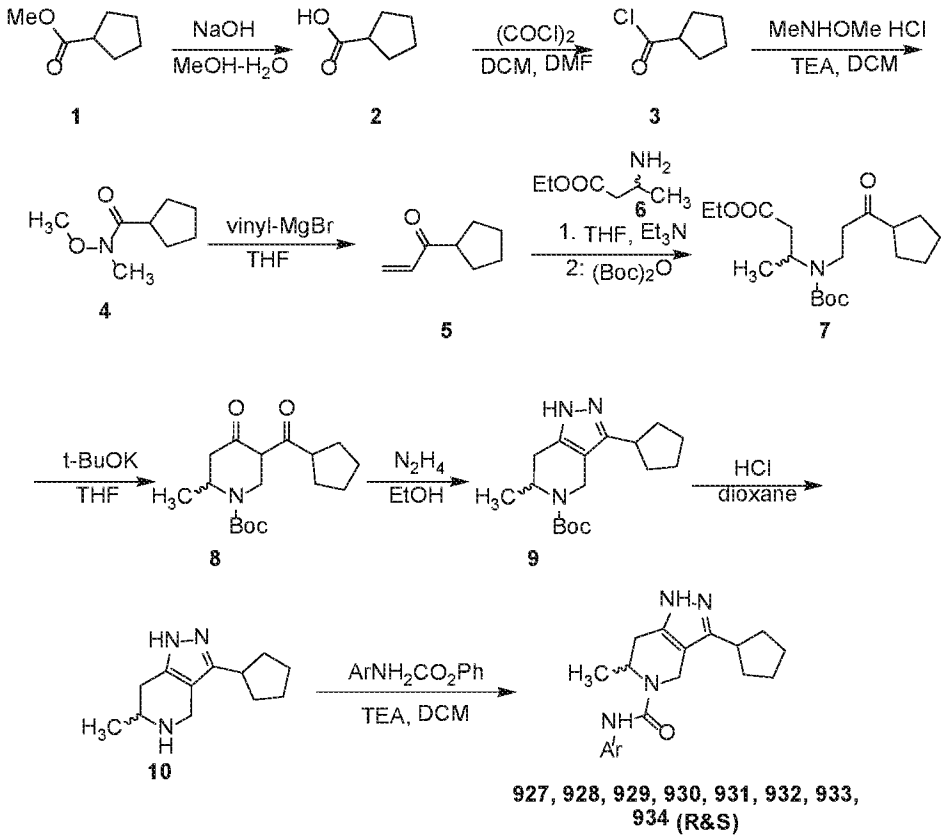
To a mixture of tert-butyl 3-tetrahydrofuran-2-yl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (80.00 mg, 272.70 umol, 1.00 *eq*) in dioxane (1.00 mL) was added HCl/dioxane (4 M, 4.00 mL, 58.67 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 hours. TLC (Petroleum ether : Ethyl acetate=1:1) showed the reaction was completed. The mixture was concentrated in vacuum to afford 3-tetrahydrofuran-2-yl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c] pyridine (62.64 mg, 272.69 umol, 100.00% yield, HCl) as yellow solid.

Preparation of Compound 861

To a mixture of 3-tetrahydrofuran-2-yl-4,5,6,7-tetrahydro-1H-pyrazolo [4,3-c] pyridine (62.64 mg, 272.69 umol, 1.00 *eq*, HCl) and phenyl N-(3-chlorophenyl) carbamate (67.54 mg, 272.69 umol, 1.00 *eq*) in DCM (8.00 mL) was added TEA (82.78 mg, 818.07 umol, 113.40 uL, 3.00 *eq*) in one portion at 30 °C under N_2. The mixture was stirred at 30 °C for 12 hours. LCMS showed the reaction was completed. The mixture was poured

into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL*2). The combined organic phase was washed with brine (10 mL*2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(FA) to afford N-(3-chlorophenyl)-3-tetrahydrofuran-2-yl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxamide (31.66 mg, 91.29 umol, 33.48% yield, 100% purity) as white solid. ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.51 (t, J=1.95 Hz, 1H), 7.23 (s, 2H), 6.97-7.04 (m, 1H), 4.92-4.96 (m, 1H), 4.58 (s, 2H), 3.99-4.08 (m, 1H), 3.73-3.92 (m, 3H), 2.74-2.87 (m, 2H), 2.23-2.37 (m, 1H), 1.95-2.13 (m, 3H). LCMS: 347 [M+1].

Example 37: Preparation of Compounds 927, 928, 929, 930, 931, 932, 933, and 934



Step 1: Preparation of Compound 2

To a solution of methyl cyclopentanecarboxylate (10.00 g, 78.02 mmol, 1.00 *eq*) in MeOH (100.00 mL) was added a solution of NaOH (6.24 g, 156.04 mmol, 2.00 *eq*) in H_2O (40.00 mL), the reaction mixture was stirred at 25 °C for 2 hours. TLC indicated starting material was consumed completely, and one major new spot with larger polarity was detected. The pH of the reaction mixture was adjusted to around 6 by adding diluted hydrochloride acid (6 N, 40 mL), then extracted with EA (200 mL*4), the organic phase was

dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford cyclopentanecarboxylic acid (8.80 g, 77.10 mmol, 98.82% yield) as yellow oil. The crude product was used in the next step directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.90 (br. s., 1 H) 2.56 - 2.67 (m, 1 H) 1.73 - 1.82 (m, 2 H) 1.46 - 1.71 (m, 6 H).

Step 2: Preparation of Compound 3

To a solution of cyclopentanecarboxylic acid (8.80 g, 77.10 mmol, 8.38 mL, 1.00 *eq*) in DCM (60.00 mL) was added DMF (563.52 mg, 7.71 mmol, 593.18 uL, 0.10 *eq*), followed by $(COCl)_2$ (19.57 g, 154.20 mmol, 13.50 mL, 2.00 *eq*) dropwise at 0 °C, the reaction mixture was warmed to 25 °C and stirred at 25 °C for 2 hours. TLC indicated starting material was consumed completely (treating with MeOH and monitoring the ester). Removed the solvent on a rotary evaporator to afford cyclopentanecarbonyl chloride (9.80 g, 73.91 mmol, 95.87% yield) as yellow oil. The crude product was used in the next step directly without purification.

Step 3: Preparation of Compound 4

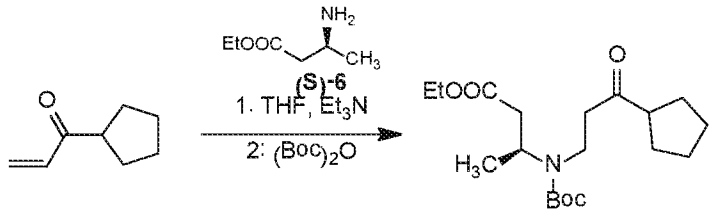
To a mixture of N-methoxymethanamine (7.21 g, 73.91 mmol, 1.00 *eq*, HCl) in DCM (100.00 mL) was added TEA (22.44 g, 221.73 mmol, 30.74 mL, 3.00 *eq*) at 0 °C, followed by cyclopentanecarbonyl chloride (9.80 g, 73.91 mmol, 8.99 mL, 1.00 *eq*), the reaction mixture was stirred at 25 °C for 2 hours. One main peak with desired MS was detected by LCMS. The mixture was extracted with DCM (500 mL*2) and water (400 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford N-methoxy-N-methyl-cyclopentanecarboxamide (10.80 g, 68.70 mmol, 92.95% yield) as yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.67 (s, 3 H) 3.16 (s, 3 H) 2.98 - 3.13 (m, 1 H) 1.67 - 1.87 (m, 6 H) 1.47 - 1.62(m, 2 H).

Step 4: Preparation of Compound 5

Cooled the three-necked round bottom flask to -78 °C, bromo(vinyl)magnesium (1 M, 25.44 mL, 2.00 *eq*) was added to a solution of N-methoxy-N-methyl- cyclopentane carboxamide (2.00 g, 12.72 mmol, 1.00 *eq*) in THF (25.00 mL) dropwise under N_2, the reaction mixture was stirred at -78 °C for one hour, then warmed to 25 °C and stirred at 25 °C for another 30 minutes. TLC indicated starting material was consumed completely, and one major new spot with lower polarity was detected. The reaction mixture was added to diluted hydrochloride acid (2N, 100 mL) dropwise and then extracted with EA (150 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in

vacuum to afford 1-cyclopentylprop-2-en-1-one (1.30 g, 10.47 mmol, 82.30% yield) as yellow oil. The crude product was used in the next step directly without purification. ^{1}H NMR (400 MHz, CHLOROFORM-d) d ppm 6.33 - 6.46 (m, 1 H) 6.19 - 6.27 (m, 1 H) 5.73 - 5.79 (m, 1 H) 3.08 - 3.18 (m, 1 H) 1.74 - 1.84 (m, 4 H) 1.56 - 1.69 (m, 4 H).

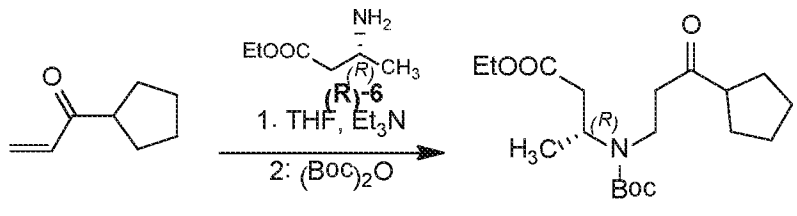
Preparation of Compound (S)-7



5 (S)-7

To a mixture of ethyl (3S)-3-aminobutanoate (1.76 g, 10.47 mmol, 1.00 *eq*, HCl) in THF (10.00 mL) was added TEA (3.18 g, 31.41 mmol, 4.36 mL, 3.00 *eq*), followed by a solution of 1-cyclopentylprop-2-en-1-one (1.30 g, 10.47 mmol, 1.00 *eq*) in THF (10.00 mL), the reaction mixture was stirred at 25 °C for 16 hours. TLC showed the reaction was completed. To the mixture was added $(Boc)_2O$ (2.29 g, 10.47 mmol, 2.41 mL, 1.00 *eq*) , the mixture was stirred at 25 °C for 2 hours, 60% of desired compound was detected by LCMS. The reaction mixture was extracted with EA (100 mL) and diluted hydrochloride acid (1N, 80 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford ethyl (3S)-3-[tert-butoxycarbonyl-(3- cyclopentyl-3-oxo-propyl)amino]butanoate (1.90 g, 5.35 mmol, 51.05% yield) as light yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.10 - 4.49 (m, 1 H) 4.02 - 4.09 (m, 2 H) 3.20 - 3.45 (m, 2 H) 2.60 - 2.86 (m, 3 H) 2.32 - 2.57 (m, 2 H) 1.49 - 1.78 (m, 8 H) 1.40 (s, 9 H) 1.14 - 1.21 (m, 6 H).

Preparation of Compound (R)-7

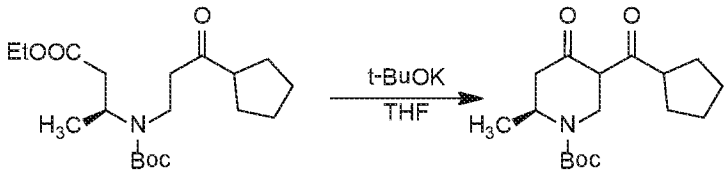


5 (R)-7

To a solution of ethyl (3R)-3-aminobutanoate (1.62 g, 9.66 mmol, 1.00 *eq*, HCl) in THF (10.00 mL) was added TEA (2.93 g, 28.99 mmol, 4.02 mL, 3.00 *eq*) , followed by a solution of 1-cyclopentylprop-2-en-1-one (1.20 g, 9.66 mmol, 1.00 *eq*) in THF (10.00 mL),

the reaction mixture was stirred at 25 °C for 16 hours. TLC showed the reaction was completed. To the mixture was $(Boc)_2O$ (2.11 g, 9.66 mmol, 2.22 mL, 1.00 *eq*), the mixture was stirred at 25 °C for 2 hours, 65% of desired compound was detected by LCMS. The reaction mixture was dissolved with EA (100 mL) and washed with diluted HCl (1N, 80 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford ethyl (3R)-3-[tert-butoxycarbonyl -(3-cyclopentyl-3-oxo-propyl)amino]butanoate (2.10 g, 5.91 mmol, 61.16% yield) as yellow oil.

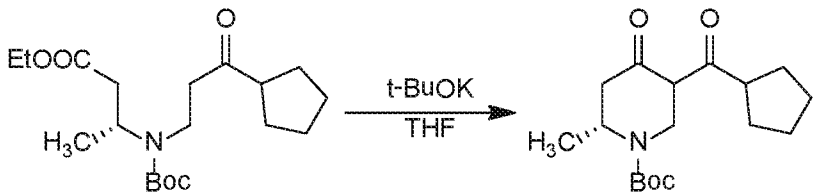
Preparation of Compound (S)-8



(S)-7 (S)-8

To a solution of ethyl (3S)-3-[tert-butoxycarbonyl-(3-cyclopentyl-3-oxo-propyl) amino]butanoate (1.70 g, 4.78 mmol, 1.00 *eq*) in THF (20.00 mL) was added t-BuOK (1.18 g, 10.52 mmol, 2.20 *eq*) at -40 °C under N_2, the reaction mixture was warmed to 0 °C and stirred at 0 °C for one hour. TLC indicated starting material was consumed completely, and one major new spot with lower polarity was detected. The reaction was quenched with aqueous solution of NH_4Cl (70 mL) and then extracted with EA (100 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl (2S)-5-(cyclopentanecarbonyl)-2- methyl-4-oxo-piperidine-1-carboxylate (1.38 g, crude) as yellow oil. The crude product was used in the next step directly without purification.

Preparation of Compound (R)-8

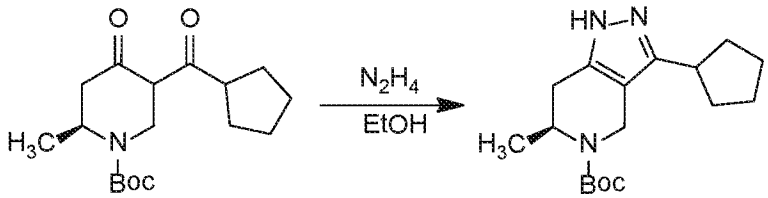


(R)-7 (R)-8

To a solution of ethyl (3R)-3-[tert-butoxycarbonyl-(3-cyclopentyl-3-oxo-propyl) amino]butanoate (1.90 g, 5.35 mmol, 1.00 *eq*) in THF (20.00 mL) was added t-BuOK (1.32 g, 11.77 mmol, 2.20 *eq*) at -40 °C under N_2, the reaction mixture was warmed to 0 °C and stirred at 0 °C for one hour. TLC indicated starting material was consumed

completely, and one major new spot with lower polarity was detected. The reaction was quenched with aqueous solution of NH_4Cl (80 mL) and then extracted with EA (100 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl (2R)-5-(cyclopentanecarbonyl)-2-methyl-4-oxo-piperidine-1-carboxylate (1.53 g, crude) as yellow oil. The crude product was used in the next step directly without purification.

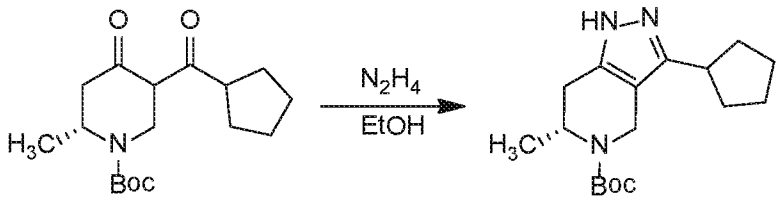
Preparation of Compound (S)-9



(S)-8 (S)-9

To a solution of tert-butyl (2S)-5-(cyclopentanecarbonyl)-2-methyl-4-oxo- piperidine-1-carboxylate (1.38 g, 4.46 mmol, 1.00 *eq*) in EtOH (20.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (525.36 mg, 8.92 mmol, 510.06 uL, 85% purity, 2.00 *eq*) , the reaction mixture was warmed to 50 °C and stirred at 50 °C for one hour. TLC indicated starting material was consumed completely, and one major new spot with larger polarity was detected. The mixture was extracted with EA (180 mL*2) and water (80 mL*3), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford tert-butyl (6S)-3-cyclopentyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (1.30 g, 4.21 mmol, 94.48% yield, 99% purity) as yellow solid.

Preparation of Compound (R)-9

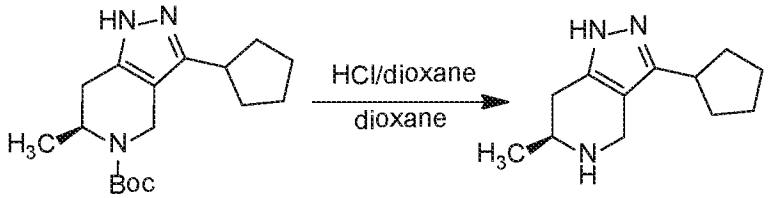


(R)-8 (R)-9

To a solution of tert-butyl (2R)-5-(cyclopentanecarbonyl)-2-methyl-4-oxo- piperidine-1-carboxylate (1.53 g, 4.95 mmol, 1.00 *eq*) in EtOH (20.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (582.47 mg, 9.90 mmol, 565.50 uL, 85% purity, 2.00 *eq*) , the reaction mixture was warmed to 50 °C and stirred at 50 °C for one hour. TLC indicated starting material was consumed completely, and one major new spot with larger polarity was detected. The mixture was extracted with EA (200 mL*2) and water (100 mL*3), the organic phase was dried with

anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford tert-butyl (6R)-3-cyclopentyl-6-methyl-1,4,6,7-tetrahydropyrazolo[4,3-c] pyridine-5-carboxylate (1.40 g, 4.54 mmol, 91.68% yield, 99% purity) as yellow solid.

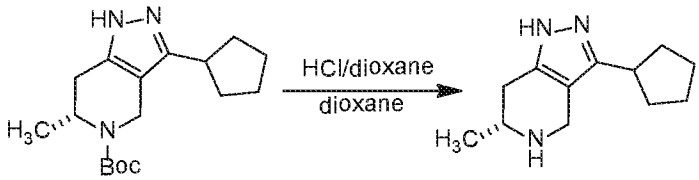
Preparation of Compound (S)-10



(S)-9 (S)-10

To a solution of tert-butyl (6S)-3-cyclopentyl-6-methyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (1.40 g, 4.58 mmol, 1.00 *eq*) in dioxane (10.00 mL) was added HCl/dioxane (4 M, 20.00 mL, 17.47 *eq*) , the reaction mixture was stirred at 25 °C for 2 hours. TLC indicated starting material was consumed completely, and one major new spot with larger polarity was detected. Removed the solvent on a rotary evaporator to afford (6S)-3-cyclopentyl-6-methyl-4,5,6,7-tetrahydro-1H- pyrazolo[4,3-c]pyridine (1.10 g, 4.55 mmol, 99.34% yield, HCl) as white solid. The product was used in the next step directly without purification. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 4.29 - 4.50 (m, 2 H) 3.79 (td, J=10.57, 5.46 Hz, 1 H) 3.17 - 3.29 (m, 2 H) 2.87 - 3.01 (m, 1 H) 2.12 - 2.27 (m, 2 H) 1.66 - 1.90 (m, 6 H) 1.53 - 1.59 (m, 3 H).

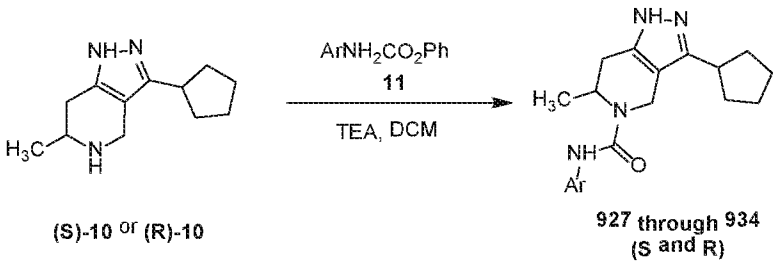
Preparation of Compound (R)-10



(R)-9 (R)-10

To a solution of tert-butyl (6R)-3-cyclopentyl-6-methyl-1,4,6,7-tetrahydropyrazolo [4,3-c]pyridine-5-carboxylate (1.50 g, 4.91 mmol, 1.00 *eq*) in dioxane (10.00 mL) was added HCl/dioxane (4 M, 20.00 mL, 16.29 *eq*) , the reaction mixture was stirred at 20 °C for one hour. TLC showed the reaction was completed. Evaporate the solution on a water bath under reduced pressure using a rotary evaporator to afford (6R)-3-cyclopentyl-6-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (1.20 g, crude, HCl) as white solid. The product was used in the next step directly without purification.

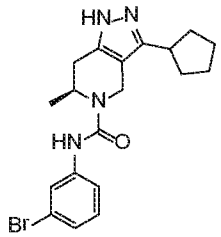
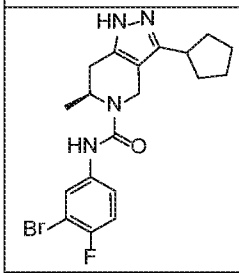
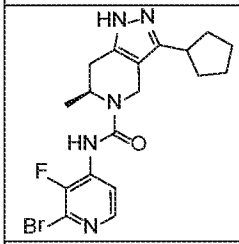
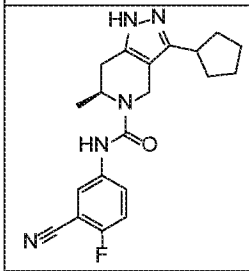
General procedure for preparation of Compounds 927 through 934

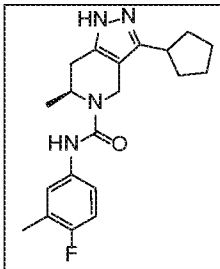
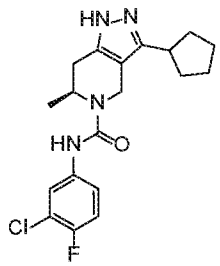
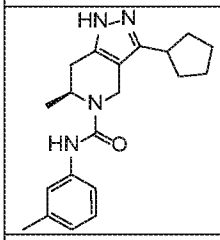
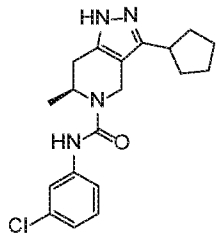
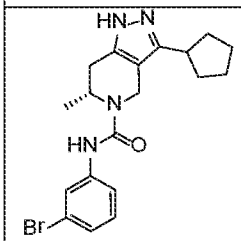
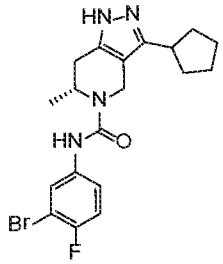


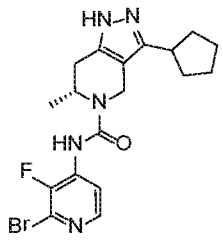
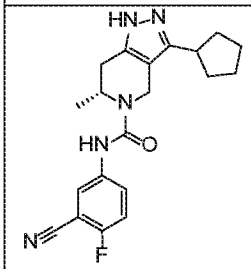
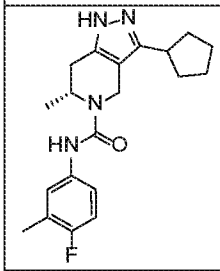
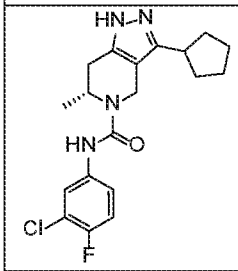
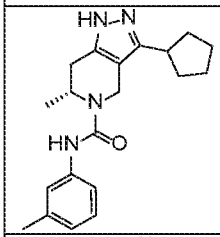
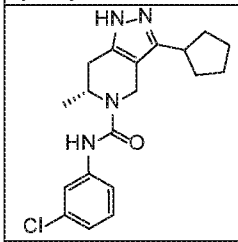
(S)-10 or (R)-10

927 through 934 (S and R)

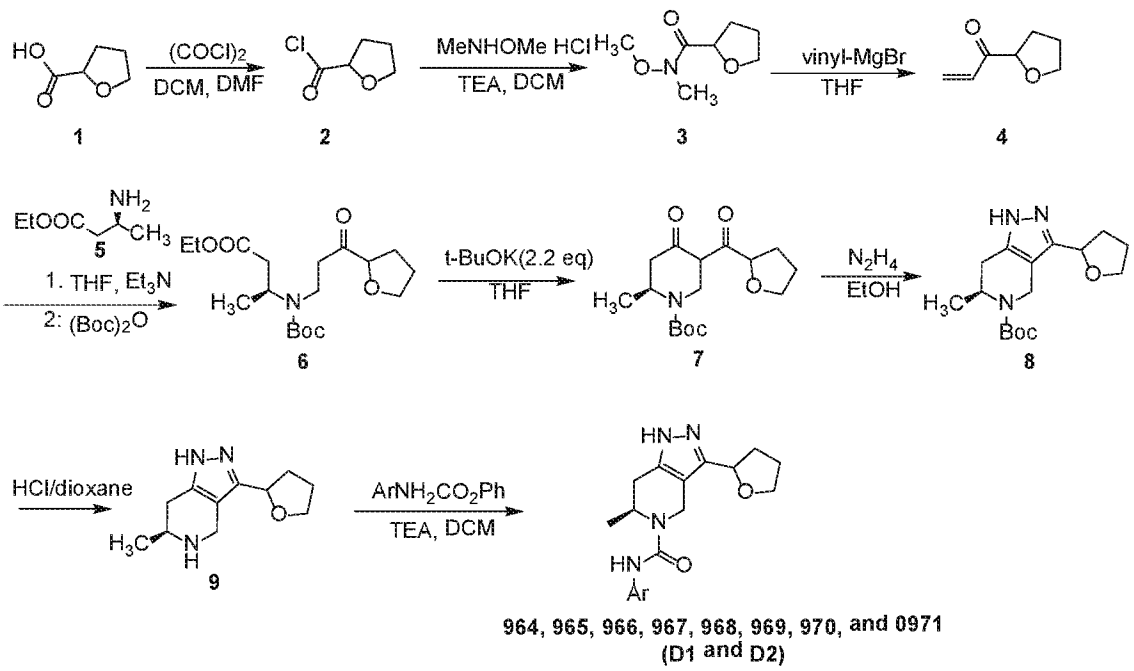
A solution of compound **10** (40.00 mg, 157.62 umol, 1.00 *eq*, HCl), phenyl carbamate **11** (1.00 *eq*) and TEA (73.00 mg, 721.42 umol, 100.00 uL, 4.58 *eq*) in DCM (2.00 mL) and MeOH (0.1 mL) was stirred at 25 °C for 12 hours. LCMS showed desired product was detected. The solvent was removed. The residue was purified by prep-HPLC(FA) to afford the desired product.

Structure	Comp. ID	Analytical Data
	927 (S)	LCMS (M+1) : 403.1 ^{1}H NMR (400 MHz, Methanol-d_4) ppm 7.65 - 7.70 (m, 1 H) 7.33 - 7.36 (m, 1 H) 7.14 - 7.21 (m, 2 H) 4.91 (s, 2 H) 4.20 (d, *J*=15.06 Hz, 1 H) 2.93 - 3.16 (m, 2 H) 2.60 (d, *J*=15.56 Hz, 1 H) 2.09 (d, *J*=3.51 Hz, 2 H) 1.78 - 1.88 (m, 2 H) 1.64 - 1.76 (m, 4 H) 1.18 (d, *J*=6.78 Hz, 3 H)
	928 (S)	LCMS (M+1) : 421.1
	929 (S)	LCMS (M+1) : 422.1
	930 (S)	LCMS (M+1) : 368.2

	931 (S)	LCMS (M+1) : 357.2
	932 (S)	LCMS (M+1) : 377.1 ^{1}H NMR (400 MHz, Methanlo-d_4) ppm 7.58 (dd, *J*=6.65, 2.64 Hz, 1 H) 7.27 - 7.33 (m, 1 H) 7.14 (t, *J*=8.91 Hz, 1 H) 4.88 - 4.93 (m, 2 H) 4.19 (d, *J*=14.81 Hz, 1 H) 2.92 - 3.17 (m, 2 H) 2.60 (d, *J*=15.81 Hz, 1 H) 2.09 (s, 2 H) 1.85 (s, 2 H) 1.65 - 1.78 (m, 4 H) 1.18 (d, *J*=6.78 Hz, 3 H)
	933 (S)	LCMS (M+1) : 339.2
	934 (S)	LCMS (M+1) : 359.2
	927 (R)	LCMS (M+1) : 403.1
	928 (R)	LCMS (M+1) : 421.1 ^{1}H NMR (400 MHz, Methanol-d_4) ppm 7.72 (dd, *J*=6.15, 2.64 Hz, 1 H) 7.35 (m, 1 H) 7.12 (t, *J*=8.66 Hz, 1 H) 4.88 - 4.93 (m, 2 H) 4.19 (d, *J*=15.06 Hz, 1 H) 3.04 - 3.16 (m, 1 H) 2.97 - 3.00 (m, 1 H) 2.60 (d, *J*=15.81 Hz, 1 H) 2.09 (d, *J*=3.76 Hz, 2 H) 1.84 (s, 2 H) 1.63 - 1.78 (m, 4 H) 1.18 (d, *J*=6.78 Hz, 3 H)

	929 (R)	LCMS (M+1) : 422.1 ^{1}H NMR (400 MHz Methanlo-d_4) ppm 8.01 (d, *J*=5.52 Hz, 1 H) 7.80 (t, *J*=5.65 Hz, 1 H) 4.82 - 4.86 (m, 2 H) 4.28 (d, *J*=15.31 Hz, 1 H) 3.10 (m, 2 H) 2.62 (d, *J*=15.81 Hz, 1 H) 2.09 (s, 2 H) 1.84 (s, 2 H) 1.71 (s, 4 H) 1.21 (d, *J*=6.78 Hz, 3 H)
	930 (R)	LCMS (M+1) : 368.1
	931 (R)	LCMS (M+1) : 357.2
	932 (R)	LCMS (M+1) : 377.1
	933 (R)	LCMS (M+1) : 339.2
	934 (R)	LCMS (M+1) : 359.1

Example 38: Preparation of Compounds 964, 965, 966, 967, 968, 969, 970, and 971 (D1&D2)



Step 1: Preparation of Compound 2

To a solution of tetrahydrofuran-2-carboxylic acid (8.00 g, 68.90 mmol, 6.61 mL, 1.00 *eq*) in DCM (80.00 mL) was added DMF (503.59 mg, 6.89 mmol, 530.10 uL, 0.10 *eq*), followed by $(COCl)_2$ (17.49 g, 137.80 mmol, 12.06 mL, 2.00 *eq*) dropwise at 0 °C, the reaction mixture was stirred at 0 °C for 2 hours. The solvent was removed on a rotary evaporator to afford tetrahydrofuran-2-carbonyl chloride (9.00 g, crude) as yellow oil. The product was used in the next step directly without purification.

Step 2: Preparation of Compound 3

To a mixture of N-methoxymethanamine (9.79 g, 100.32 mmol, 1.50 *eq*, HCl) in DCM (100.00 mL) was added TEA (20.30 g, 200.64 mmol, 27.81 mL, 3.00 *eq*), followed by tetrahydrofuran-2-carbonyl chloride (9.00 g, 66.88 mmol, 1.00 *eq*), the reaction mixture was stirred at 20 °C for 2 hours. One main peak with desired MS was detected by LCMS. The mixture was diluted with DCM (300 mL) and washed with diluted HCl (1N, 100 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford N-methoxy-N-methyl-tetrahydrofuran-2- carboxamide (8.80 g, 55.28 mmol, 82.66% yield) as yellow oil. ^1H NMR (400 MHz, CHLOROFORM-d) d ppm 4.71 (br. s., 1 H) 3.80 - 4.00 (m, 2 H) 3.63 - 3.67 (m, 3 H) 3.13 (s, 3 H) 2.06 -2.19 (m, 1 H) 1.79 - 1.99 (m, 3 H).

Step 3: Preparation of Compound 4

Cooled the three-necked round bottom flask to -78 °C, bromo(vinyl)magnesium (1 M, 50.26 mL, 2.00 *eq*) was added to a solution of N-methoxy-N-methyl- tetrahydrofuran-2-carboxamide (4.00 g, 25.13 mmol, 1.00 *eq*) in THF (40.00 mL) dropwise under N_2, the reaction mixture was stirred at -78 °C for one hour, then warmed to 15 °C and stirred at 15 °C for another 30 minutes. TLC indicated starting material was consumed completely, and one major new spot with lower polarity was detected. The reaction mixture was added to diluted HCl (2N, 200 mL) dropwise and then extracted with EA (300 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford 1-tetrahydrofuran-2-ylprop-2-en-1-one (2.10 g, crude) as yellow oil. The product was used in the next step directly without purification.

Step 4: Preparation of Compound 6

To a solution of ethyl (3S)-3-aminobutanoate (2.79 g, 16.65 mmol, 1.00 *eq*, HCl) in THF (20.00 mL) was added TEA (5.05 g, 49.95 mmol, 6.92 mL, 3.00 *eq*), followed by a solution of 1-tetrahydrofuran-2-ylprop-2-en-1-one (2.10 g, 16.65 mmol, 1.00 *eq*) in THF (20.00 mL), the reaction mixture was stirred at 15 °C for 4 hours. TLC showed the reaction was completed. $(Boc)_2O$ (3.63 g, 16.65 mmol, 3.83 mL, 1.00 *eq*) was added. the mixture was stirred at 15 °C for another 12 hours. TLC indicated many new spots formed. The reaction mixture was dissolved with EA (300 mL) and washed with diluted HCl (1N, 100 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford ethyl (3S)-3-[tert-butoxycarbonyl -(3-oxo-3-tetrahydrofuran-2-yl-propyl)amino]butanoate (3.10 g, 7.81 mmol, 46.88% yield, 90% purity) as yellow oil.

Step 5: Preparation of Compound 7

To a solution of ethyl (3S)-3-[tert-butoxycarbonyl-(3-oxo-3-tetrahydrofuran -2-yl-propyl)amino]butanoate (1.40 g, 3.92 mmol, 1.00 *eq*) in THF (15.00 mL) was added t-BuOK (879.00 mg, 7.83 mmol, 2.00 *eq*) at -40 °C under N_2, the reaction mixture was stirred at -10 °C for one hour, then warmed to 10 °C and stirred at 10 °C for another one hour. TLC indicated starting material was consumed completely, and three new spots formed. The reaction mixture was quenched with aqueous solution of NH_4Cl (70 mL) and then extracted with EA (150 mL*3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford tert-butyl (2S)-2-methyl-4-oxo-5- (tetrahydrofuran-2-carbonyl)piperidine-1-carboxylate (750.00 mg, crude) as yellow oil. The product was used in the next step directly without purification.

Step 6: Preparation of Compound 8

To a solution of tert-butyl (2S)-2-methyl-4-oxo-5-(tetrahydrofuran-2-carbonyl) piperidine-1-carboxylate (750.00 mg, 2.41 mmol, 1.00 *eq*) in EtOH (10.00 mL) was added $NH_2NH_2{\cdot}H_2O$ (283.72 mg, 4.82 mmol, 275.46 uL, 85% purity, 2.00 *eq*). The reaction mixture was stirred at 10 °C for 16 hours. Several new peaks were shown on LCMS and about 50% of desired compound was detected. The reaction mixture was diluted with EA (150 mL) and washed with diluted HCl (1N, 80 mL*2), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue combined with another two batch was purified by prep-HPLC(FA) to give desired compound (800 mg, purity 90%) as yellow oil, which was further separated by SFC to get peak one (D1, 0.36 g) and peak two (D2, 0.23 g).

Compound 8 (D1) (Peak one) ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.98 (t, J=6.90 Hz, 1 H) 4.83 (d, J=14.05 Hz, 2 H) 3.97 - 4.05 (m, 2 H) 3.86 -3.93 (m, 1 H) 2.95 (dd, J=15.69, 5.90 Hz, 1 H) 2.54 (d, J=15.69 Hz, 1 H) 2.24 - 2.34 (m, 1 H) 1.95 - 2.07 (m, 3 H) 1.49 (s, 9 H) 1.13 (d, J=6.90 Hz, 3 H).

Compound 8 (D2) (Peak two) ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.91 - 5.00 (m, 1 H) 4.84 (d, J=14.68 Hz, 2 H) 3.95 - 4.05 (m, 2 H) 3.86 - 3.94 (m, 1 H) 2.95 (dd, J=15.56, 5.77 Hz, 1 H) 2.55 (d, J=15.69 Hz, 1 H) 2.25 - 2.35 (m, 1 H) 1.99 - 2.08 (m, 3 H) 1.49 (s, 9 H) 1.13 (d, J=6.90 Hz, 3 H).

SFC separation condition:

Instrument: Waters Q 80 preparative

SFCcolumn: ChiralPak AD-H, 250×30mm I.D., particle size 10um

Mobile Phase : Phase A for CO2

Phase B for Ethanol (0.1%Ammonia)

Isocratic:25% Phase B

Flow rate:55g /min

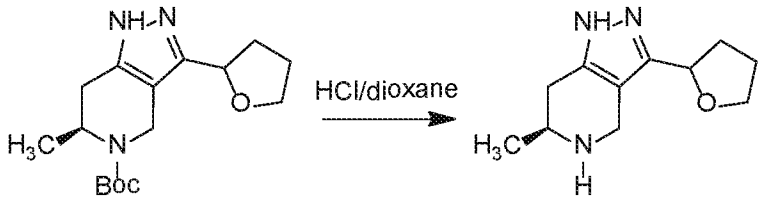
Column Temp: room temperature

Back pressure: 100bar

UV:220nm

Cycle Time:3.3min.

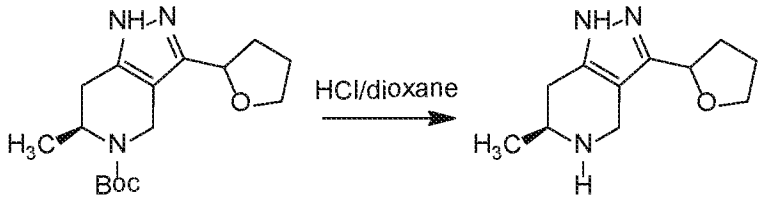
Preparation of Compound 9 (D1)



8_D1 9_D1

To a solution of tert-butyl (6S)-6-methyl-3-tetrahydrofuran-2-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (360.00 mg, 1.17 mmol, 1.00 *eq*) in dioxane (2.00 mL) was added HCl/dioxane (4 M, 10.00 mL, 34.19 *eq*), the reaction mixture was stirred at 10 °C for 2 hours. TLC showed the reaction was completed. Evaporated the solution on a water bath under reduced pressure using a rotary evaporator to afford (6S)-6-methyl-3-tetrahydrofuran-2-yl-4,5,6,7- tetrahydro-1H-pyrazolo[4,3-c]pyridine (330.00 mg, crude, 2HCl) as yellow solid. The product product was used in the next step directly without purification.

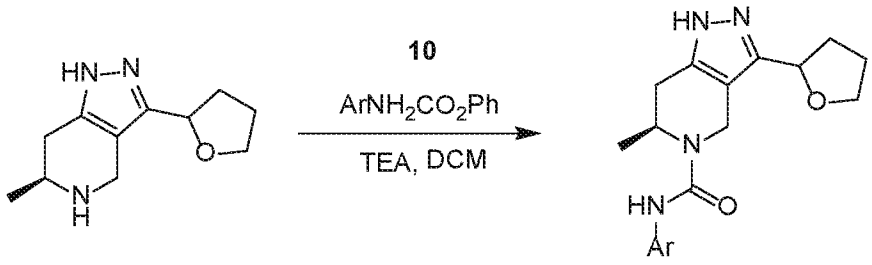
Preparation of Compound 9 (D2)



8_D2 9_D2

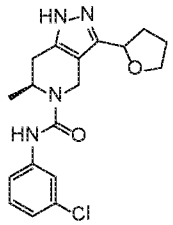
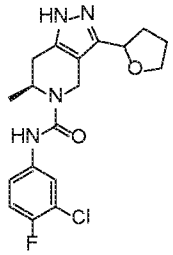
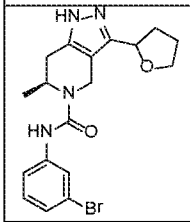
To a solution of tert-butyl (6S)-6-methyl-3-tetrahydrofuran-2-yl-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (230.00 mg, 748.24 umol, 1.00 *eq*) in dioxane (2.00 mL) was added HCl/dioxane (4 M, 8.00 mL, 42.77 *eq*), the reaction mixture was stirred at 10 °C for 2 hours. TLC showed the reaction was completed. Evaporated the solution on a water bath under reduced pressure using a rotary evaporator to afford (6S)-6-methyl-3-tetrahydrofuran-2-yl-4,5,6,7- tetrahydro-1H-pyrazolo[4,3-c]pyridine (170.00 mg, crude, 2HCl) as yellow solid. The product product was used in the next step directly without purification.

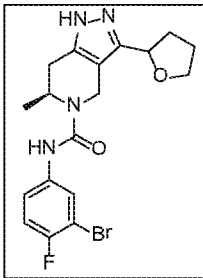
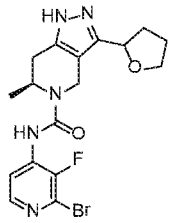
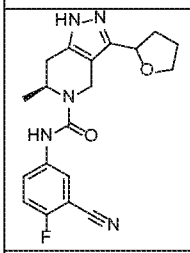
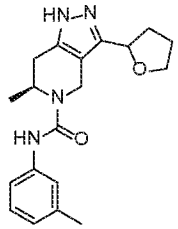
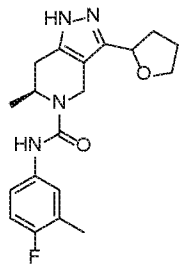
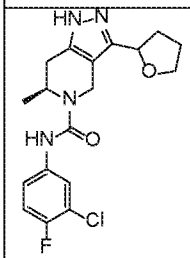
General Preparation of Compounds 964 through 971 (D1&D2)

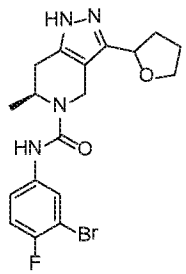
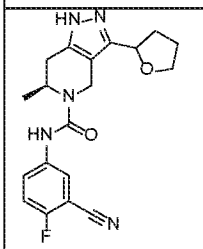
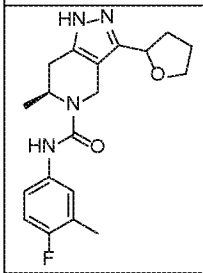


9_D1 or 9_D2 **Compounds 964 through 0971 (D1 and D2)**

A mixture of compound **9** (40 mg, 142.76 umol, 1.00 *eq*, 2HCl), phenyl carbamate **10** (142.76 umol, 1.00 *eq*) and TEA (146.00 mg, 1.44 mmol, 200.00 uL, 10.11 *eq*) in DCM (2.00 mL) was stirred at 25 °C for 16 hours. LCMS showed desired product was detected. The solvent was removed. The residue was purified by prep-HPLC(FA) to afford the desired product.

Structure	Comp. ID	Analytical Data
	964 (D1)	LCMS (M+1) : 361.1
	965 (D1)	LCMS (M+1) : 379.1 ^{1}H NMR (400 MHz, Methanol-d_4) ppm 7.57 (dd, *J*=6.78, 2.51 Hz, 1 H) 7.22 - 7.37 (m, 1 H) 7.08 - 7.19 (m, 1 H) 4.90 - 4.99 (m, 3 H) 4.22 (d, *J*=15.56 Hz, 1 H) 3.99 - 4.13 (m, 1 H) 3.82 - 3.95 (m, 1 H) 3.00 (dd, *J*=15.81, 5.77 Hz, 1 H) 2.62 (d, *J*=16.06 Hz, 1 H) 2.21 - 2.37 (m, 1 H) 1.94 - 2.17 (m, 3 H) 1.19 (d, *J*=6.78 Hz, 3 H)
	966 (D1)	LCMS (M+1) : 405.0

	967 (D1)	LCMS (M+1) : 423.1
	968 (D1)	LCMS (M+1) : 424.1 ^{1}H NMR (400 MHz, Methanol-d_4) ppm 8.01 (d, J=5.52 Hz, 1 H) 7.81 (t, J=5.65 Hz, 1 H) 4.90 - 4.99 (m, 3 H) 4.31 (d, J=15.56 Hz, 1 H) 3.99 - 4.11 (m, 1 H) 3.84 - 3.94 (m, 1 H) 3.04 (dd, J=15.81, 5.77 Hz, 1 H) 2.64 (d, J=15.81 Hz, 1 H) 2.23 - 2.37 (m, 1 H) 1.94 - 2.15 (m, 3 H) 1.22 (d, J=6.78 Hz, 3 H)
	969 (D1)	LCMS (M+1) : 370.1
	970 (D1)	LCMS (M+1) : 341.2 ^{1}H NMR (400 MHz, Methanol-d_4) 7.19 (s, 1 H) 7.14 (d, J=4.52 Hz, 2 H) 6.86 (m, 1 H) 4.88 - 4.98 (m, 3 H) 4.22 (d, J=15.31 Hz, 1 H) 4.05 (m, 1 H) 3.82 - 3.94 (m, 1 H) 3.00 (dd, J=15.69, 5.65 Hz, 1 H) 2.62 (d, J=15.81 Hz, 1 H) 2.22 - 2.36 (m, 4 H) 1.98 - 2.15 (m, 3 H) 1.19 (d, J=6.78 Hz, 3 H)
	971 (D1)	LCMS (M+1) : 359.1
	965 (D2)	LCMS (M+1) : 379.1

	967 (D2)	LCMS (M+1) : 423.1 ^{1}H NMR (400 MHz, METHANOL-d4) ppm 7.71 (dd, *J*=6.12, 2.54 Hz, 1 H) 7.34 (ddd, *J*=8.90, 4.10, 2.64 Hz, 1 H) 7.12 (t, *J*=12.0, 1 H) 4.92 - 4.99 (m, 3 H) 4.22 (d, *J*=15.45 Hz, 1 H) 3.97 - 4.10 (m, 1 H) 3.83 - 3.95 (m, 1 H) 3.00 (dd, *J*=15.82, 5.65 Hz, 1 H) 2.62 (d, *J*=15.82 Hz, 1 H) 2.24 - 2.37 (m, 1 H) 1.95 - 2.15 (m, 3 H) 1.19 (d, *J*=6.78 Hz, 3 H)
	969 (D2)	LCMS (M+1): 370.2
	971 (D2)	LCMS (M+1): 359.1

Example 39: HBV Assembly Assay

The interference of compounds from this invention with HBV capsid assembly could be measured using an *in vitro* assembly assay based on fluorescence quenching, which was developed according to a method described by Zlotnick and coworkers (Nature Biotechnology 2006, 24:358). In a typical assay, a mutant HBV C150 protein (amino acids 1-150, C49A, C61A, C107A, 150C) is cloned into a T7 RNA-polymerase based expression vector, expressed in *E.coli* and purified to homogeneity as a dimer. The purified HBV core protein is desalted and labeled with BODIPY-FL Dye.

In a non-limiting embodiment, the assembly assay is conducted in 96-well plate format. The assembly reactions are carried out in 50 mM Hepes buffer, pH 7.5 and 150 mM NaCl. The compounds are pre-incubated with the HBV CA protein for 15 min, and the assembly reactions are initiated by addition of NaCl. The reaction is allowed to continue for 1 hour at room temperature. The changes in fluorescence between DMSO treated and compound treated samples are recorded and analyzed for assembly modulation.

Example 40: HBV Replication Inhibition Assay

HBV replication inhibition by the compounds of this invention could be determined in cells infected or transfected with HBV, or cells with stably integrated HBV, such as HepG2.2.15 cells (Sells et al. 1987). In this example, HepG2.2.15 cells were maintained in cell culture medium containing 10% fetal bovine serum (FBS), Geneticin, L-glutamine, penicillin and streptomycin. HepG2.2.15 cells could be seeded in 96-well plates at a density of 40,000 cells/well and be treated with serially diluted compounds at a final DMSO concentration of 0.5% either alone or in combination by adding drugs in a checker box format. Cells were incubated with compounds for three days, after which medium was removed and fresh medium containing compounds was added to cells and incubated for another three days. At day 6, supernatant was removed and treated with DNase at 37°C for 60 minutes, followed by enzyme inactivation at 75°C for 15 minutes. Encapsidated HBV DNA was released from the virions and covalently linked HBV polymerase by incubating in lysis buffer (Affymetrix QS0010) containing 2.5 μg proteinase K at 50°C for 40 minutes. HBV DNA was denatured by addition of 0.2 M NaOH and detected using a branched DNA (BDNA) QuantiGene assay kit according to manufacturer recommendation (Affymetrix). HBV DNA levels could also be quantified using qPCR, based on amplification of encapsidated HBV DNA extraction with QuickExtraction Solution (Epicentre Biotechnologies) and amplification of HBV DNA using HBV specific PCR probes that can hybridize to HBV DNA and a fluorescently labeled probe for quantitation. In addition, cell viability of HepG2.2.15 cells incubated with test compounds alone or in combination was determined by using CellTitre-Glo reagent according to the manufacturer protocol (Promega). The mean background signal from wells containing only culture medium was subtracted from all other samples, and percent inhibition at each compound concentration was calculated by normalizing to signals from HepG2.2.15 cells treated with 0.5% DMSO using equation E1.

E1: % inhibition = (DMSOave – Xi)/DMSOave x 100%

where DMSOave is the mean signal calculated from the wells that were treated with DMSO control (0% inhibition control) and Xi is the signal measured from the individual wells. EC50 values, effective concentrations that achieved 50% inhibitory effect, were determined by non-linear fitting using Graphpad Prism software (San Diego, CA) and equation E2

E2: Y = Ymin + (Ymax - Ymin) / (1+10(LogEC50-X) x HillSlope)

where Y represents percent inhibition values and X represents the logarithm of compound concentrations.

Selected compounds of the invention were assayed in the HBV replication assay (BDNA assay), as described above and a representative group of these active compounds is shown in **Table 3**. **Table 3** shows EC_{50} values obtained by the BDNA assay for a group of select compounds. In Table 3, "A" represents $0.01 < EC_{50} < 0.10$; "B" represents $0.10 \leq EC_{50} < 0.50$; and "C" represents $0.50 \leq EC_{50} < 1.0$; ('+' indicates >50% activity at 10 μM).

Table 3: Activity in BDNA-assay (EC_{50})

Compound	EC_{50} (μM)		Compound	EC_{50} (μM)
264	A		441	B
267	B		455	B
274	B		515	B
275	B		546	A
336	A		547	B
337	A		548	A
338	A		549	B
861	A		554	A
761 R	B		761 S	B
927 R	A		927 S	A
928 R	A		928 S	A
929 R	A		929 S	A
930 R	A		930 S	A
931 R	A		931 S	A
932 R	A		932 S	A
933 R	A		933 S	A
934 R	A		934 S	A
964 D1	A			
965 D1	A		965 D2	A
966 D1	A			
967 D1	A		967 D2	B
968 D1	C			
969 D1	B		969 D2	B

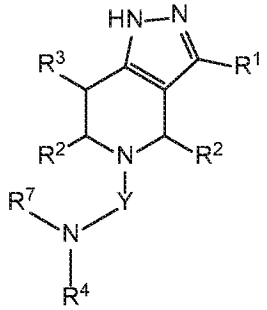
970 D1	B			
971 D1	A		971 D2	B
238	+		260	+
241	+		388	+
604	B		669	B
642	A		782	A
644	B		783	A
693	A		784	A
694	A		785	A
696	B		786	A
700	B		787	A
660	B		788	A
661	B		789	A
662	A		790	A
663	A		791	A
664	B		792	B
665	A		760 S	B
440	B		760 R	B
742	B		762 E1/E2	A
744	A		763 E1/E2	A
757 E1/E2	A		764 E1/E2	A
758 E1/E2	A		765 E1/E2	A
759 E1/E2	B		667	A
666	A		668	A

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety.

While the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS

1. A compound having the structure of Formula III:



III,

or a pharmaceutically acceptable salt thereof, wherein

Y is –C(O)– or –SO_2–;

R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, -OH, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from $(CR^8R^9)_p$-C_1-C_9-heteroaryl and $(CR^8R^9)_p$-C_6-C_{12}-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H and C_1-C_6-alkyl; and

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

2. The compound of claim 1, wherein Y is –C(O)–.

3. The compound of claim 1 or 2, wherein R^1 is C_3-C_8-cycloalkyl or C_2-C_8-heterocyclyl,

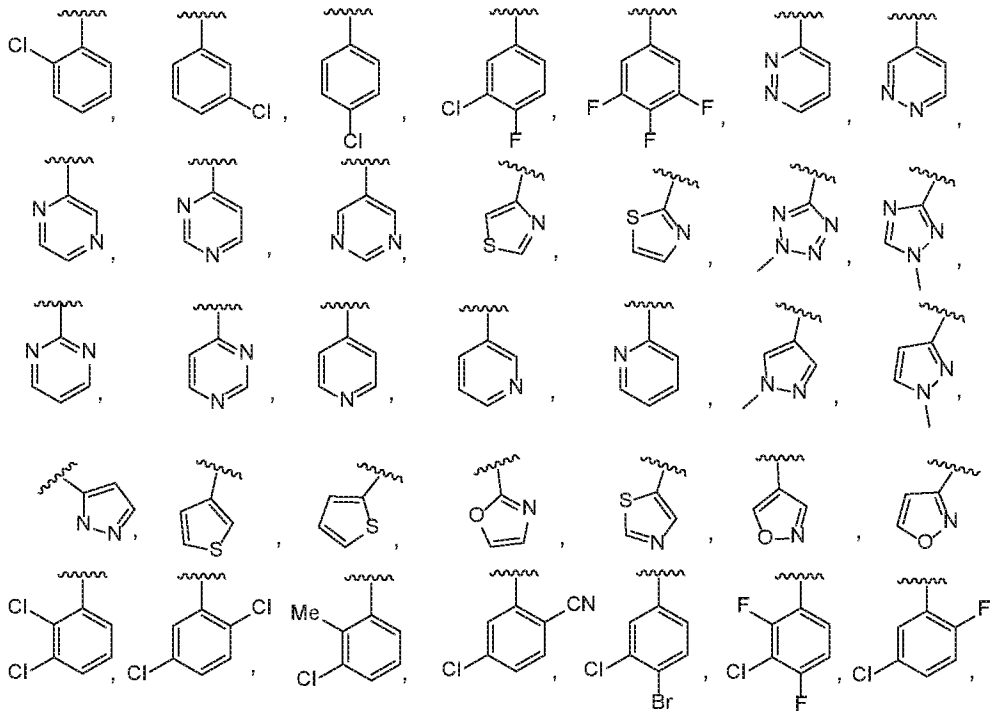
wherein cycloalkyl and heterocyclyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

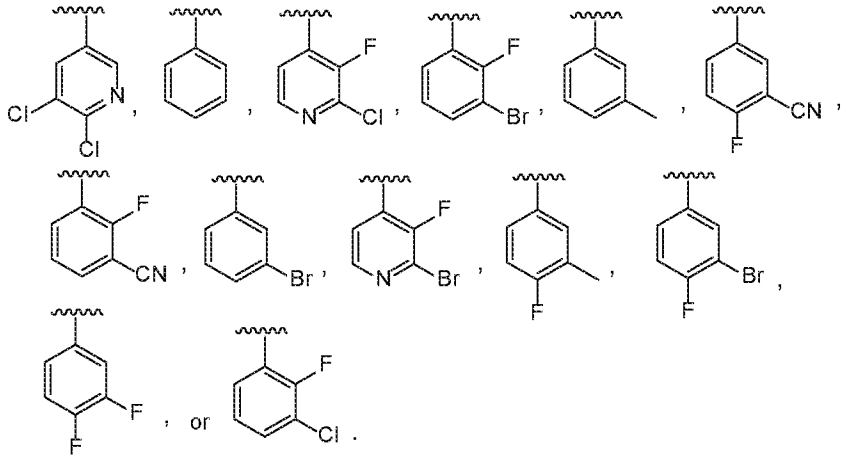
4. The compound of any one of claims 1-3, wherein R^1 is C_3-C_6-cycloalkyl or C_2-C_5-heterocyclyl, wherein cycloalkyl and heterocyclyl are optionally substituted with 1 or 2 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

5. The compound of any one of claims 1-4, wherein each R^2 is independently selected from H or C_1-C_4-alkyl and R^3 is H.

6. The compound of any one of claims 1-5, wherein R^4 is is C_1-C_5-heteroaryl or C_6-aryl, wherein heteroaryl and aryl are optionally substituted with 1, 2, or 3 groups, each independently selected from –OH, halo, CN, and C_1-C_6-alkyl.

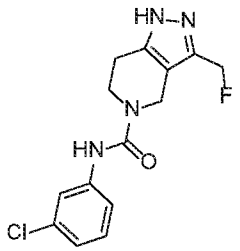
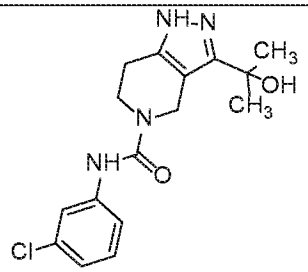
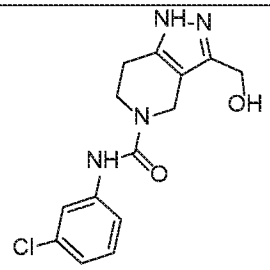
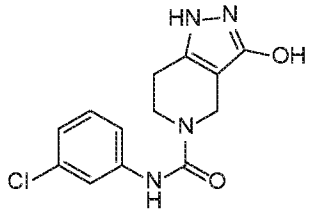
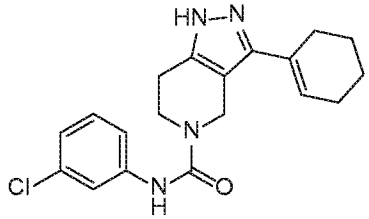
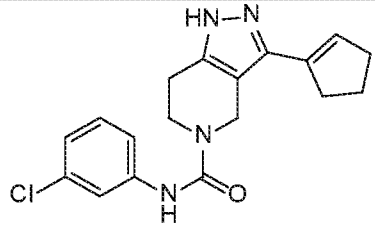
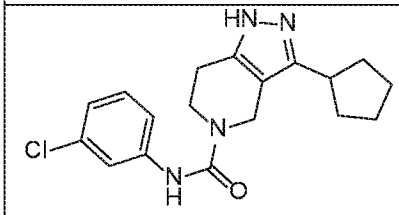
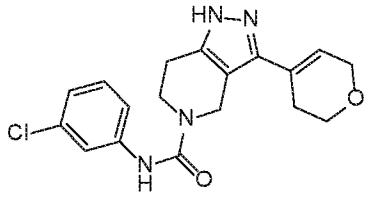
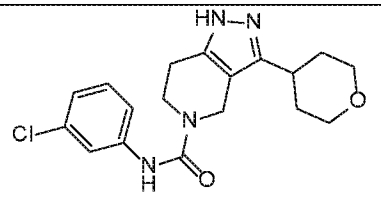
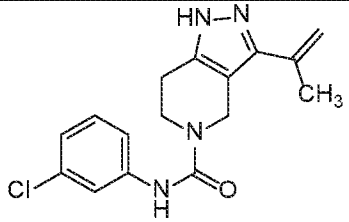
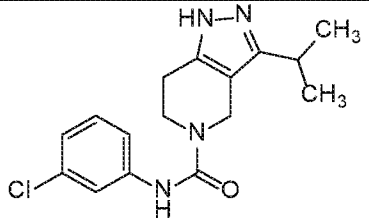
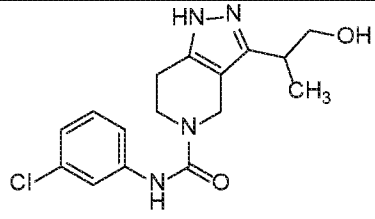
7. The compound of any one of claims 1-6 wherein R^4 is

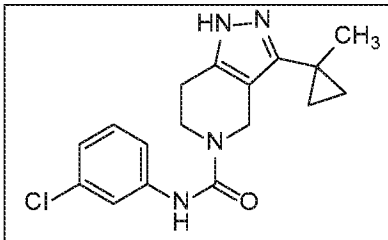
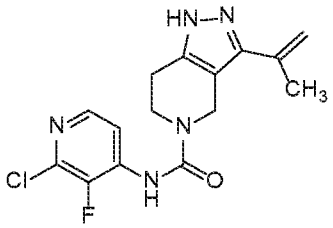
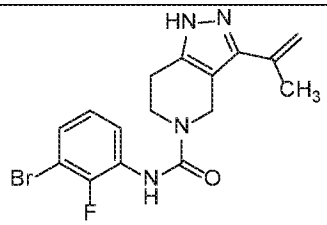
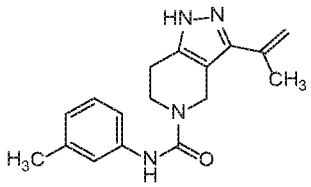
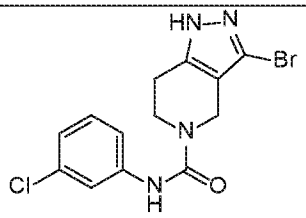
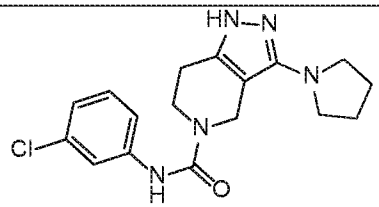
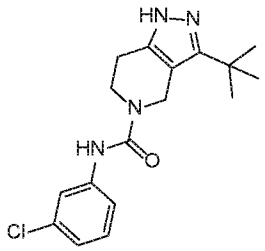
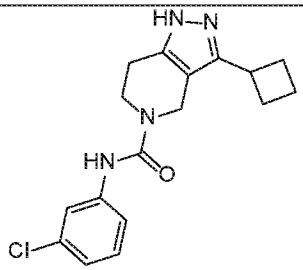
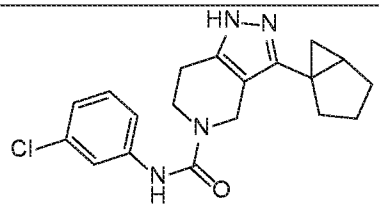
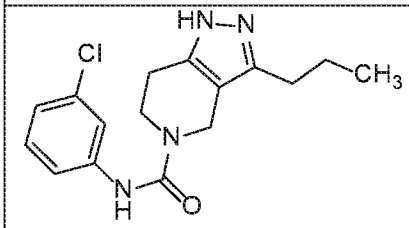
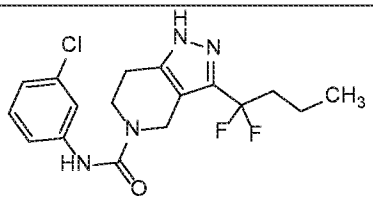
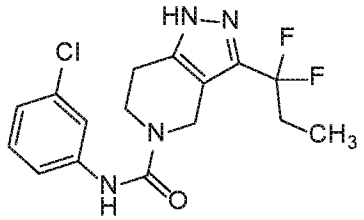
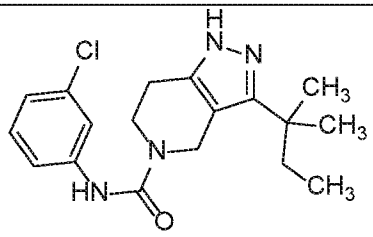
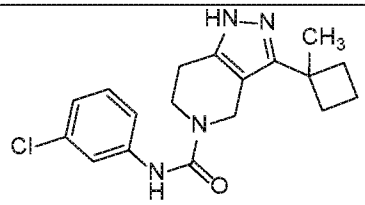
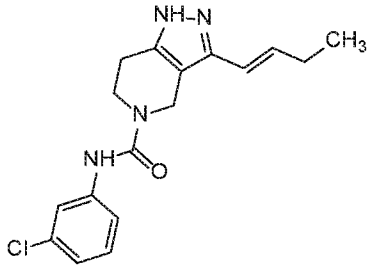
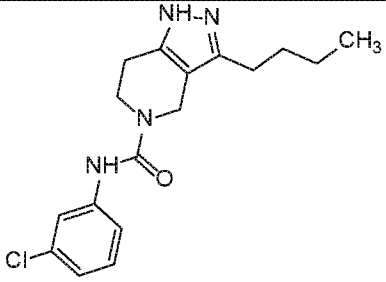
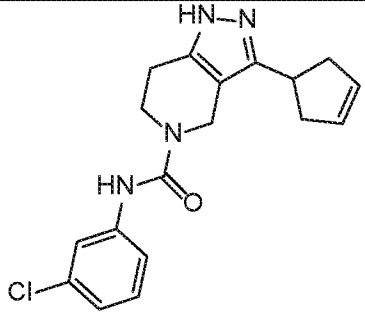


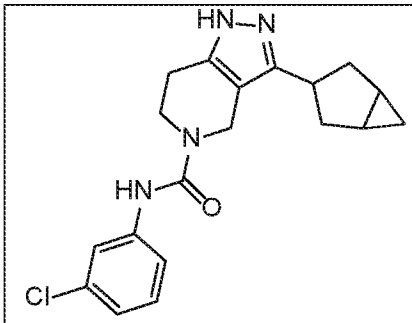
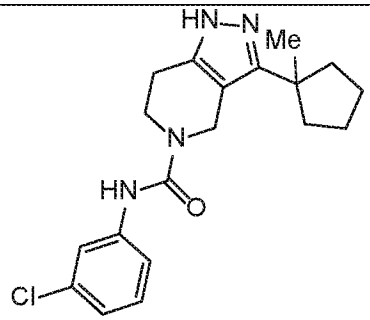
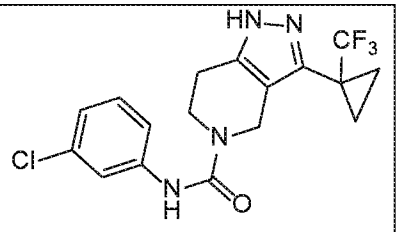
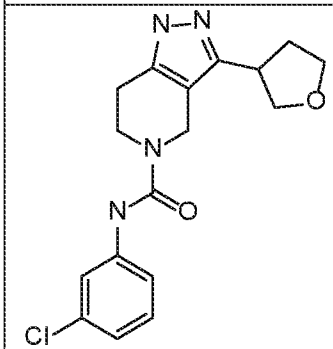
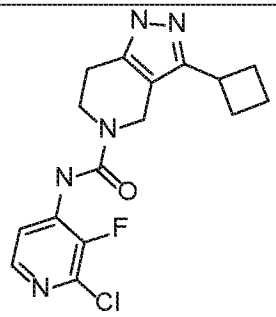
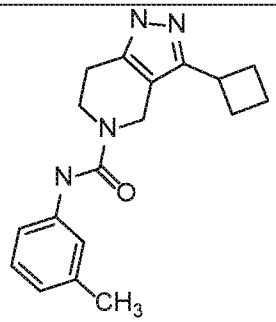
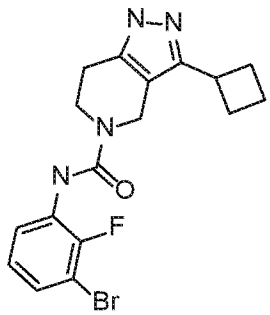
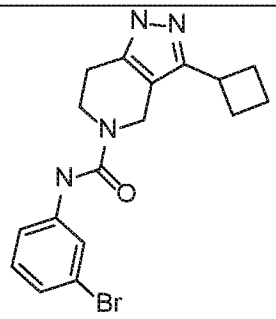
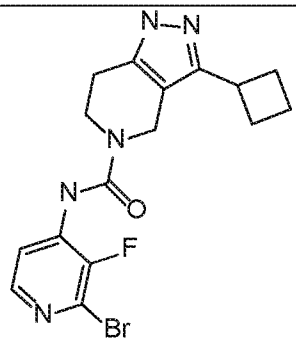
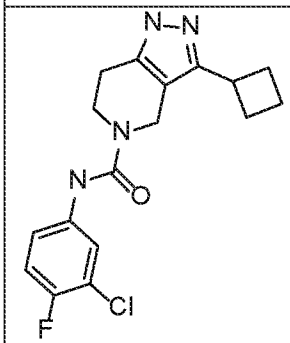
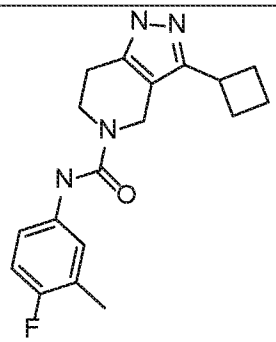
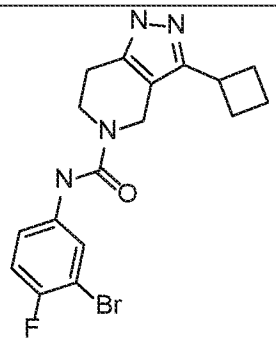


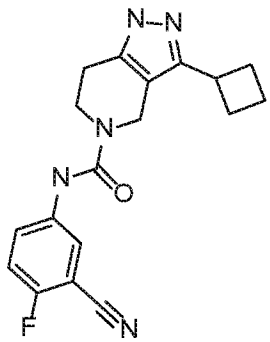
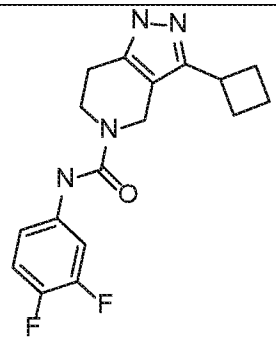
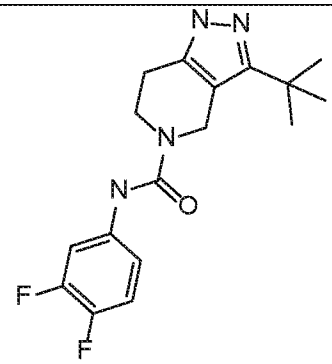
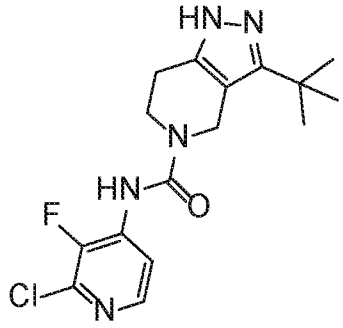
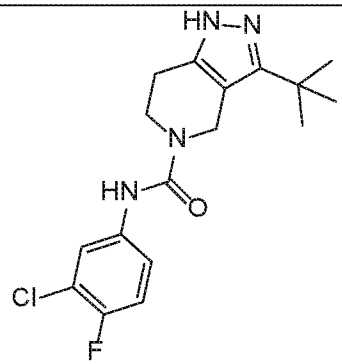
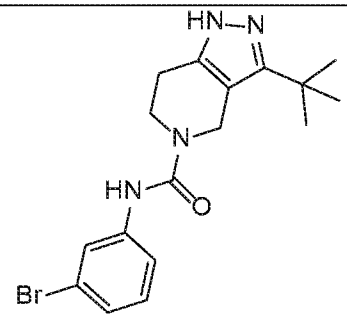
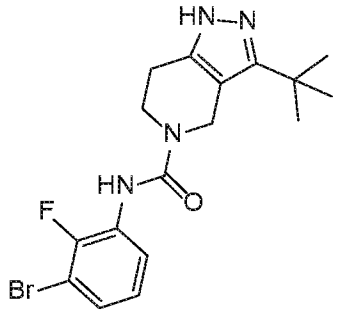
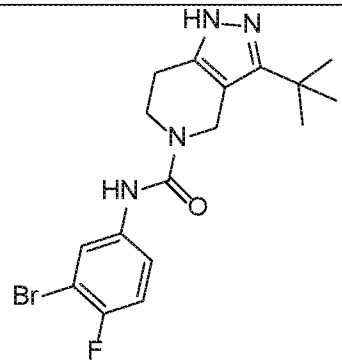
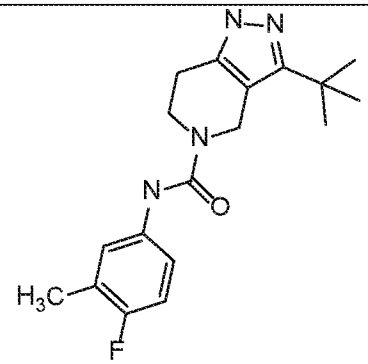
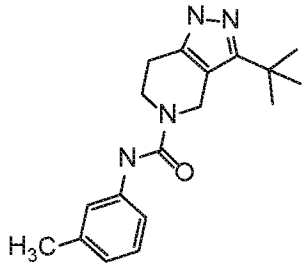
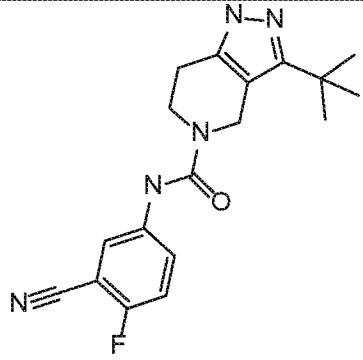
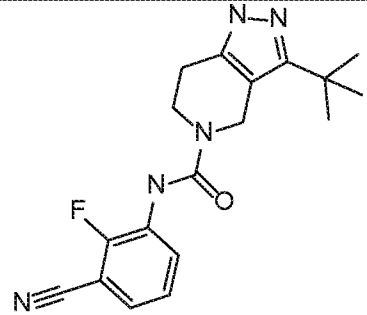
8. The compound of any one of claim 1-7, wherein R^7 is H.

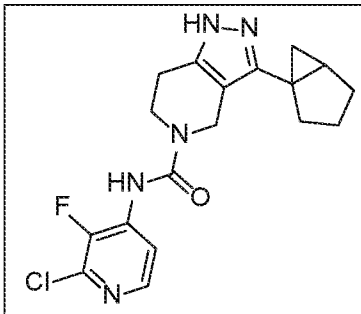
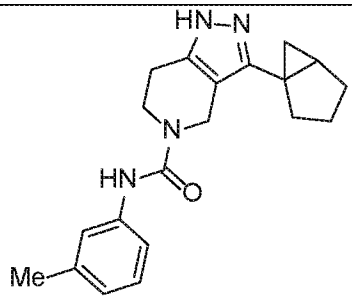
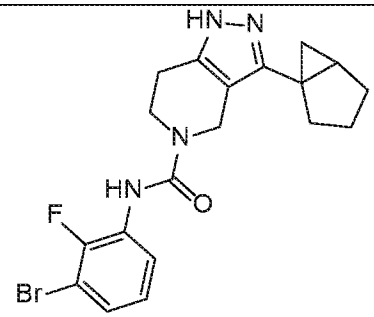
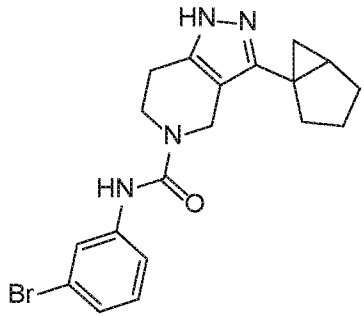
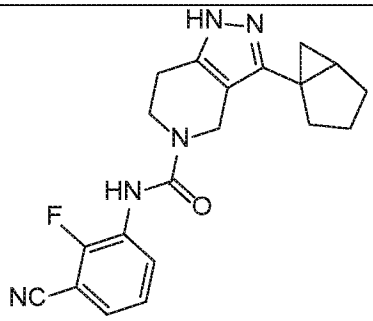
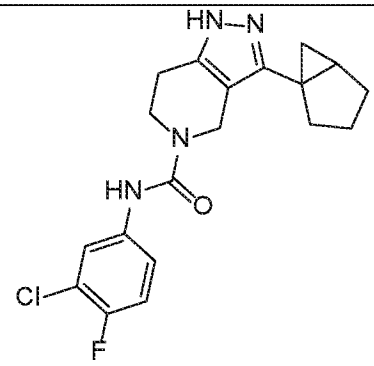
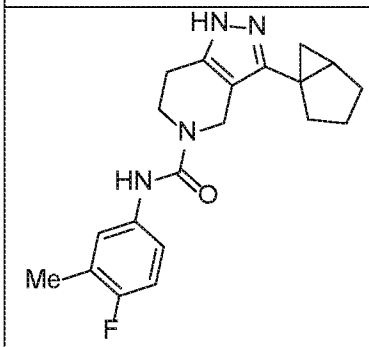
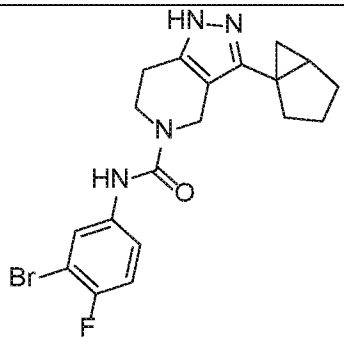
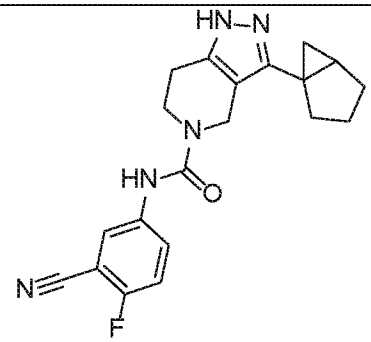
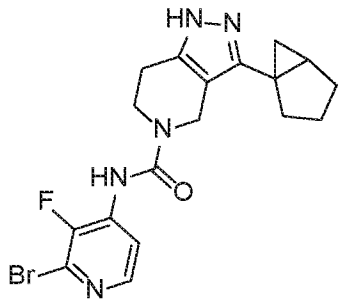
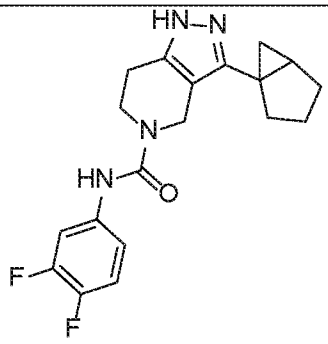
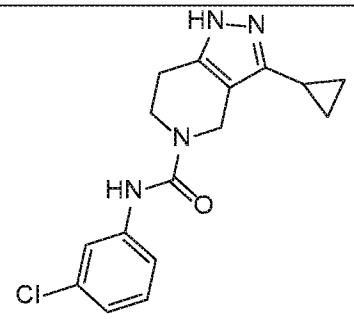
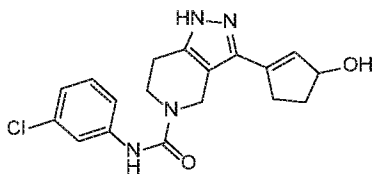
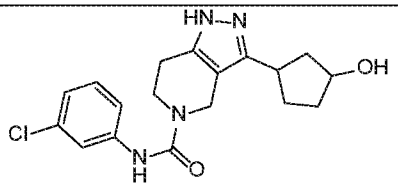
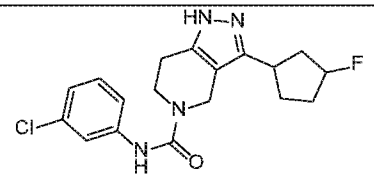
9. The compound of any one of claims 1-8, selected from

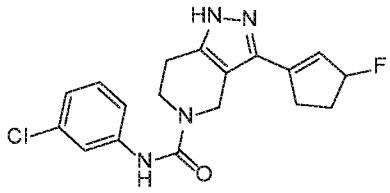
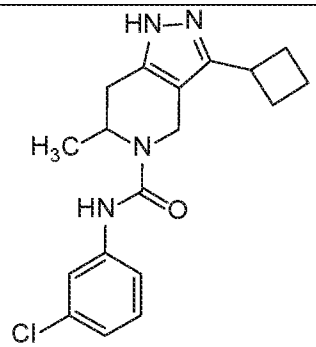
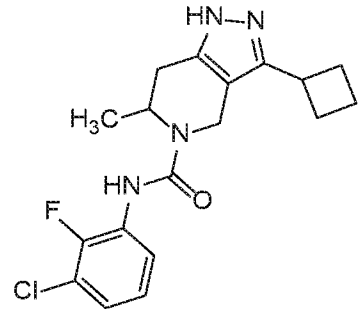
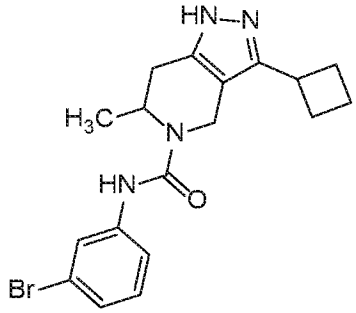
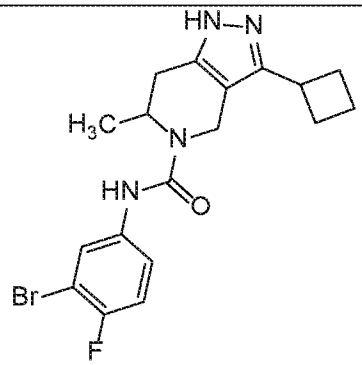
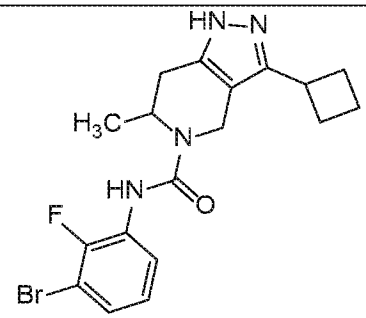
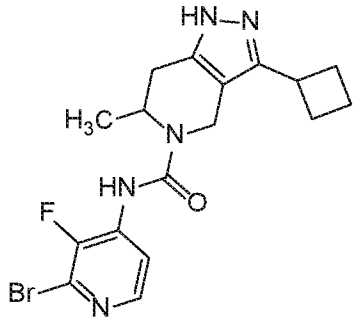
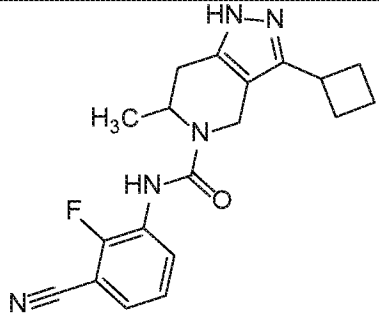
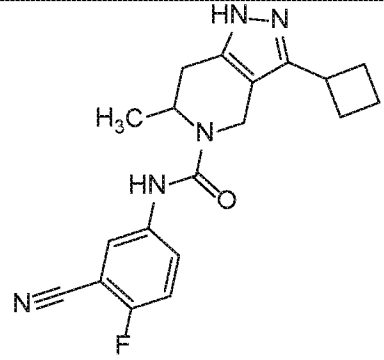
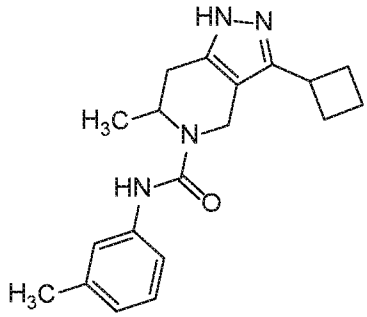
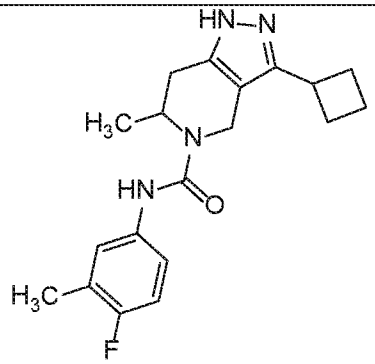
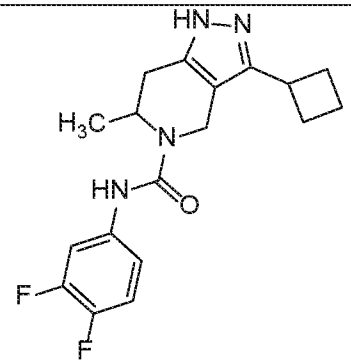
 324	 238	 239
 241	 337	 338
 264	 274	 275
 336	 267	 388

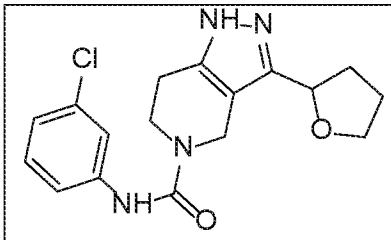
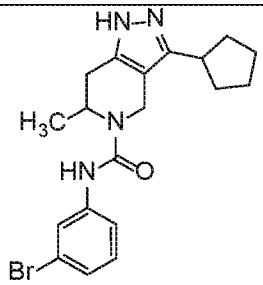
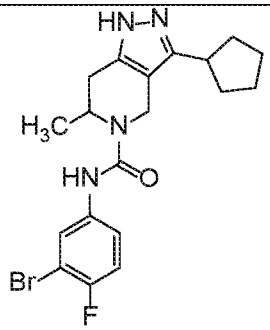
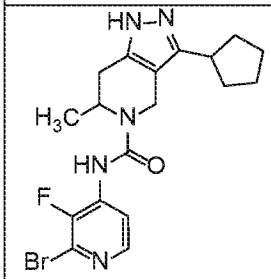
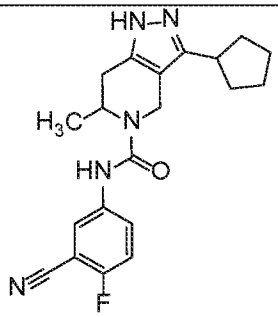
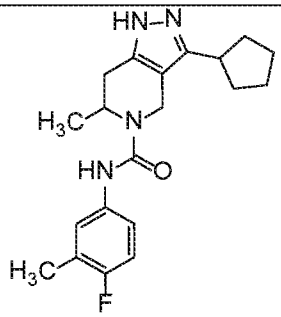
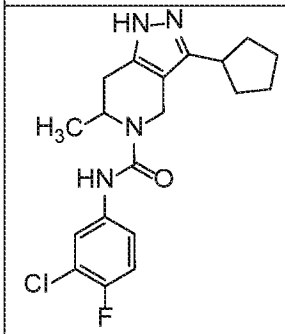
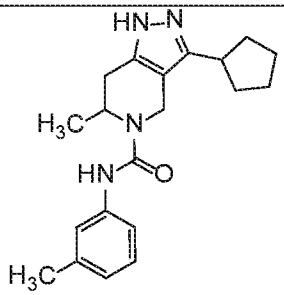
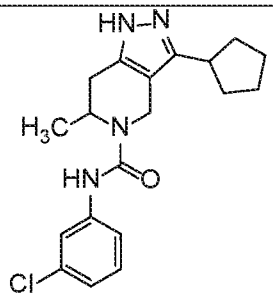
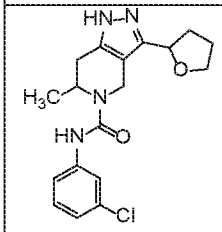
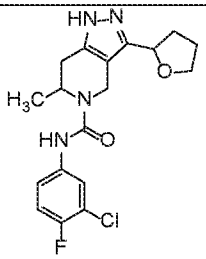
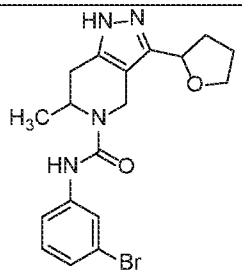
 441	 547	 548
 549	 260	 455
 515	 554	 546
 644	 642	
 696	 604	 694
 508	 509	 693

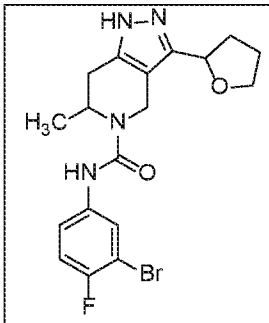
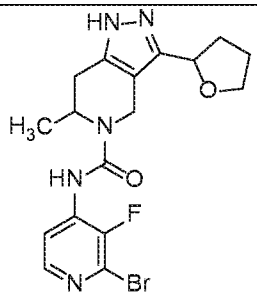
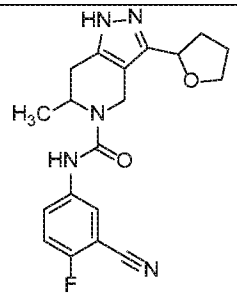
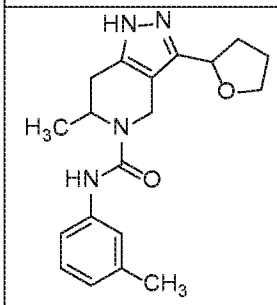
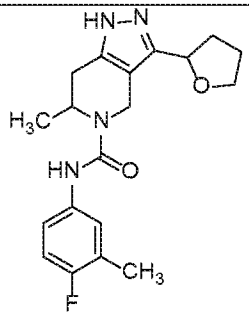
 734	 827	 700
 446	 660	 661
 662	 663	 664
 665	 666	 667

 668	 669	 648
 649	 650	 651
 652	 653	 654
 655	 656	 657

 782	 783	 784
 785	 786	 787
 788	 789	 790
 791	 792	 440
 535	 742	 743

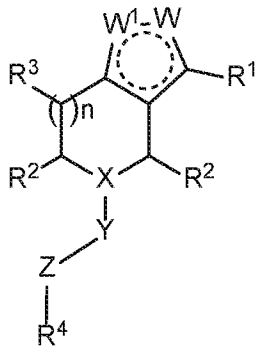
 744	 704	 756
 757	 758	 759
 760	 761	 762
 763	 764	 765

 861	 927	 928
 929	 930	 931
 932	 933	 934
 964	 965	 966

 967	 968	 969
 970	 971	

and pharmaceutically acceptable salts thereof.

10. A compound of Formula I



I,

or a pharmaceutically acceptable salt thereof,

wherein

W^1 and W are each independently selected from N, NR^a, and CR^a, wherein one of W^1 and W is NR^a;

X is N or CR^b;

Y is selected from a bond, –C(O)–, and $–SO_2–$;

Z is selected from $–(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$, $–(CR^5R^6)_mCR^5=CR^5–$, $–(CR^5R^6)_m$-C_3-C_6-cycloalkylene–, and $–(CR^5R^6)_m$-$NR^7–$;

R^1 is selected from C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, $-OR^c$, C_1-C_6-alkyl, halo, and C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^2 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^3 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^4 is selected from C_1-C_6-alkyl, $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, and $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $-OCH_2C(O)OR^f$, $-SO_2R^f$, and C_1-C_6-alkyl-OH;

R^5 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

alternatively, R^4 and R^5 are optionally joined to form a heterocyclic ring;

R^6 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^7 is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^8 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^9 is, at each occurrence, independently selected from H, –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^a is selected from H, C_1-C_6-alkyl, and C_1-C_6-alkyl-OH;

R^b is selected from H and C_1-C_6-alkyl;

R^c is selected from H, C_1-C_6-alkyl, C_1-C_6-alkyl-OH, C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_6-C_{12}-aryl, and C_1-C_9-heteroaryl;

R^f is, at each occurrence, independently selected from H and C_1-C_6-alkyl;

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

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

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

11. The compound of claim 10, wherein W^1 is NR^a and W is N or CR^a.

12. The compound of claim 10, wherein W^1 is N or CR^a and W is NR^a.

13. The compound of any one of claims 10-12, wherein X is N.

14. The compound of any one of claims 10-13, wherein Y is –C(O)– or $–SO_2–$.

15. The compound of any one of claims 10-14, wherein Z is–$(CR^5R^6)_m–$, $–(CR^5R^6)_mO–$, or $–(CR^5R^6)_m-NR^7–$.

16. The compound of any one of claims 10-15, wherein
m is 0 or 1;
R^5 is H, –OH, or C_1-C_6-alkyl;
R^6 is H or C_1-C_6-alkyl; and
R^7 is H or C_1-C_6-alkyl.

17. The compound of any one of claims 10-16, wherein R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, or C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

18. The compound of any one of claims 10-17, wherein each R^2 is independently selected from H or C_1-C_4-alkyl and R^3 is H.

19. The compound of any one of claims 10-18, wherein R^4 is $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH.

20. The compound of any one of claims 10-19, wherein R^4 is $(CR^8R^9)_p$-C_6-C_{12}-aryl or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein aryl and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $–OCH_2C(O)OR^f$, $–SO_2R^f$, and C_1-C_6-alkyl-OH.

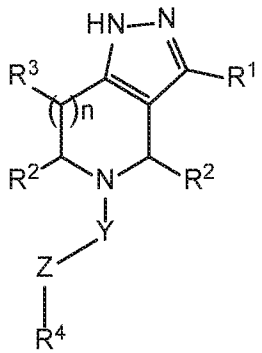
21. The compound of any one of claims 10-20, wherein
p is 0 or 1;
R^8 is H, –OH, or C_1-C_6-alkyl; and
R^9 is H or C_1-C_6-alkyl.

22. The compound of any one of claims 10-21, wherein n is 1.

23. The compound of any one of claims 10-22, wherein
X is N;
Y is –C(O)–;
Z is NR^7; and
R^7 is H or C_{1-4}-alkyl.

24. The compound of any one of claims 10-23, wherein
X is N;
Y is –C(O)–;
Z is NR^7;
R^7 is H or C_{1-4}-alkyl; and
n is 1.

25. The compound of any one of claims 10-24, having the structure of Formula II:



II,

or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25, wherein Y is –C(O)– or $–SO_2–$.

27. The compound of claim 25 or 26, wherein Z is $-(CR^5R^6)_m-$, $-(CR^5R^6)_mO-$ or $-(CR^5R^6)_m-NR^7-$.

28. The compound of any one of claims 25-27, wherein

m is 0 or 1;

R^5 is H, –OH, or C_1-C_6-alkyl;

R^6 is H or C_1-C_6-alkyl; and

R^7 is H or C_1-C_6-alkyl.

29. The compound of any one of claims 25-28, wherein R^1 is C_3-C_8-cycloalkyl, C_2-C_8-heterocyclyl, C_1-C_6-alkyl, or C_2-C_8-alkenyl, wherein alkyl, cycloalkyl, heterocyclyl, and alkenyl are optionally substituted with 1, 2, 3, or 4 groups each independently selected from –OH, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, and C_1-C_6-alkyl-OH.

30. The compound of any one of claims 25-29, wherein each R^2 is independently selected from H or C_1-C_4-alkyl and R^3 is H.

31. The compound of any one of claims 25-30, wherein R^4 is $(CR^8R^9)_p$-C_3-C_8-cycloalkyl, $(CR^8R^9)_p$-C_2-C_8-heterocyclyl, $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $-OCH_2C(O)OR^f$, $-SO_2R^f$, and C_1-C_6-alkyl-OH.

32. The compound of any one of claims 25-31, wherein R^4 is $(CR^8R^9)_p$-C_6-C_{12}-aryl, or $(CR^8R^9)_p$-C_1-C_9-heteroaryl, and wherein aryl and heteroaryl are optionally substituted with 1, 2, 3, or 4 groups, each independently selected from –OH, halo, CN, C_1-C_6-alkyl, C_1-C_6-haloalkyl, –O-C_1-C_6-alkyl, $C(O)N(R^f)_2$, $C(O)OR^f$, $-OCH_2C(O)OR^f$, $-SO_2R^f$, and C_1-C_6-alkyl-OH.

33. The compound of any one of claims 25-32, wherein

p is 0 or 1;

R^8 is independently selected from H, –OH, or C_1-C_6-alkyl; and

R^9 is independently selected from H or C_1-C_6-alkyl.

34. The compound of any one of claims 25-33, wherein n is 1.

35. The compound of any one of claims 25-34, wherein

Y is –C(O)–;

Z is NR^7; and

R^7 is H or C_{1-4}-alkyl.

36. The compound of any one of claims 25-35, wherein

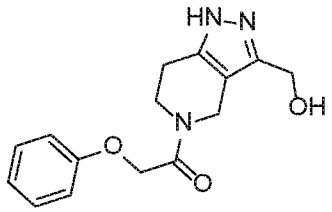
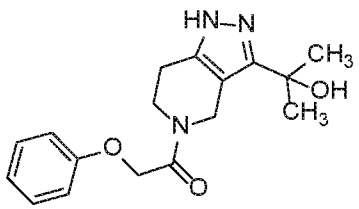
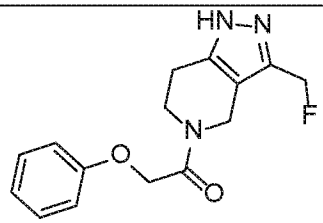
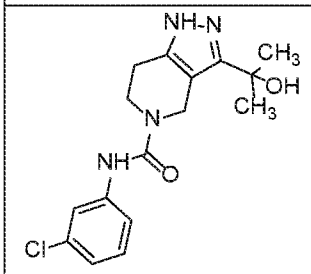
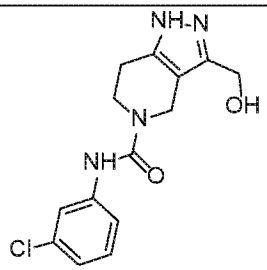
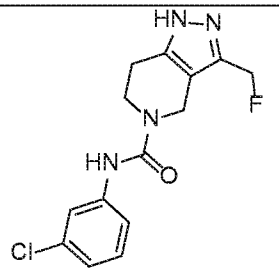
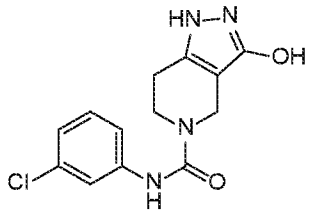
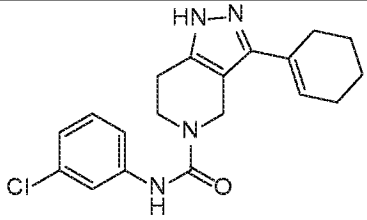
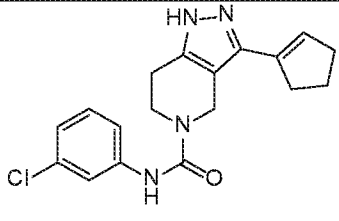
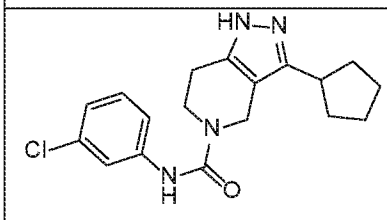
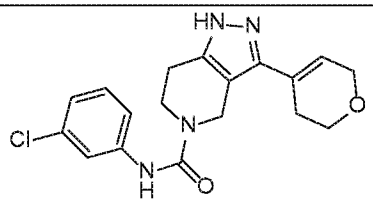
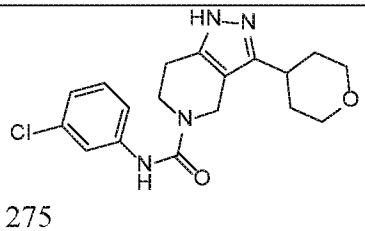
Y is –C(O)–;

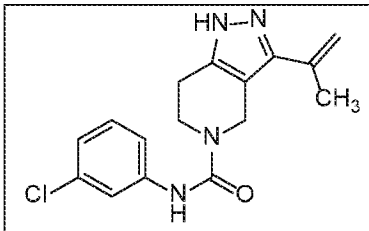
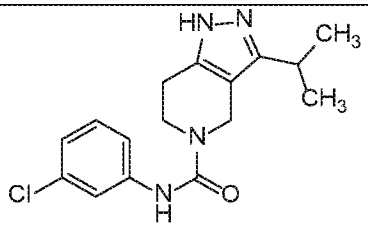
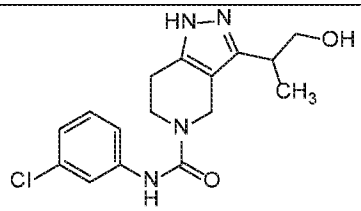
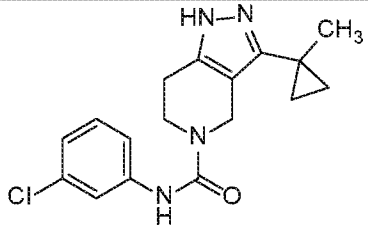
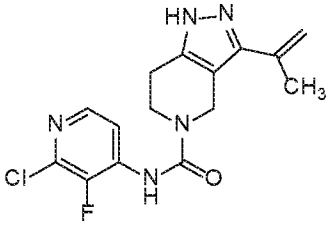
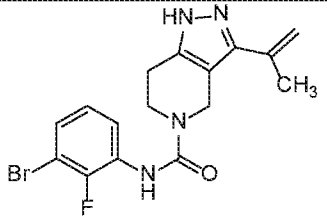
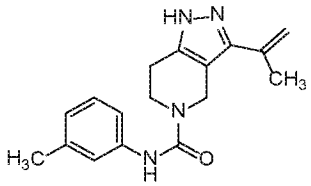
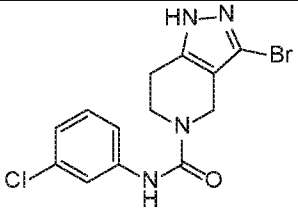
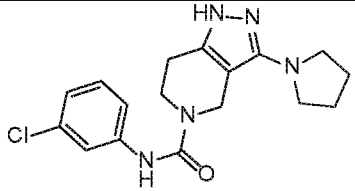
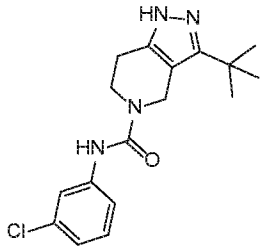
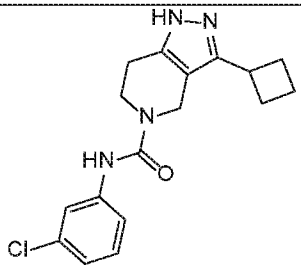
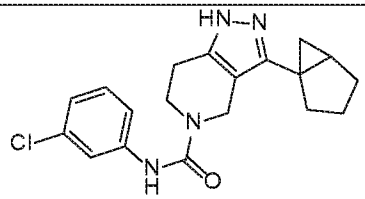
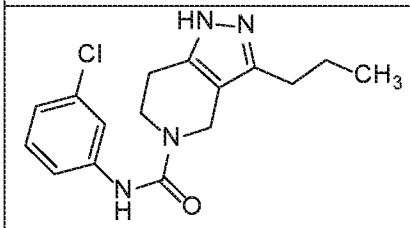
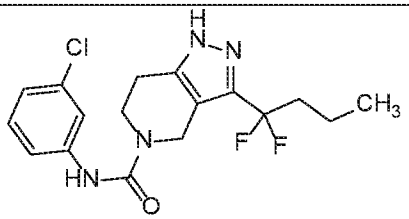
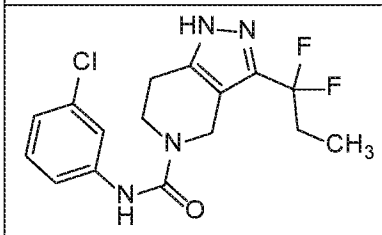
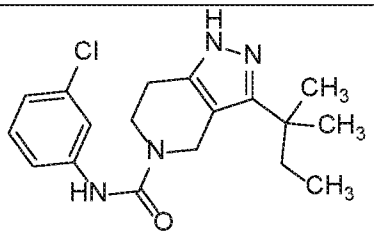
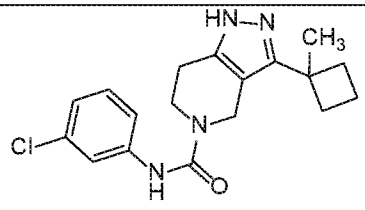
Z is NR^7;

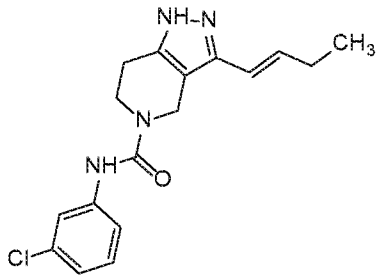
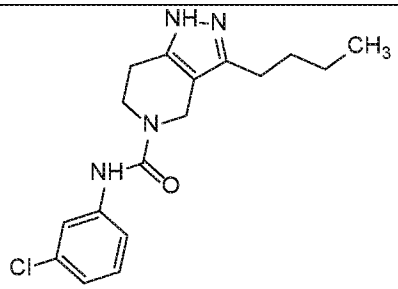
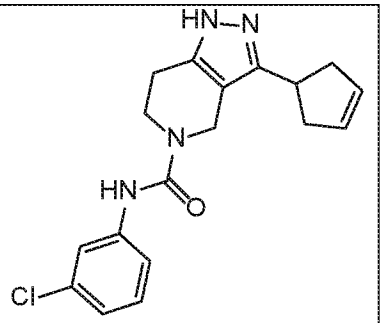
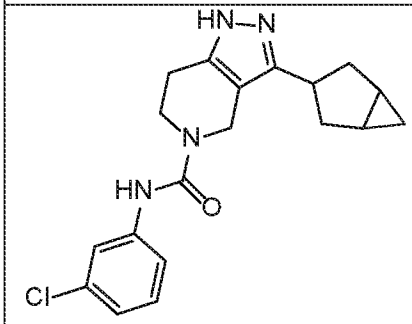
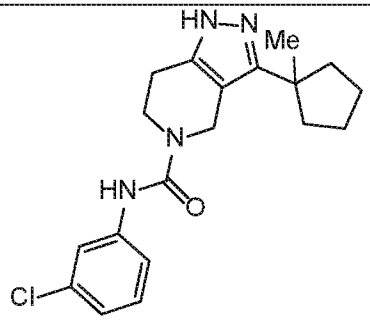
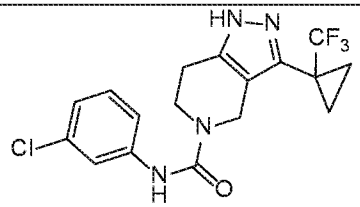
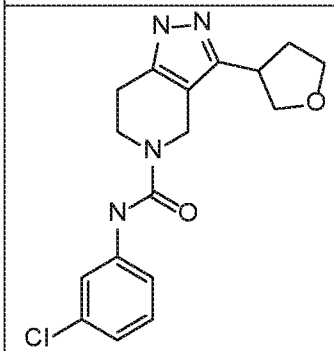
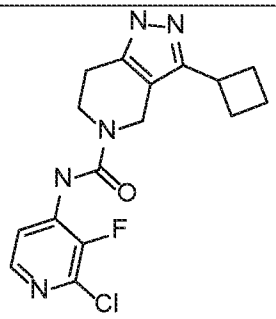
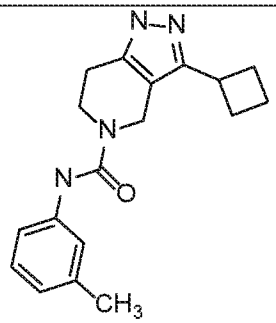
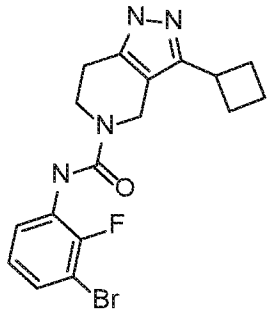
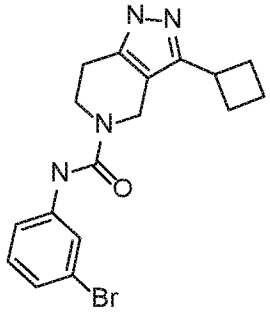
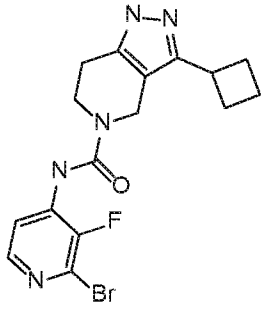
R^7 is H or C_{1-4}-alkyl; and

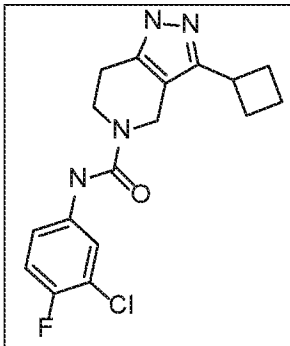
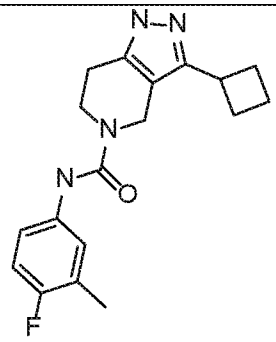
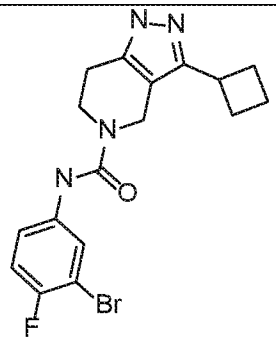
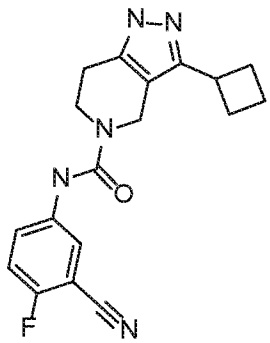
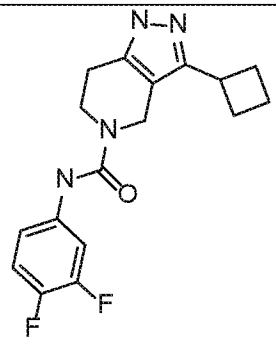
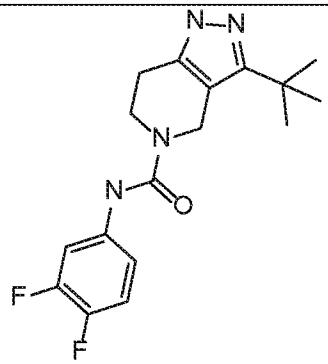
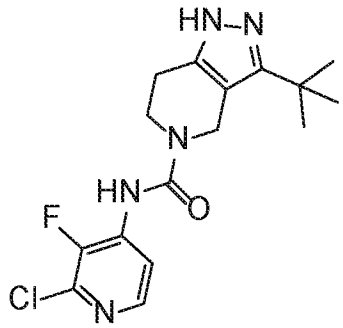
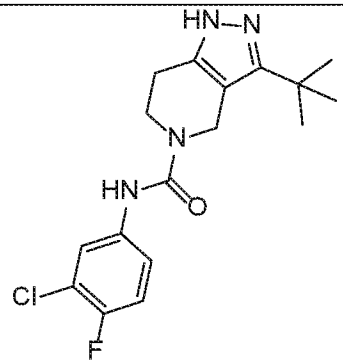
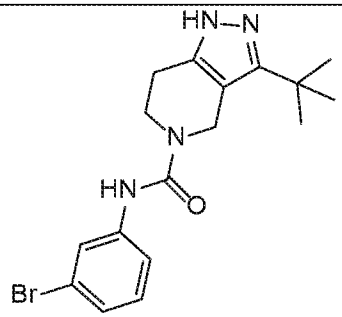
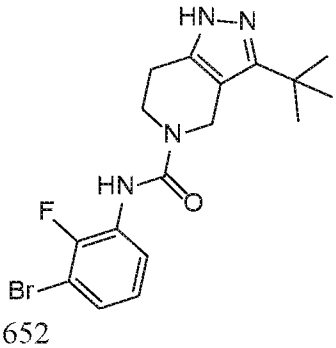
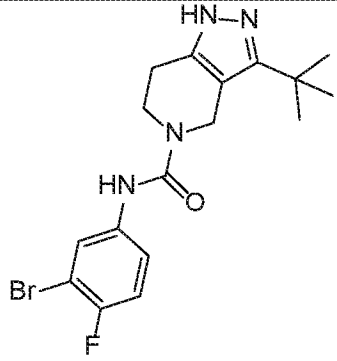
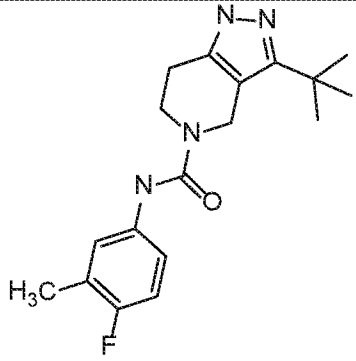
n is 1.

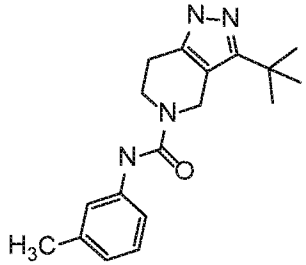
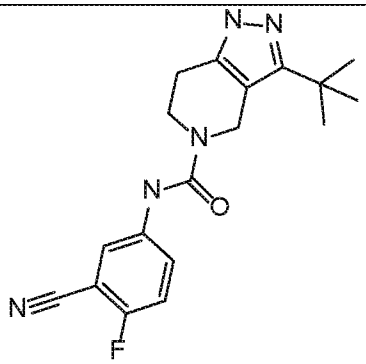
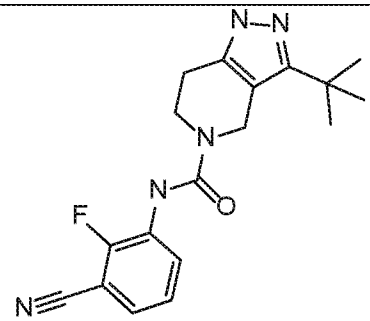
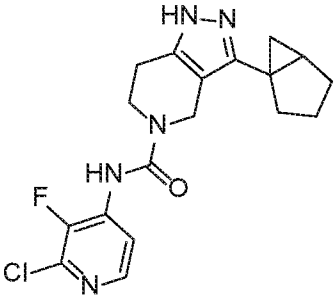
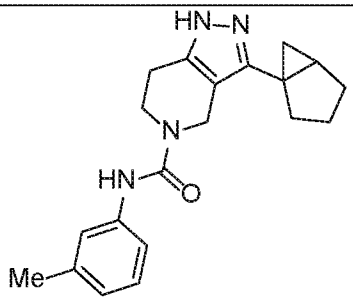
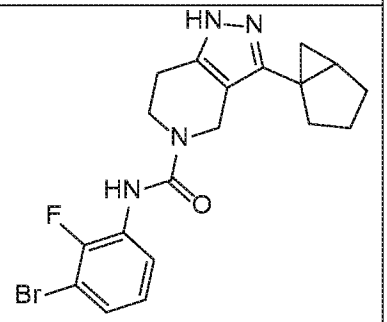
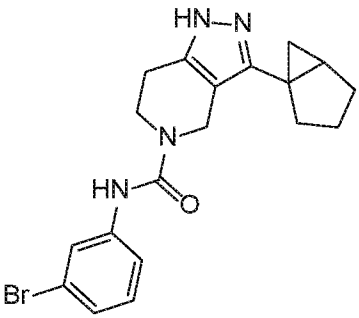
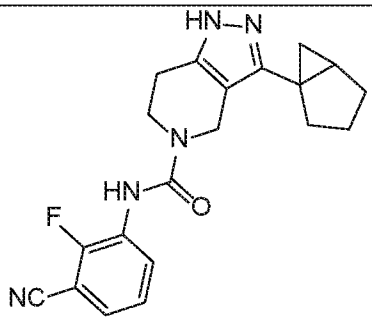
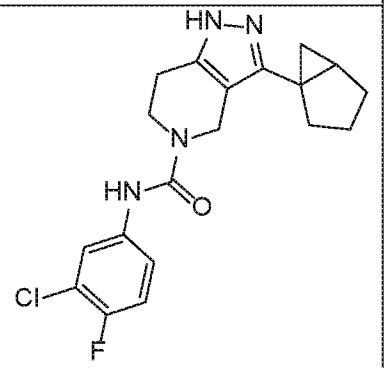
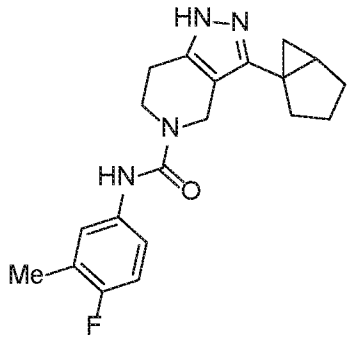
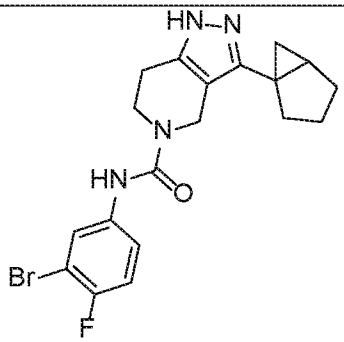
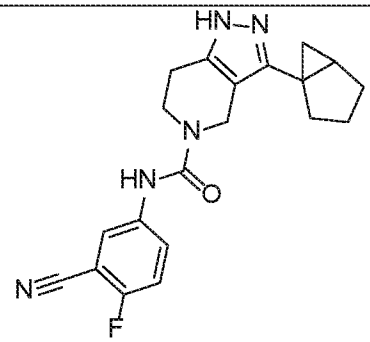
37. The compound of claim 10 or 25, wherein the compound is selected from

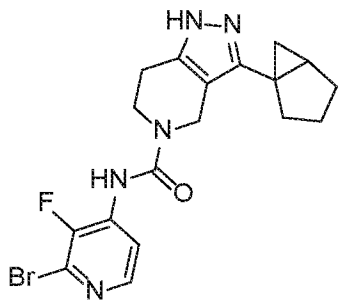
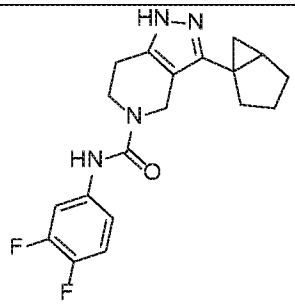
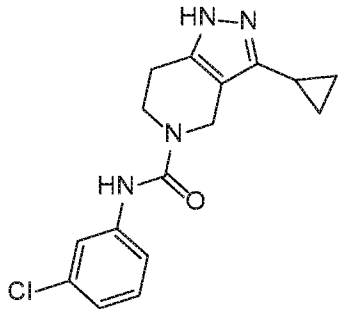
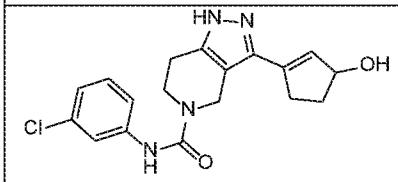
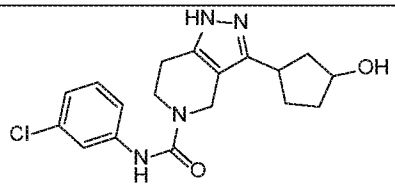
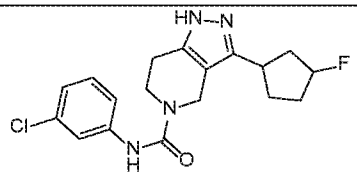
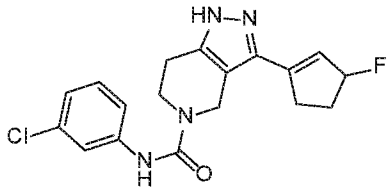
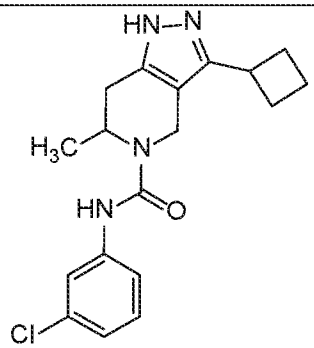
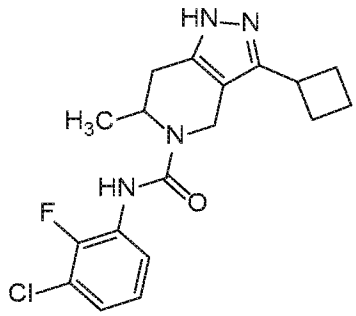
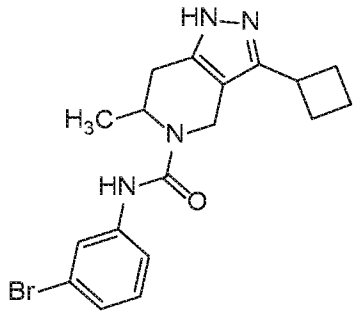
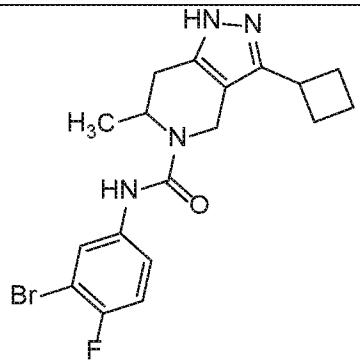
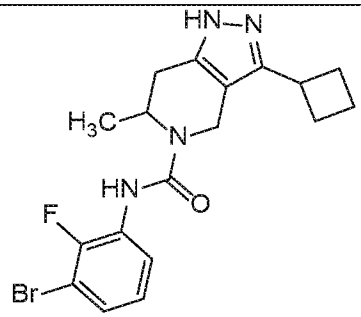
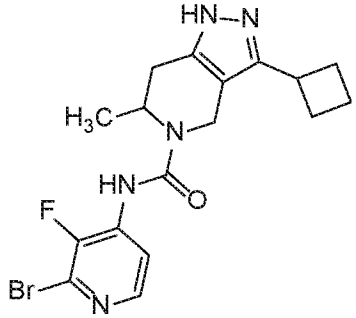
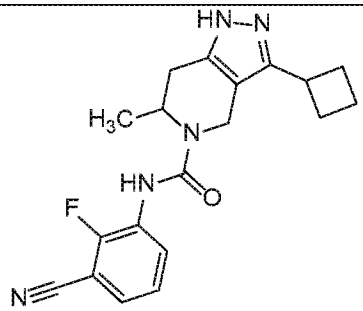
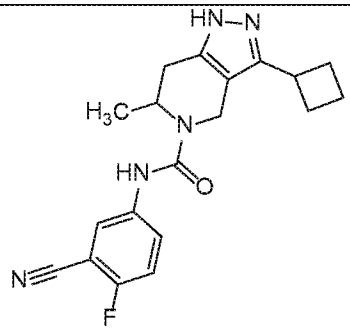
 040	 041	 042
 238	 239	 324
 241	 337	 338
 264	 274	 275

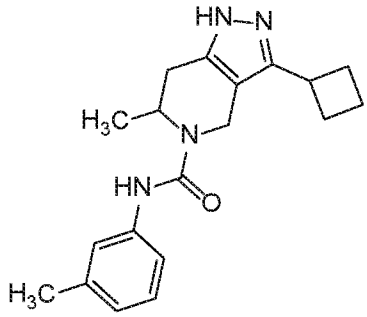
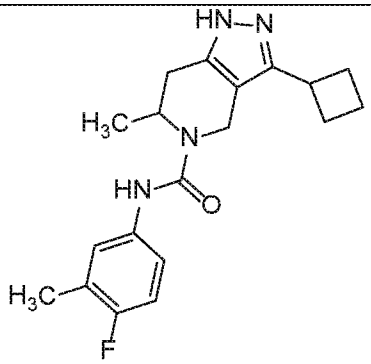
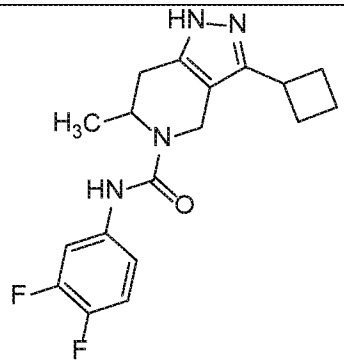
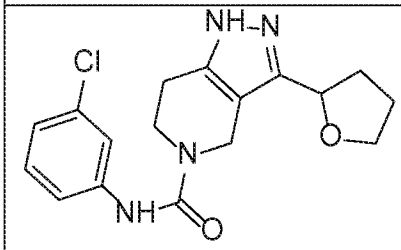
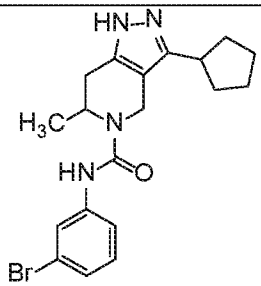
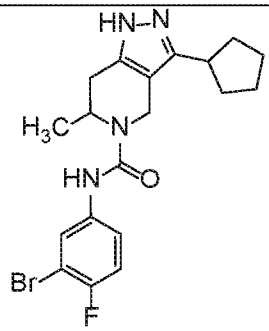
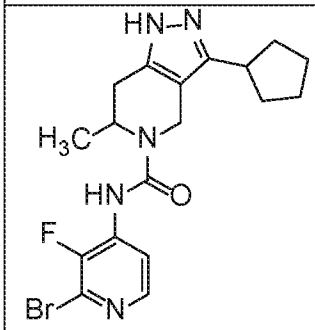
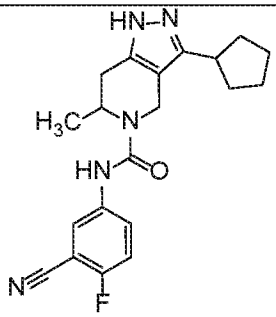
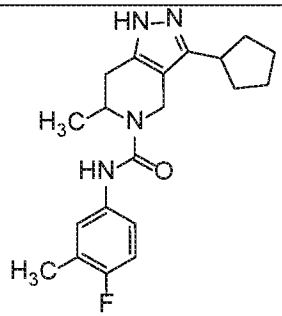
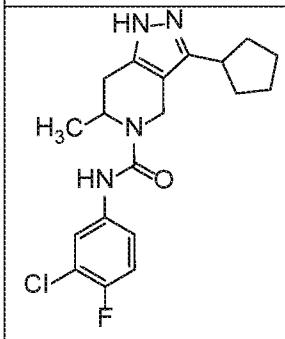
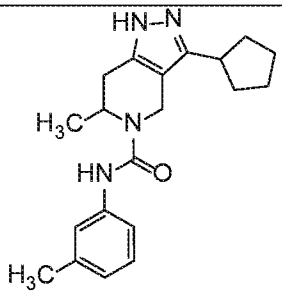
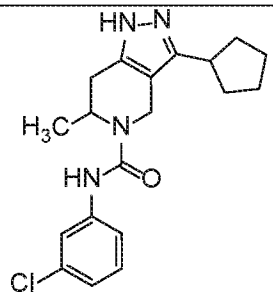
 336	 267	 388
 441	 547	 548
 549	 260	 455
 515	 554	 546
 644	 642	
 696	 604	 694

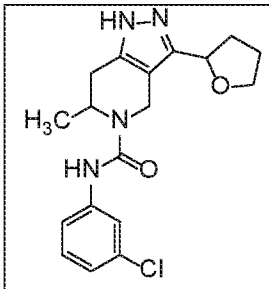
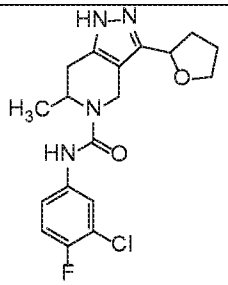
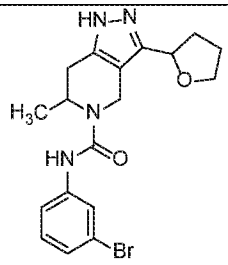
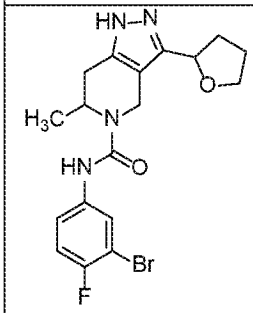
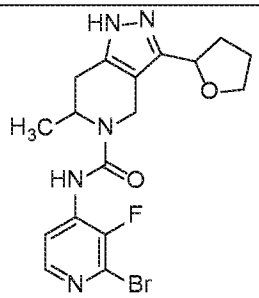
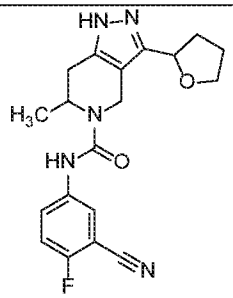
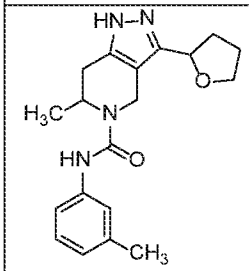
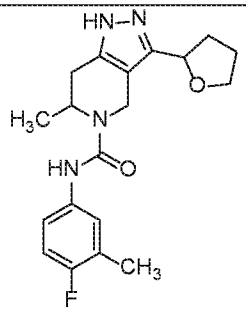
 508	 509	 693
 734	 827	 700
 446	 660	 661
 662	 663	 664

 665	 666	 667
 668	 669	 648
 649	 650	 651
 652	 653	 654

 655	 656	 657
 782	 783	 784
 785	 786	 787
 788	 789	 790

 791	 792	 440
 535	 742	 743
 744	 704	 756
 757	 758	 759
 760	 761	 762

 763	 764	 765
 861	 927	 928
 929	 930	 931
 932	 933	 934

 964	 965	 966
 967	 968	 969
 970	 971	

and pharmaceutically acceptable salts thereof.

38. A pharmaceutical composition comprising a compound of any one of claims 1-37, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

39. A method of treating an HBV infection in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound according to any one of claims 1-37.

40. A method of inhibiting or reducing the formation or presence of HBV DNA-containing particles or HBV RNA-containing particles in an individual in need thereof,

comprising administering to the individual a therapeutically effective amount of a compound according to any one of claims 1-37.

41. The method of claim 39 or 40 further comprising administering to the individual at least one additional therapeutic agent selected from the group consisting of an HBV polymerase inhibitor, immunomodulatory agents, pegylated interferon, viral entry inhibitor, viral maturation inhibitor, literature-described capsid assembly modulator, reverse transcriptase inhibitor, a cyclophilin/TNF inhibitor, a TLR-agonist, an HBV vaccine, and agents of distinct or unknown mechanism, and a combination thereof.

42. The method of claim 41, wherein the therapeutic agent is a reverse transcriptase inhibitor, and is at least one of Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, and Etravirine.

43. The method of claim 41, wherein the therapeutic agent is a TLR agonist, and wherein the TLR agonist is a TLR-7 agonist selected from the group consisting of SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine) and AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate).

44. The method of claim 41, wherein the therapeutic agent is an interferon selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), and interferon gamma (IFN-γ).

45. The method of claim 44, wherein the interferon is interferon-alpha-2a, interferon-alpha-2b, or interferon-alpha-n1.

46. The method of claim 45, wherein the interferon-alpha-2a or interferon-alpha-2b is pegylated.

47. The method of any one of claims 39-46, further comprising administering to the individual at least one HBV vaccine, a nucleoside HBV inhibitor, an interferon or any combination thereof.

48. The method of claim 47, wherein the HBV vaccine is selected from the group consisting of RECOMBIVAX HB, ENGERIX-B, ELOVAC B, GENEVAC-B, and SHANVAC B.