HETEROCYCLIC COMPOUNDS FOR MEDIATING TYROSINE KINASE 2 ACTIVITY

TECHNICAL FIELD

The present invention relates to heterocyclic compounds or pharmaceutically acceptable salts thereof, suitable for regulating or inhibiting the activity of Janus kinase (JAK), particularly tyrosine kinase 2 (TYK2). The present invention also relates to methods for preparing the heterocyclic compounds. The present invention further relates to methods for treating and/or preventing diseases mediated by the kinase, particularly autoimmune diseases, inflammatory diseases and cancers.

BACKGROUND ART

JAK is a non-receptor tyrosine protein kinase composed of four family members, namely: JAK1, JAK2, JAK3 and TYK2. JAK has 7 homology domains in structure (JAK homology domain, JH), of which JH1 is a kinase domain, JH2 is a pseudo-kinase domain (which regulates the kinase activity of JH1), and JH6 and JH7 are receptor binding domains. When the cell surface area of the cytokine receptor is bound to cytokine, its intracellular area where JAKs are bound to is phosphorylated, thereby creating a docking site for the signal transducer and activator of transcription proteins (STATs). The STAT proteins are further phosphorylated by activated JAKs to form a dimer, which enters the nucleus, regulates the expression and transcription of related genes, and enables signal transduction from the cell membrane to the nucleus (Lionard et. al, Ann. Rev. Immunol. 1998, 16, 293-322). Therefore, JAK transduces cytokine-mediated signals through the JAK-STAT pathway and plays an important role in many cellular functions such as cytokine-dependent regulation of cell proliferation, differentiation, apoptosis and immune response, and is a popular target for the treatment of inflammatory diseases, autoimmune diseases and cancers (Alicea-Velazquez et. al, Curr. Drug Targets 2011, 12, 546-55). Several pharmaceuticals that regulate JAKs have been approved for marketing or have been submitted for approval, including JAK1/JAK2 inhibitor ruxolitinib and JAK2 inhibitor fedratinib for treating myelofibrosis, and pan-JAK inhibitor tofacitinib, JAK1/JAK2 inhibitor baricitinib, pan-JAK inhibitor peficitinib and JAK1 inhibitor upadacitinib for treating rheumatoid arthritis, etc.

Gene knockout studies have shown that JAKs and STATs play a highly specific role in controlling different immune responses. A JAK enzyme can participate in the signal

transduction processes induced by multiple cytokines, and a cytokine signaling pathway can also activate multiple JAK enzymes, but cytokine itself has certain selectivity for STAT activation. For example, interleukin-4 (IL-4) activates STAT6, while IL-12 specifically activates STAT4. JAK1, JAK2 and TYK2 are widely present in various tissues and cells. JAK1 is closely related to the activation of inflammatory factors such as IL-6 and interferon (IFN), so JAK1 selective inhibitor is considered having a potential therapeutic effect on autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. JAK2 independently mediates cytokines such as erythropoietin (EPO) and thrombopoietin (TPO) (Won et. al, BMC Bioinformatics 2009, 10, S53), and is closely related to the proliferation and differentiation of blood cells. JAK3 is present only in the bone marrow and lymphatic system, and mediates the signal transduction of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. These cytokines play an important role in inducing the proliferation and differentiation of T cells, activating B cells to produce antibodies, activating macrophages, enhancing the activity of natural killer cells (NK cells), and inducing other cytokines such as IFN. Therefore, JAK3 selective inhibitor is expected to play an important role in organ transplantation and treating autoimmune diseases and inflammatory pneumonia.

The JAK/STAT pathway can be over-activated by autocrine and paracrine cytokines, as well as some mutations, and is associated with a variety of malignant tumors, such as breast cancer, liver cancer, prostate cancer, colon cancer, lung cancer, pancreatic cancer, bladder cancer, and diffuse large B-cell lymphoma (Tan et. al, Curr. Drug Targets 2014, 15, 1341-53; Lam et. al, Blood 2008, 111, 3701-13). The JAK2 mutant JAK2/V617F occurs in the JH2 pseudo-kinase domain, causing change in JAK2 conformation, resulting in continuous activation of the JH1 kinase domain independent on extracellular cytokine signals, which in turn causes cell hyperplasia and blood cancer, and is closely related to polycythaemia vera (PV), essential thrombocythemia and myelofibrosis (MF) (O'Shea et. al, Ann. Rev. Med. 2015, 66, 311-28). JAK2 inhibitor ruxolitinib can be used for the treatment of such blood diseases, but the efficacy is not related to the presence of JAK2/V617F mutation, indicating that anti-tumor activity is not solely based on the inhibition of signal transmission participated in by JAK2/V617F and may also come from the regulation to JAK1-STAT.

TYK2 is involved in the signal transduction of inflammatory cytokines such as interferons (IFNs), IL-12 and IL-23, and plays a key role in congenital immunity and adaptive immunity. TYK2 knockout mice have normal red blood cell counts and can survive, but JAK3-deficient mice have severe immunodeficiency, and JAK1 or JAK2 knockout mice may die during the embryonic period. However, the diseases caused by JAK1/2 malfunctions

have not been found in human, indirectly indicating the importance of physiological functions of JAK1/2. One patient with a null mutation of TYK2 gene has hyperimmunoglobulin E syndrome, but seven other cases with null mutation of TYK2 homozygote do not have hyperimmunoglobulin E syndrome, while due to reduced response to IL-12 and INF-α/β, sensitivity to mycobacterial or viral infections increases. Therefore, inhibiting TYK2 does not cause acute toxicity. The lack of TYK2 expression is manifested as weakened signaling of multiple proinflammatory cytokines and severe imbalance of T helper cell differentiation. In addition, evidences from genetically related research support TYK2 as a common susceptibility gene of autoimmune diseases. The importance of TYK2 regulated pathways has been further confirmed by effectiveness of antibody therapies in disease treatment in clinical settings, such as ustekinumab targeting IL-12/IL-23 for treating psoriasis and anifrolumab targeting type-I interferon receptor for treating systemic lupus erythematosus (SLE). Therefore, TYK2 has received great attention as a drug target for autoimmune diseases. For example, TYK2 inhibitor can be used for potential treatment of psoriasis, SLE, and inflammatory bowel disease (IBD), etc.

TYK2 is also associated with some cancers. For example, the abnormal survival of acute lymphoblastic leukemia (T-ALL) cells is related to the activation of TYK2. Gene knockout experiments have showed that 88% of T-ALL cell lines and 63% of patient-derived T-ALL cells are dependent on TYK2, so TYK2 is an oncogene of T-ALL (Sanda et. al, Cancer Disc. 2013, 3, 564-77). TYK2 selective inhibitor NDI-031301 can induce apoptosis to inhibit the growth of human T-ALL cell lines and has desirable safety and efficacy in mouse models with KOPT-K1 T-ALL tumor cells (Akahane et. al, British J. Haematol. 2017, 177, 271-82), showing a prospect of TYK2 selective inhibitor in the treatment of T-ALL.

In addition to many inhibitors mainly targeting JAK1/2/3, TYK2 specific inhibitor BMS-986165 and JAK1/TYK2 dual inhibitor PF-06700841 have also entered the advanced stage of clinical trials. Since JAK regulates different immune responses in JAK-STAT, different JAK selective inhibitors exhibit different toxic and side effects in the clinical applications and have different clinical uses. Ruxolitinib is used to treat bone marrow fibrosis, shows good safety, and has no toxic and side effects on non-target organs. Tofacitinib inhibits the activity of JAK2 in addition to JAK1, affects the production of blood cells and lymphocytes, and exhibits certain toxic side effect of anemia, thereby limiting its clinical efficacy in RA. Due to the prospect of JAK inhibitors in the treatment of inflammatory diseases, autoimmune diseases and cancers, the development of selective JAK inhibitors has attracted great

attention from the pharmaceutical industry. However, due to the high sequence similarity of the active sites of the JAK kinase family, it is difficult to develop a selective JAK inhibitor. Despite that some patent applications of TYK2 selective inhibitors have been disclosed, including WO2010142752, WO2012062704, WO2013180265, WO2015032423, WO2015131080 and WO2017040757, there is a continuous need to develop new compounds that have better druggability, stronger efficacy, and higher selectivity to TYK2 or TYK2/JAK1.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in this application have the following meanings.

"C_{x-y}" refers to a range of the number of carbon atoms, where x and y are both integers, for example, C_{3-8} cycloalkyl stands for cycloalkyl having 3 to 8 carbon atoms. It should be also understood that "C_{3-8}" further comprises any of sub-ranges, such as C_{3-7}, C_{3-6}, C_{4-7}, C_{4-6} and C_{5-6}.

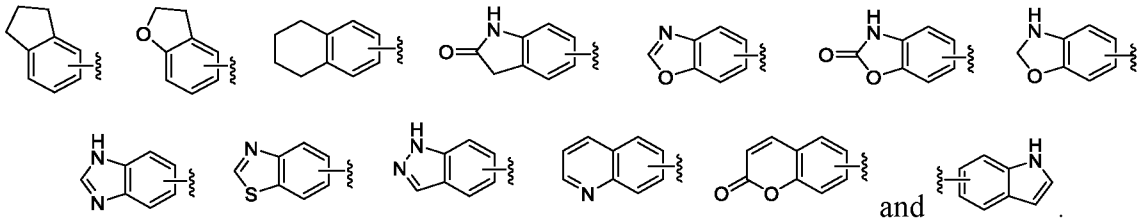
"Alkyl" refers to a saturated straight-chain or branched-chain hydrocarbyl substituent containing 1 to 20 carbon atoms, for example, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. Unrestricted examples of alkyl include but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl.

"Alkylene" refers to a saturated straight-chain or branched-chain hydrocarbyl divalent substituent containing 1 to 20 carbon atoms, for example, 1 to 6 carbon atoms or 1 to 4 carbon atoms. Unrestricted examples of alkylene include but are not limited to $-CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-(CH_3)C(CH_3)-$, $-CH_2CH_2CH_2CH_2-$ and $-CH_2CH(CH_3)CH_2-$.

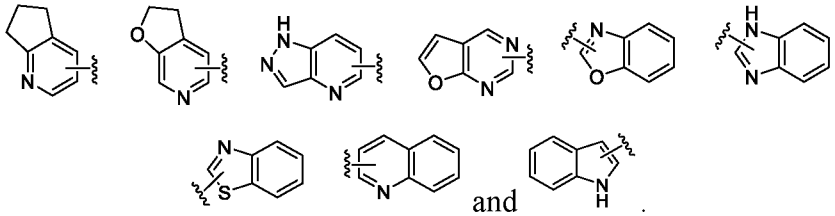
"Cycloalkyl" refers to a saturated cyclic hydrocarbyl substituent containing 3 to 14 annular carbon atoms. Cycloalkyl can be a mono carbon ring substituent, typically containing 3 to 8, 3 to 7, or 3 to 6 carbon atoms. Unrestricted examples of monocyclic cycloalkyl include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cycloalkyl can also be a substituent with two or three mono carbon rings that are fused together, such as decahydronaphthyl.

"Heterocyclyl or heterocycle" refers to a saturated or partially unsaturated monocyclic or polycyclic group containing 3 to 20 annular atoms, for example, 3 to 14, 3 to 12, 3 to 10, 3 to 8, 3 to 6, or 5 to 6 annular atoms in which one or more of the annular atoms are selected from N, O and $S(O)_m$ (where m is an integer from 0 to 2), but does not include -O-O-, -O-S- or -S-S- in the ring structure and the rest are carbon atoms. Preferably, it can have 3 to 12 annular atoms, 3 to 10 annular atoms, 4 to 7 annular atoms, and 4 to 6 annular atoms, wherein 1 to 4 are heteroatoms, 1 to 3 are heteroatoms, or 1 to 2 are heteroatoms. Unrestricted examples of monocyclic heterocyclyl include but are not limited to pyrrolidinyl, oxetanyl, piperidyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, homopiperazinyl and azetidinyl. Polycyclic heterocyclyl includes fused, bridged or spiro polycyclic heterocycle, such as octahydrocyclopenta[c]pyrrole, octahydropyrrole[1,2-a]pyrazine, 3,8-diazabicyclo[3.2.1]octane, 5-azaspiro[2.4]heptane and 2-oxa-7-azaspiro[3.5]nonane.

"Aryl or aryl ring" refers to an aromatic monocyclic or fused polycyclic group containing 6 to 14 carbon atoms, preferably 6- to 10- membered, such as phenyl and naphthyl, most preferably phenyl. The aryl ring can be fused with a heteroaryl, heterocyclyl or cycloalkyl ring, and unrestricted examples include but are not limited to:



"Heteroaryl or heteroaryl ring" refers to a heteroaromatic system containing 5 to 14 annular atoms, of which 1 to 4 annular atoms are selected from heteroatoms including O, S and N. Heteroaryl preferably is 5- to 10-membered, and more preferably 5- or 6-membered, such as furyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl and isoindolyl. The heteroaryl ring can be fused with an aryl, heterocyclyl or cycloalkyl ring, and unrestricted examples include but are not limited to:



"Halogen" refers to F, Cl, Br or I.

"Cyano" refers to -CN.

"Oxo" refers to =O.

"Carbonyl" refers to -C(=O)- group.

"Sulfonyl" refers to a $-S(O)_2-$ group.

"Sulfinyl" refers to a -S(O)- group.

"Optional substitution or optionally substituted" refers to that one or more hydrogen atoms in a group, preferably 5, more preferably 1 to 3 hydrogen atoms, are independently substituted by a corresponding number of substituents. It goes without saying, the substituents are located only in the chemical positions where they may be located, and those skilled in the art can determine possible or impossible substitutions without making much effort (by experiment or theory). For example, amino or hydroxyl groups with free hydrogen may be unstable when bound with carbon atoms with unsaturated bonds (such as olefinic). The substituents include but are not limited to halogen, cyano, nitro, oxo, $-SF_5$, C_{1-4} alkyl, C_{3-7} cycloalkyl, etc.

"Isomers" refer to compounds that have the same molecular formula but the nature or sequence of their atomic binding or spatial arrangement is different. Isomers with different arrangement of their atoms in space are called "stereoisomers". Stereoisomers include optical isomers, geometric isomers and conformational isomers.

The compounds of the present invention can exist in form of optical isomers. Optical isomers include enantiomers and diastereoisomers. An enantiomer is one of two stereoisomers that are mirror images of each other that are non-superposable. A racemic mixture, or racemate is one that has equal amounts of left- and right-handed enantiomers of a chiral molecule. Diastereomers are stereoisomers that are not mirror images of one another and are non-superimposable on one another. Methods for preparing and separating optical isomers are known in the art. When a compound is a single isomer and its absolute configuration is determined, it is referred as a "R" or "S" isomer according to the configuration of the substituents around the chiral carbon atom; when its absolute configuration is not determined, it is referred as a (+) or (-) isomer according to its measured optical rotation value.

The compounds of the present invention may also have geometric isomers resulting from the distribution of substituents around carbon-carbon double bonds, carbon-nitrogen double bonds, cycloalkyl or heterocyclyl groups. The substituents around the carbon-carbon double bond or carbon-nitrogen bond are designated to be in a Z or E configuration, and the substituents around the cycloalkyl or heterocycle are designated to be in a cis or trans

configuration.

The compounds of the present invention may also show tautomerism, such as keto-enol tautomerism.

The present invention includes any tautomeric or stereoisomeric forms and mixtures thereof and is not limited to any tautomeric or stereoisomeric forms used in the compound nomenclature or chemical structural formulae.

"Isotopes" include all isotopes of the atoms appearing in the compounds of the present invention. Isotopes include those atoms with the same atomic number but in different masses. Examples of isotopes suitable for incorporation into the compounds of the present invention are isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example but not limited to ^{2}H (D), ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl. The isotopically labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by methods similar to those described in the embodiments using appropriate isotopically labeled reagents instead of non-isotopically labeled reagents. Such compounds have various potential uses, for example, as standards and reagents in the determination of biological activities. In the case of stable isotopes such as deuterium ^{2}H (D), ^{13}C and ^{15}N, such compounds have the potential to beneficially alter biological, pharmacological or pharmacokinetic properties. Deuterium ^{2}H (D) is a preferable isotope of the present invention. For example, the hydrogens of $-CH_3$ can be substituted by D to $-CD_3$. For example, one or more hydrogens of cyclopropyl can be substituted by D.

The compounds of the present invention can be administered in form of prodrugs. "Prodrugs" refer to derivatives that are converted into biologically active compounds under the physiological condition in vivo, for example, by oxidation, reduction and hydrolysis (each of which occurs with or without the participation of enzymes). Examples of a prodrug are a compound of the present invention in which an amino is acylated, alkylated or phoshorylated, for example eicosanoyl amino, alanyl amino and pivaloyloxymethyl amino; a hydroxyl is acylated, alkylated or phoshorylated or converted into borate, for example acetoxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaroyloxy and alanyloxy; a carbonyl is esterified or amidated; and a thiol forms a disulfide bridge with a carrier molecule that selectively delivers the drug to the target and/or to the cytosol of cells, such as peptide. Prodrugs can be prepared from the compounds of the present invention according to well-known methods.

"Pharmaceutically acceptable salts" refer to the salts made from the compounds of the present invention with pharmaceutically acceptable bases or acids, including inorganic alkalis

or acids and organic bases or acids, under the condition that the compounds contain one or more acidic or basic groups. Therefore, the compounds of the present invention that contain acidic groups can exist in form of salts, for example, as alkali metal salts, alkaline earth metal salts, or ammonium salts. For example, such salts include sodium salts, potassium salts, calcium salts, magnesium salts or ammonia or organic amine salts such as salts of ethylamine, ethanolamine, triethanolamine or amino acids. The compounds of the present invention that contain basic groups can exist in form of salts as inorganic or organic acid salts. Examples of suitable acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalene disulfonic acid, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propanoic acid, pivalic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid and other acids known to those skilled in the art. If the compounds of the present invention contain both acidic and basic groups in the molecule, the present invention further includes internal salts in addition to the mentioned salt forms. Each salt can be obtained by conventional methods known to those skilled in the art, for example by mixing a compound of the present invention with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with another salt.

"Pharmaceutical composition" refers to a composition containing one or more of the compounds described herein or pharmaceutically acceptable salts, prodrugs, stable isotope derivatives and isomers thereof, and other components such as pharmaceutically acceptable carriers and excipients.

When "compounds" are mentioned in the present application, all the compound forms are included, such as pharmaceutically acceptable salts, prodrugs, stable isotope derivatives and isomers thereof as well as mixtures thereof.

"Autoimmune diseases or inflammatory diseases" include but are not limited to arthritis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, hepatitis, primary sclerosing cholangitis, chronic invasive hepatitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, ulcerative colitis, membranous glomerulopathy, systemic lupus erythematosus, rheumatoid arthritis, psoriasis arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis, dermatomyositis, I-type interferon disease including Aicardi-Goutières syndrome and other systemic sclerosis that

overexpresses I-type interferon, Mendelian disease, polyarteritis nodosa, multiple sclerosis, relapsing multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, and bullous pemphigoid; further, autoimmune diseases based on O-cell (body fluid) or T-cell include Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, type I or juvenile diabetes, and thyroiditis.

In this document, term "enteritis" includes but is not limited to Crohn's disease, ulcerative colitis, inflammatory bowel disease, celiac disease, proctitis, eosinophilic gastroenteritis, and mastocytosis.

"Cancers/tumors" include but are not limited to digestive/gastrointestinal cancer, colon cancer, liver cancer, skin cancer (including mast cell tumor and squamous cell carcinoma), breast cancer, ovarian cancer, prostate cancer, lymphoma, leukemia (including acute myeloid leukemia and chronic myelogenous leukemia), kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer, brain cancer, melanoma (including oral and metastatic melanoma), Kaposi's sarcoma (myeloma including multiple myeloma), myeloproliferative diseases, proliferative diabetic retinopathy, and vascular hyperplasia-related disorders/tumors.

"Skin diseases" include but are not limited to atopic dermatitis, eczema, psoriasis, scleroderma, pruritus or other itching symptoms, vitiligo, and hair loss.

"Diabetes" include but are not limited to type I diabetes and diabetic complications.

"Eye diseases" include but are not limited to keratoconjunctivitis, uveitis (including uveitis associated with Behcet's disease and uveitis caused by the lens), keratitis, herpetic keratitis, keratoconus, dystrophia epithelialis corneae, corneal leukopenia, anterior uveitis, Mooren's ulcer, scleritis, Graves' eye disease, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), blisters, iridocyclitis sarcoidosis, endocrine ophthalmopathy, sympathetic ophthalmia, allergic conjunctivitis and ocular neovascularization.

"Neurodegenerative diseases" include but are not limited to motor neuron disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia; neurodegenerative disease caused by trauma, injury, glutamate neurotoxicity or hypoxia; ischemia/reperfusion injury in stroke, myocardial ischemia, renal ischemia, heart attack, cardiac hypertrophy, atherosclerosis and arteriosclerosis, organ hypoxia or platelet aggregation.

"Anaphylaxis" includes but is not limited to allergic dermatitis in mammals (including anaphylactic diseases of horses, such as bite hypersensitivity), summer eczema, itchy horseshoes, spasm, inflammatory airway diseases, repeated airway obstruction, airway

hyperresponsiveness, and chronic obstructive pulmonary disease.

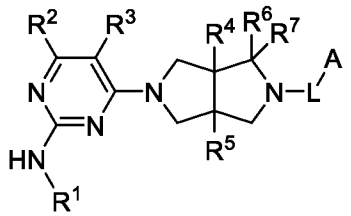
"Asthma and other obstructive airway diseases" include but are not limited to chronic or excessive asthma, delayed asthma, bronchitis, bronchial asthma, allergic asthma, endogenous asthma, exogenous asthma, and dusty asthma.

"Transplant rejection" includes but is not limited to islet transplant rejection, bone marrow transplant rejection, graft versus host disease, organ and cell transplant rejection (such as bone marrow, cartilage, cornea, heart, intervertebral disc, islet, kidney, limb, liver, lung, muscle, myoblast, nerve, pancreas, skin, small intestine or trachea), and xenotransplantation.

"Therapeutically effective amount" refers to the amount of the compound of the present invention that can effectively inhibit the function of JAK, in particular TYK2, and/or treat or prevent the disease mediated by the kinase.

"Patients" refer to mammals, preferably humans.

The present invention provides compounds useful as inhibitors of JAK, in particular TYK2. The compounds are shown in Formula (I), or prodrugs, stable isotope derivatives, pharmaceutically acceptable salts and isomers thereof.



(I)

where:

R^1 is aryl or heteroaryl, where one or more hydrogens of the aryl and heteroaryl are optionally substituted by D, halogen, cyano, $-OR^b$, $-NR^bR^c$, $-COOR^b$, $-C(O)R^b$, $-NR^bC(O)R^c$, $-C(O)NR^bR^c$, $-S(O)_2R^b$, $-S(O)_2NR^bR^c$, $-S(O)(NR^b)R^c$, $-P(O)(CH_3)_2$, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl or 5- to 6-membered heteroaryl;

R^2 is H, D or $-NHR^a$;

R^3 is H, D, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl or OC_{1-6} alkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D or F;

R^4 and R^5 are independently selected from H, D, halogen, C_{1-6} alkyl or OC_{1-6} alkyl, where one or more hydrogens of the alkyl are optionally substituted by D or F;

R^6 and R^7 are independently selected from H, D, cyano or C_{1-6} alkyl, where one or more hydrogens of the alkyl is optionally substituted by D or F, or R^6 and R^7 combine as oxo;

L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, -C(O)N(R^a)-, -S(O)$_2$- or -S(O)$_2$N(R^a)-;

A is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, aryl or heteroaryl, where one or more hydrogens of the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by D, halogen, cyano, -OR^d, -NR^dR^e, C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 8-membered heterocyclyl;

R^a is H, C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D or F;

R^b and R^c are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 8-membered heterocyclyl containing N and/or O, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by D, halogen, CN, -OH, -NH_2, C_{1-6} alkyl and -OC_{1-6} alkyl, and

R^d and R^e are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 8-membered heterocyclyl, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by D or F.

In one embodiment, R^1 is phenyl.

In one embodiment, R^1 is 5- to 6-membered heteroaryl, for example, R^1 is pyridyl, pyrimidyl, or pyrazolyl.

In one embodiment, one or more hydrogens of the phenyl and heteroaryl of R^1 are optionally substituted by halogen, -$COOR^b$, -C(O)R^b, -C(O)NR^bR^c, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl containing N and/or O, preferably, by C_{1-6} alkyl, 4- to 6-membered heterocyclyl, -C(O)R^b or -C(O)NR^bR^c, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by D, halogen, CN, -OH, -NH_2, C_{1-6} alkyl and -OC_{1-6} alkyl, preferably, by D, F, CN, -OH or C_{1-6} alkyl.

In one embodiment, R^b and R^c are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl containing N and/or O, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by C_{1-6} alkyl.

In one preferred embodiment, R^2 is H.

In one preferred embodiment, R^3 is H, halogen, cyano, C_{1-6} alkyl or OC_{1-6} alkyl.

In one preferred embodiment, R^4 and R^5 are independently H or C_{1-6} alkyl.

In one preferred embodiment, R^6 and R^7 are H, or R^6 and R^7 combine as oxo.

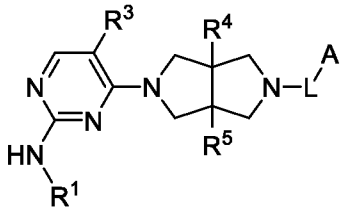
In one preferred embodiment, L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, -C(O)NH- or -S(O)$_2$-.

In one embodiment, A is C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of

the alkyl and cycloalkyl are optionally substituted by halogen, cyano, -OH, -OC_{1-2} alkyl or C_{1-2} alkyl.

In one embodiment, A is pyridyl, pyrimidyl, 5-membered heteroaryl or 4- to 6-membered heterocyclyl, where one or more hydrogens of the heterocyclyl and heteroaryl are optionally substituted by halogen, cyano, -OH, -OC_{1-2} alkyl or C_{1-2} alkyl, preferably, by C_{1-2} alkyl.

In some embodiments, the compounds shown in Formula (I) has the following Formula (II):



(II)

where:

R^1 is phenyl, pyridyl or pyrazolyl, where one or more hydrogens of the phenyl, pyridyl and pyrazolyl are optionally substituted by halogen, C_{1-6} alkyl, 4- to 6-membered heterocyclyl containing N and/or O (e.g., morpholine, piperazine, piperidine, pyrrolidine, and oxetane), -C(O)R^b or -C(O)NR^bR^c, and one or more hydrogens of the alkyl and heterocyclyl are optionally further substituted by D, F, CN, -OH or C_{1-6} alkyl;

R^b and R^c are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl containing N and/or O (e.g., morpholine, piperazine, piperidine, pyrrolidine, and oxetane), where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by C_{1-2} alkyl;

R^3 is H, halogen, cyano, C_{1-6} alkyl or OC_{1-6} alkyl;

R^4 and R^5 are independently H or C_{1-6} alkyl;

L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, -C(O)NH- or -$S(O)_2$-, and

A is C_{1-6} alkyl, C_{3-6} cycloalkyl, 4- to 6-membered heterocyclyl containing N and/or O (e.g., morpholine, piperazine, piperidine, pyrrolidine, and oxetane), pyridyl, pyrimidyl or 5-membered heteroaryl (e.g., isoxazole and pyrazole), where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by halogen, cyano, -OH, -OC_{1-2} alkyl or C_{1-2} alkyl, and those of the heterocyclyl and heteroaryl are optionally substituted by C_{1-2} alkyl.

In one preferred embodiment, R^1 is pyrazolyl.

In one preferred embodiment, R^3 is H, halogen or C_{1-6} alkyl.

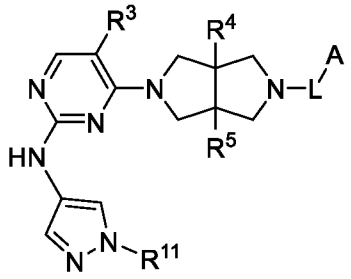
In one preferred embodiment, R^4 is H or methyl.

In one preferred embodiment, R^5 is H or methyl.

In one preferred embodiment, L is -C(O)-.

In one preferred embodiment, A is C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by halogen, cyano, -OH or -OC_{1-2} alkyl.

In some embodiments, the compounds shown in Formula (II) has the following Formula (III):



(III)

where:

R^3 is H, halogen, cyano, C_{1-6} alkyl, or OC_{1-6} alkyl;

R^4 and R^5 are independently H or C_{1-6} alkyl;

L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, -C(O)NH-, or -$S(O)_2$-;

A is C_{1-6} alkyl, C_{3-6} cycloalkyl, 4- to 6-membered heterocyclyl containing N and/or O (e.g., morpholine, piperazine, piperidine, pyrrolidine, and oxetane), pyridyl, pyrimidyl, or 5-membered heteroaryl (e.g., isoxazole and pyrrazole), where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D, halogen, cyano, -OH, -OC_{1-2} alkyl or C_{1-2} alkyl, and one or more hydrogens of the heterocyclyl and heteroaryl are optionally substituted by C_{1-2} alkyl, and

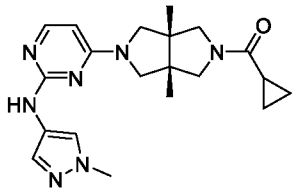
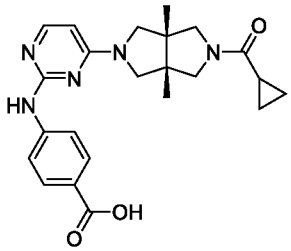
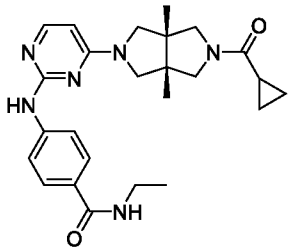
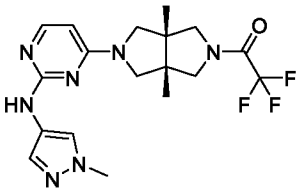
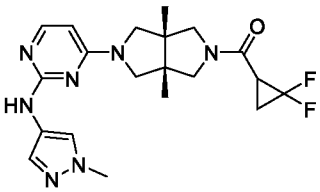
R^{11} is H, C_{1-6} alkyl or 4- to 6-membered heterocyclyl containing N and/or O (e.g., morpholine, piperazine, piperidine, pyrrolidine, and oxetane), where one or more hydrogens of the alkyl and heterocyclyl are optionally substituted by D, F, CN, -OH or C_{1-6} alkyl.

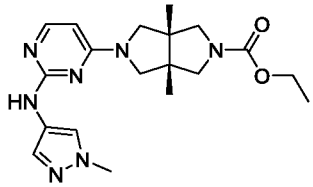
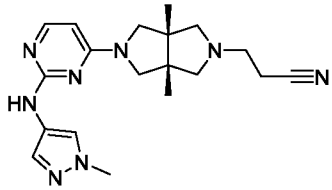
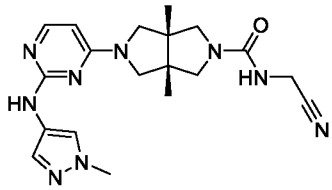
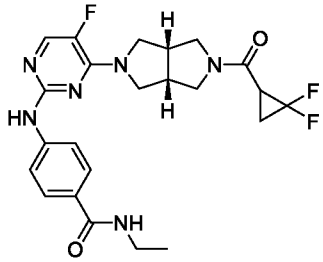
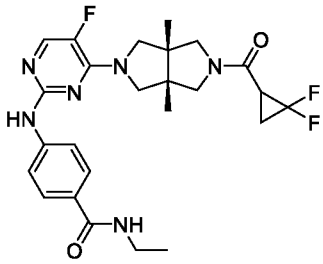
Preferred A of Formula III is C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by halogen, cyano, -OH or -OC_{1-2} alkyl.

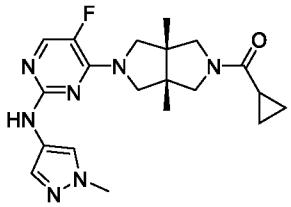
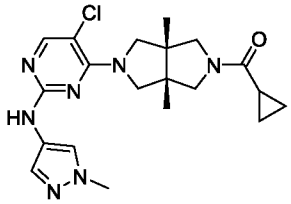
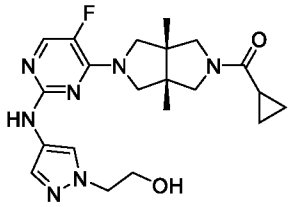
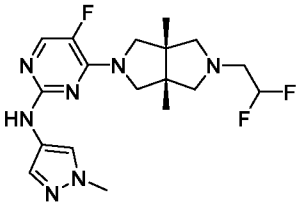
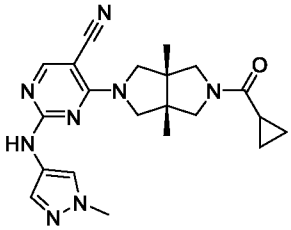
Preferred R^{11} is C_{1-6} alkyl (e.g., methyl), wherein one or more hydrogens of the alkyl are optionally substituted by D, F, CN, -OH, or C_{1-6} alkyl.

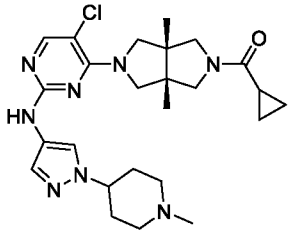
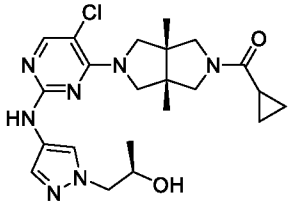
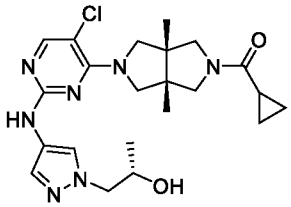
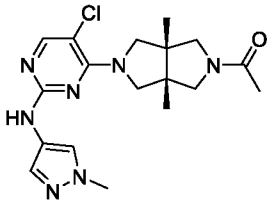
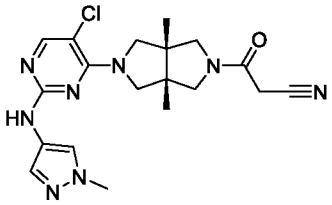
The present invention further relates to the following Compounds 1-100, or their

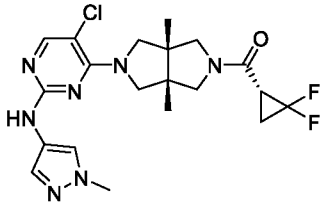
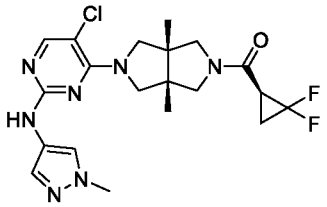
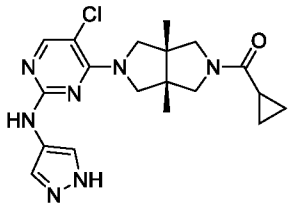
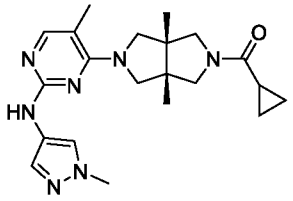
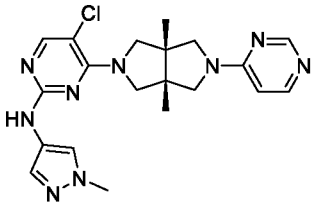
pharmaceutically acceptable salts, prodrugs, stable isotope derivatives, isomers and mixtures thereof.

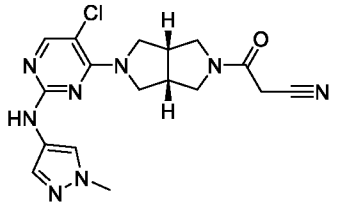
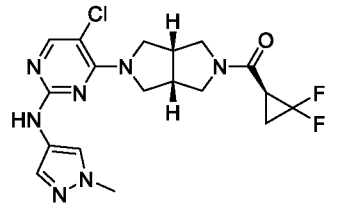
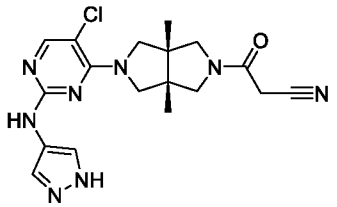
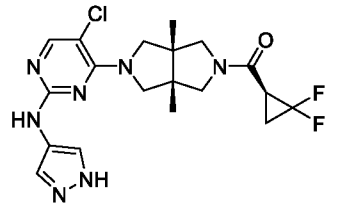
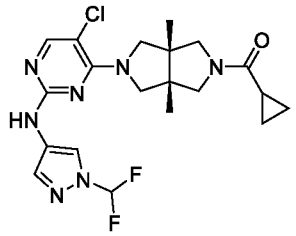
Compound No.	Compound Structure and Chemical Name
1.	
	cyclopropyl((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
2.	
	4-((4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)benzoic acid
3.	
	4-((4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-N-ethylbenzamide
4.	
	1-((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2,2,2-trifluoroethan-1-one
5.	

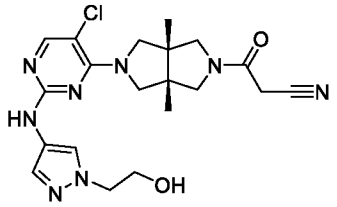
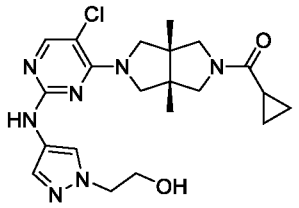
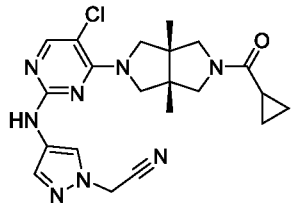
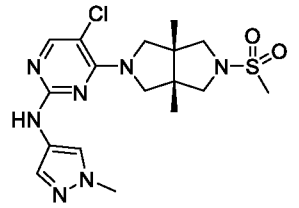
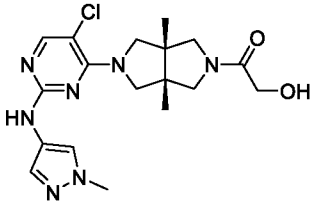
	(2,2-difluorocyclopropyl)((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidine-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)methanone
6.	
	ethyl (3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate
7.	
	3-((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propanenitrile
8.	
	(3aR,6aS)-*N*-(cyanomethyl)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide
9.	
	4-((4-((3aR,6aS)-5-(2,2-difluorocyclopropane-1-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoropyrimidin-2-yl)amino)-N-ethylbenzamide
10.	

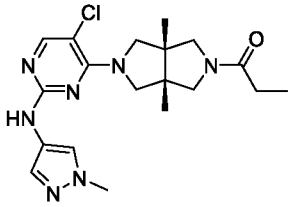
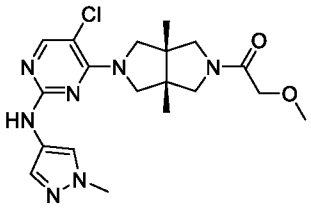
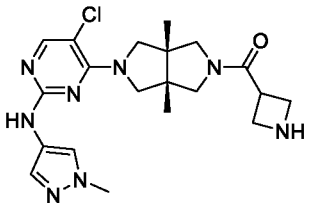
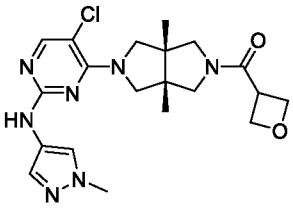
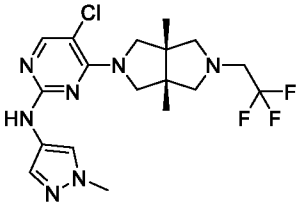
	4-((4-((3aR,6aS)-5-(2,2-difluorocyclopropane-1-carbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoropyrimidin-2-yl)amino)-N-ethylbenzamide
11.	
	cyclopropyl((3aR,6aS)-5-(5-fluoro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
12.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
13.	
	cyclopropyl((3aR,6aS)-5-(5-fluoro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
14.	
	4-((3aR,6aS)-5-(2,2-difluoroethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
15.	
	4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-

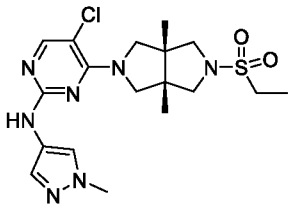
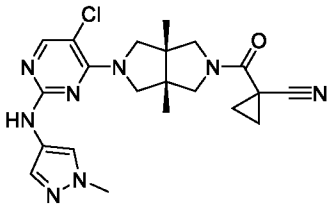
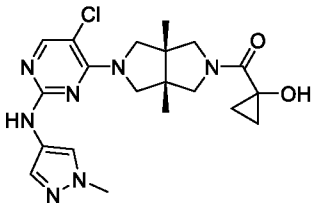
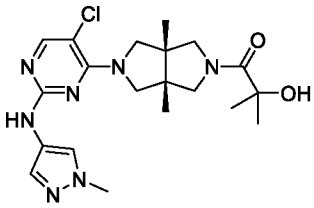
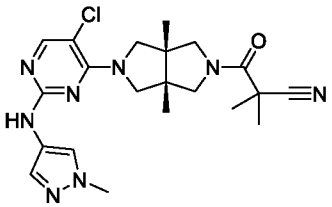
	dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidine-5-carbonitrile
16.	
	((3aR,6aS)-5-(5-chloro-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
17.	
	((3aR,6aS)-5-(5-chloro-2-((1-((R)-2-hydroxypropyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
18.	
	((3aR,6aS)-5-(5-chloro-2-((1-((S)-2-hydroxypropyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
19.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-one
20.	
	3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-

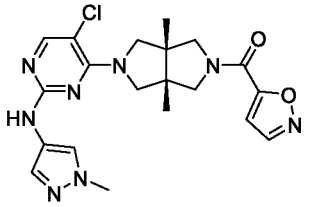
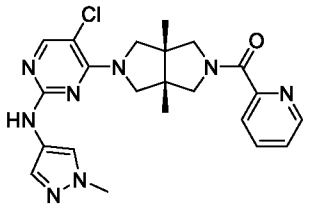
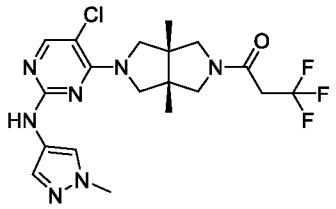
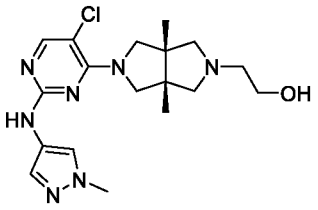
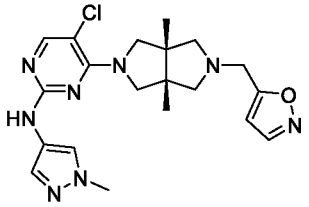
	c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
21.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((R)-2,2-difluorocyclopropyl)methanone
22.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone
23.	
	((3aR,6aS)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
24.	
	cyclopropyl((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
25.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

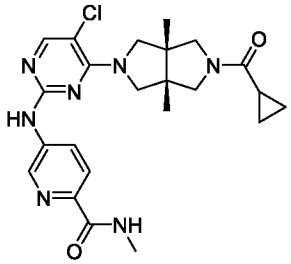
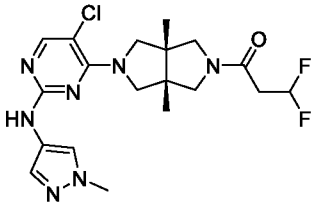
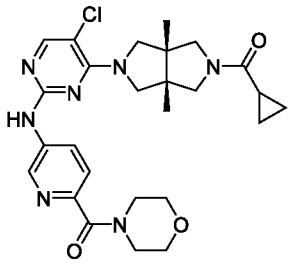
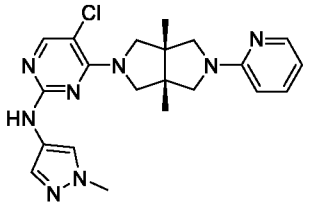
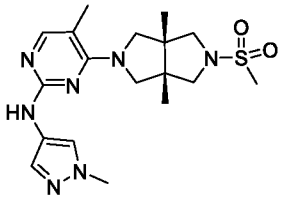
26.	
	3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
27.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone
28.	
	3-((3aR,6aS)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
29.	
	((3aR,6aS)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone
30.	
	((3aR,6aS)-5-(5-chloro-2-((1-(difluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone

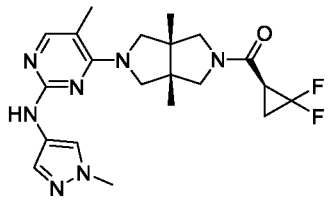
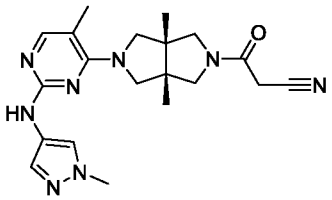
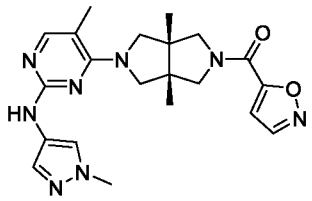
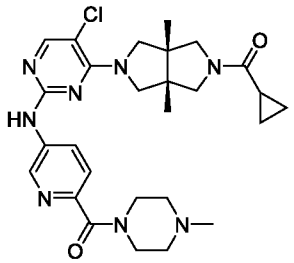
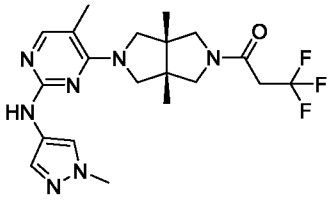
31.	
	3-((3aR,6aS)-5-(5-chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
32.	
	((3aR,6aS)-5-(5-chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
33.	
	2-(4-((5-chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)acetonitrile
34.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
35.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-hydroxyethan-1-one

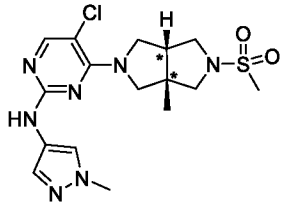
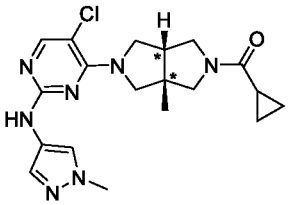
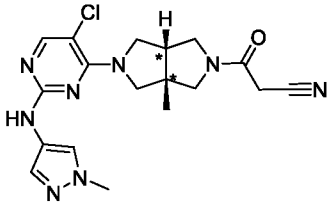
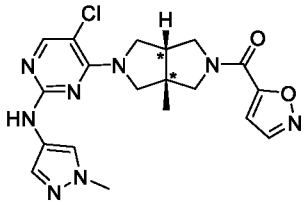
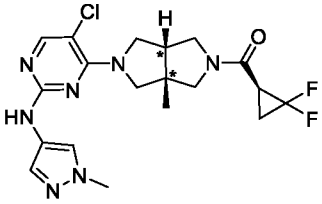
36.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one
37.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-methoxyethan-1-one
38.	
	azetidin-3-yl((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
39.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(oxetan-3-yl)methanone
40.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(2,2,2-trifluoroethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

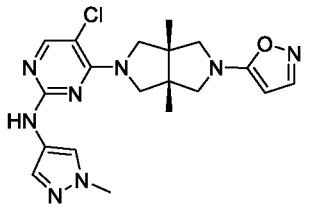
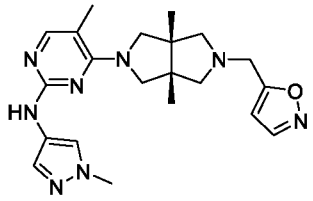
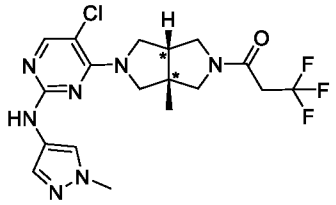
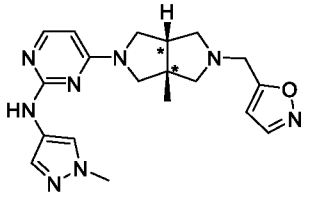
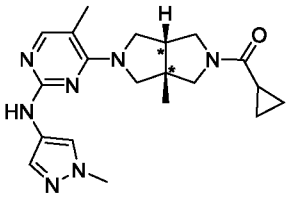
41.	
	5-chloro-4-((3aR,6aS)-5-(ethylsulfonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
42.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)cyclopropane-1-carbonitrile
43.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(1-hydroxycyclopropyl)methanone
44.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-hydroxy-2-methylpropan-1-one
45.	
	3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2,2-dimethyl-3-oxopropanenitrile

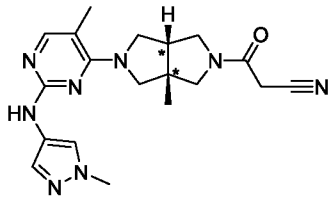
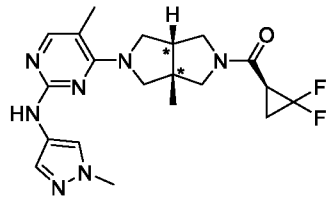
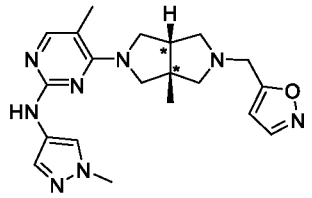
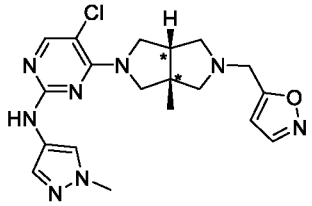
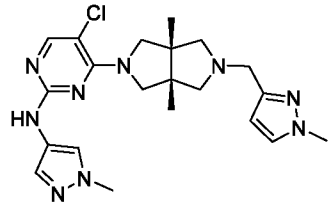
46.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(isoxazol-5-yl)methanone
47.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(pyridin-2-yl)methanone
48.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3,3-trifluoropropan-1-one
49.	
	2-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-ol
50.	
	5-chloro-4-((3aR,6aS)-5-(isoxazol-5-ylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

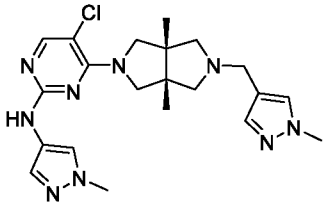
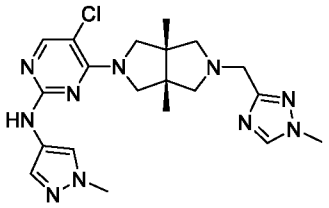
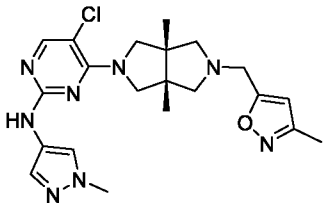
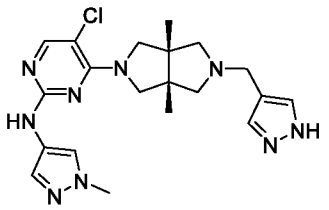
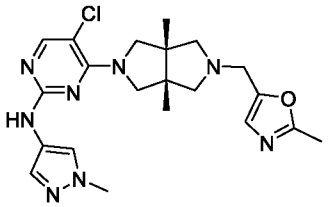
51.	
	5-((5-chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-N-methylpicolinamide
52.	
	1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3-difluoropropan-1-one
53.	
	((3aR,6aS)-5-(5-chloro-2-((6-(morpholine-4-carbonyl)pyridin-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
54.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(pyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
55.	
	4-((3aR,6aS)-3a,6a-dimethyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-

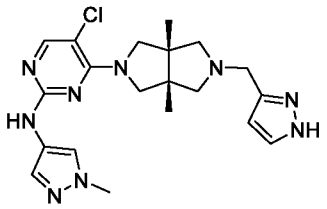
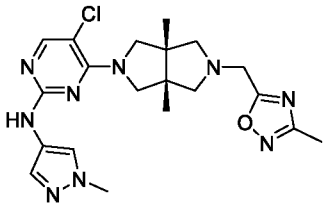
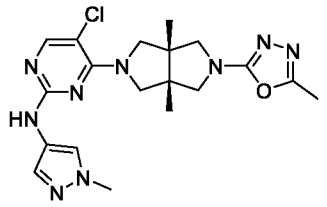
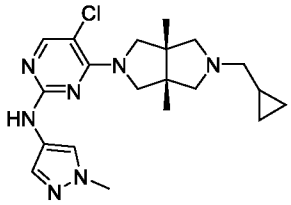
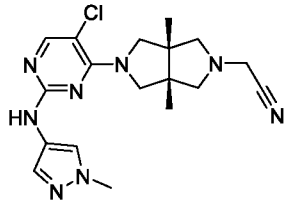
	2-amine
56.	
	((S)-2,2-difluorocyclopropyl)((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
57.	
	3-((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
58.	
	((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(isoxazol-5-yl)methanone
59.	
	((3aR,6aS)-5-(5-chloro-2-((6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
60.	
	1-((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3,3-trifluoropropan-1-one

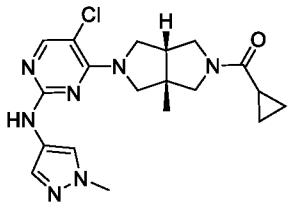
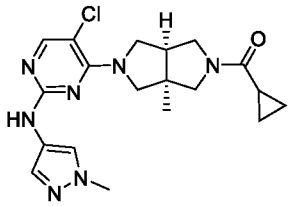
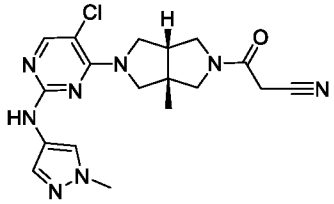
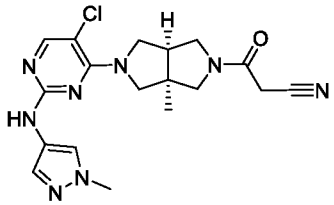
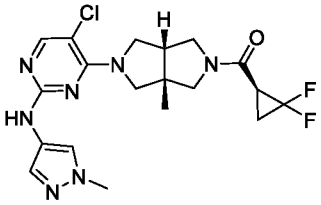
61.	
	cis-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine
62.	
	cis-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
63.	
	cis-3-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
64.	
	cis-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(isoxazol-5-yl)methanone
65.	
	cis-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone

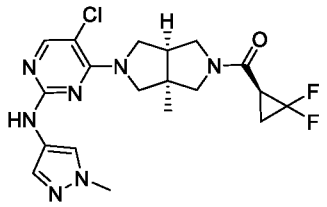
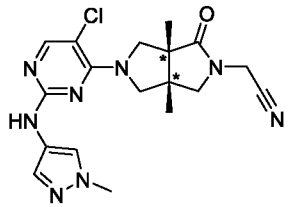
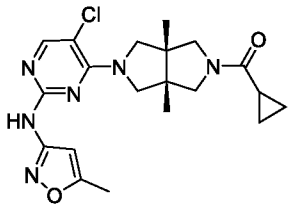
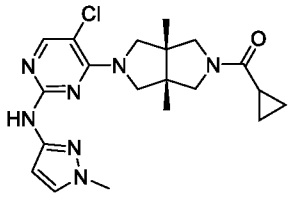
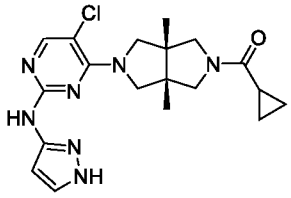
66.	
	5-chloro-4-((3aR,6aS)-5-(isoxazol-5-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
67.	
	4-((3aR,6aS)-5-(isoxazol-5-ylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
68.	
	cis-1-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3,3-trifluoropropan-1-one
69.	
	cis-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
70.	
	cis-cyclopropyl(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone

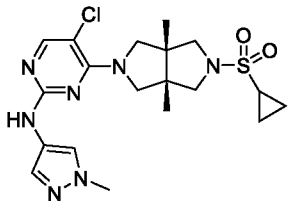
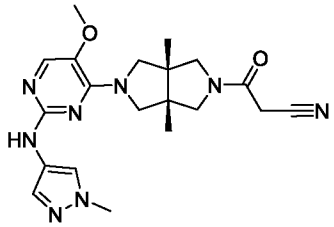
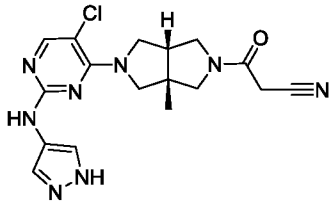
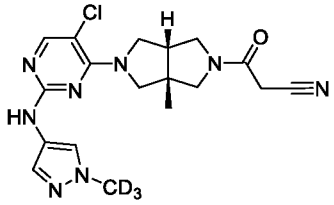
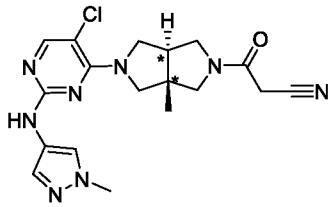
71.	
	cis-3-(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
72.	
	cis-((S)-2,2-difluorocyclopropyl)(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone
73.	
	cis-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
74.	
	cis-5-chloro-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
75.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((1-methyl-1H-pyrazol-3-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

76.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((1-methyl-1H-pyrazol-4-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
77.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((1-methyl-1H-1,2,4-triazol-3-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
78.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((3-methylisoxazol-5-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
79.	
	4-((3aR,6aS)-5-((1H-pyrazol-4-yl)methyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
80.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((2-methyloxazol-5-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

81.	
	4-((3aR,6aS)-5-((1H-pyrazol-3-yl)methyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
82.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
83.	
	5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
84.	
	5-chloro-4-((3aR,6aS)-5-(cyclopropylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
85.	
	2-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetonitrile

86.	
	((3aS,6aR)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
87.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
88.	
	3-((3aS,6aR)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
89.	
	3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
90.	
	((3aS,6aR)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone

91.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone
92.	
	cis-2-(5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetonitrile
93.	
	((3aR,6aS)-5-(5-chloro-2-((5-methylisoxazol-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
94.	
	((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone
95.	
	((3aR,6aS)-5-(2-((1H-pyrazol-3-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone

96.	
	5-chloro-4-((3aR,6aS)-5-(cyclopropylsulfonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine
97.	
	3-((3aR,6aS)-5-(5-methoxy-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
98.	
	3-((3aS,6aR)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
99.	
	3-((3aS,6aR)-5-(5-chloro-2-((1-(methyl-d_3)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile
100.	
	trans-3-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile

Compounds 61, 62, 63, 64, 65, 68, 69, 70, 71, 72, 73, 74, 92 and 100 are racemates or a

pair of diastereoisomers. Compounds 86, 87, 88, 89, 90, 91, 98 and 99 are single optical isomers. Compounds 86/87 and compounds 88/89 are a pair of enantiomers, respectively. Compounds 90 and 91 are a pair of diastereoisomers.

The compounds of the present invention effectively inhibit the activity of JAK, particularly TYK2, preferably having an IC_{50} of 10 to 100 nM, and more preferably having an IC_{50} of less than 10 nM. The compounds of the present invention have a significant inhibitory effect on IFN-γ secretion induced by IL-12 in NK92 cells, preferably having an IC_{50} of less than 1,000 nM.

The present invention further relates to pharmaceutical compositions comprising compounds of Formula (I) or pharmaceutically acceptable salts, prodrugs, stable isotope derivatives, or isomers thereof, and pharmaceutically acceptable carriers or excipients. The pharmaceutical compositions are useful for the treatment or prevention of JAK, in particular TYK2 mediated diseases, including but not limited to autoimmune diseases, inflammatory diseases including intestinal diseases, cancers, skin diseases, diabetes, eye diseases, neurodegenerative diseases, anaphylaxis, asthma, obstructive airway diseases, and transplant rejection.

The present invention further provides a method for treating or preventing diseases mediated by JAK, in particular TYK2. The method comprises administering to a patient in need thereof a therapeutically effective amount of the compounds shown in Formula (I) or pharmaceutically acceptable salts, prodrugs, stable isotope derivatives and isomers thereof. The diseases include but are not limited to autoimmune diseases, inflammatory diseases including intestinal diseases, cancers, skin diseases, diabetes, eye diseases, neurodegenerative diseases, anaphylaxis, asthma and other obstructive airway diseases such as COPD, and transplant rejection. The present compounds are particularly useful in treating psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease, SLE, lupus nephritis, vitiligo, areata alopecia, dermatitis, asthma, atopic eczema.

According to the present invention, the pharmaceuticals can be in any dosage form, including but not limited to tablets, capsules, a solution, a freeze-drying preparation and injectable.

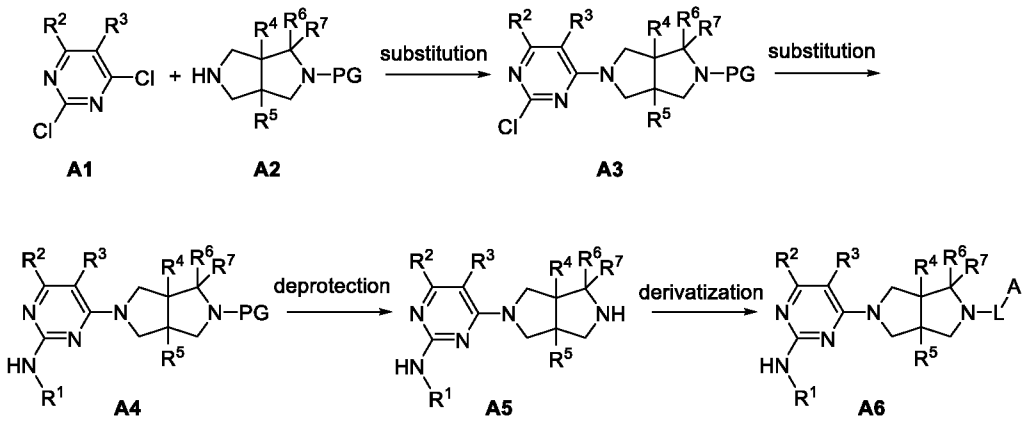
The pharmaceutical formulation of the present invention can be administered in form of a dosage unit containing a predetermined amount of active ingredient. Such a unit may contain 0.5 mg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 300 mg of a compound of the present invention, depending on the disease being treatment, the method of

administration, as well as age, weight and condition of the patients. Furthermore, the pharmaceutical formulation can be prepared using methods well known in the pharmaceutical field, for example, by formulating the active ingredient with one or more excipients or one or more adjuvants.

The pharmaceutical formulation of the present invention is suitable for administration by any appropriate method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal).

The present invention further provides a method for preparing the compounds. The preparation of the compounds of the present invention as shown in Formula (I) can be accomplished by the following exemplary methods and embodiments, but these methods and embodiments should not be considered as limitations to the scope of the present invention in any way. Alternatively, the compounds provided by the present invention can be synthesized by the synthetic techniques known to those skilled in the art, or by comprehensively using the methods known in the art and the methods described in the present invention. The products obtained at each step of reaction are isolated by the separation techniques known in the art, including but not limited to extraction, filtration, distillation, crystallization and chromatographic separation. The starting materials and chemical reagents used for the synthesis can be conventionally made based on literature (can be searched from SciFinder) or purchased.

The heterocyclic compounds shown in Formula (I) of the present invention can be synthesized according to the route shown below: 1) substitution reaction between starting materials A1 and A2 catalyzed by an organic base to give intermediate A3; 2) acid-catalyzed substitution reaction or Buchwald-Hartwig coupling of A3 with a primary amine (R^1-NH_2) to give A4; 3) deprotection of A4 in acid (e.g. PG is Boc) or under hydrogenation (e.g. PG is Bn) to give A5; 4) derivatization of A5 to give target compounds, for example, by amidation with an acyl chloride or anhydride, amide coupling with an acid, sulfonation with an sulfonyl chloride, urea formation with an amine, Buchwald-Hartwig coupling with a (hetero)aryl halide, etc.



EXAMPLES

The structures of the compounds were determined by nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR determination used a Bruker ASCEND-400 NMR spectrometer, the solvent for the determination was deuterated dimethyl sulfoxide (DMSO-*d6*), deuterated chloroform ($CDCl_3$), or deuterated methanol (CD_3OD), the internal standard was tetramethylsilane (TMS), and the chemical shift was given in a unit of 10^{-6} (ppm).

MS determination used an Agilent SQD (ESI) mass spectrometer (Agilent 6120).

HPLC determination used an Agilent 1260 DAD high pressure liquid chromatograph (column: Poroshell120 EC-C18, 50×3.0 mm, 2.7 μm) or a Waters Arc high pressure liquid chromatograph (column: Sunfire C18, 150×4.6 mm, 5 μm).

The thin layer chromatography (TLC) used GF254 silica gel plates from Qingdao Haiyang Chemical Co., Ltd. with a thickness of 0.15 to 0.2 mm, and the separation/purification of products by thin layer chromatography used silica plates with a thickness 0.4 to 0.5 mm.

Column chromatography generally used 200 to 300 mesh silica gel from Qingdao Haiyang Chemical Co., Ltd.

Known starting materials in the present invention were synthesized according to the methods known in the art, or purchased from ABCR GmbH&Co. KG, Acros Organics, Aldrich Chemical Company, Accela ChemBio Inc., Beijing Ouhe Technology Co., Ltd., etc.

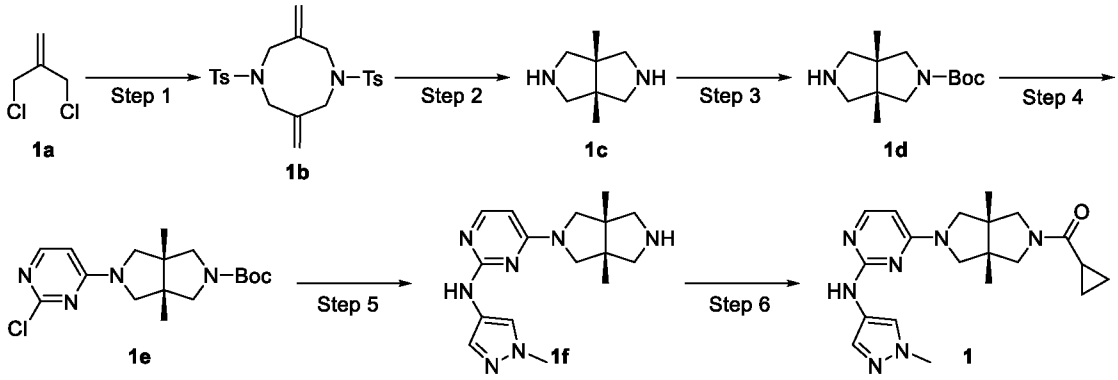
Unless otherwise stated in the embodiments, the reactions were carried out under an atmosphere of argon or nitrogen using a balloon with a volume of about 1 L.

Hydrogenation was carried out under an atmosphere of hydrogen using a balloon with a volume of about 1 L that is attached to the reaction vessel after being vacuumed and filled with hydrogen repeatedly for 3 times.

The microwave reaction used a CEM Discover-SP microwave reactor.

Unless otherwise stated in the embodiments, the reaction was run at room temperature. The reaction was monitored using an Agilent LCMS (1260/6120) or by thin layer chromatography. The solvent eluting systems for column chromatography and TLC included a) dichloromethane/methanol, b) petroleum ether/ethyl acetate, or other systems as indicated. The ratio of the solvents was adjusted according to the polarity of the compound, and further adjusted by addition of a small amount of TEA and an acidic or alkaline reagent as needed. The compound purification was alternatively done using Waters' MS-guided automated preparation system (abbreviated as prep-HPLC) with a MS detector (SQD2), eluting at a flow rate of 20 mL/min in an appropriate acetonitrile/water (containing 0.1% TFA or formic acid) or acetonitrile/water (containing 0.05% ammonia) gradient (XBridge-C18, 19×150 mm, 5 μm). Some examples were prepared as HCl salts after prep-HPLC purification by addition of 1 N HCl to the collected fractions, followed by drying under reduced pressure.

Example 1. Cyclopropyl((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



Step 1. 3,7-Dimethylene-1,5-ditosyl-1,5-diazocane (1b)

To a mixture of 4-methylbenzenesulfonamide (17.12 g, 100 mmol) and anhydrous potassium carbonate (27.6 g, 200 mmol) in MeCN (200 mL) was added slowly over 10 min a solution of 3-chloro-2-chloromethyl-1-propylene **1a** (12.5 g, 100 mmol) in MeCN (20 mL). The mixture was then heated to reflux and stirred for 18 h. After cooling to room temperature, the mixture was added with water (250 mL) and stirred for 30 min. The resulting mixture was filtered, and the precipitate was collected and purified by silica gel column chromatography (petroleum ether/dichloromethane = 100/0 to 0/100) to give the title compound **1b** (10.8 g, 48%).

MS m/z (ESI): 447 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.64 (m, 4H), 7.31 (d, J = 8.0 Hz, 4H), 5.19 (s, 4H),

3.82 (s, 8H), 2.43 (s, 6H).

Step 2. (3ar,6ar)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (1c)

To a solution of **1b** (10.8 g, 24.2 mmol) in THF (400 mL) at 0°C was added LAH (9.2 g, 242 mmol) in batches. After stirring for 4 days, the mixture was cooled to 0°C and added with a 20% sodium chloride aqueous solution (18 mL) dropwise. The resulting mixture was gradually warmed to room temperature and stirred for 1 h. The mixture was filtered through a pad of celite and the filter cake was washed with THF (3×200 mL). The combined filtrate was concentrated to dryness under vacuum to give the title compound **1c** (2.25 g, 66%). The crude product was used directly in next step without further purification.

MS m/z (ESI): 141 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (d, *J* = 11.0 Hz, 4H), 2.69 (d, *J* = 11.0 Hz, 4H), 2.39 (brs, 2H), 0.98 (s, 6H).

Step 3. Tert-butyl (3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (1d)

To a solution of **1c** (2.25 g, 16 mmol) in CH_2Cl_2 (100 mL) at 0°Cwere added TEA (4.8 g, 48 mmol) and a solution of di-tert-butyl decarbonate (3.5 g, 16 mmol) in CH_2Cl_2 (100 mL). The mixture was gradually warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with water (100 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/1 to 10/1) to give the title compound **1d** (1.37 g, 36%).

MS m/z (ESI): 241 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 2H), 3.20 (d, *J* = 10.2 Hz, 2H), 3.09 (d, *J* = 11.4 Hz, 2H), 2.90 (d, *J* = 11.4 Hz, 2H), 1.45 (s, 9H), 1.06 (s, 6H).

Step 4. Tert-butyl (3aR,6aS)-5-(2-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (1e)

To a solution of **1d** (1.37 g, 5.7 mmol) in MeCN (50 mL) were added 2,4-dichloropyrimidine (850 mg, 5.7 mmol) and DIEA (2.21 g, 17.1 mmol). The mixture was heated to reflux and stirred for 16 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was diluted with water (50 mL). The mixture was then extracted with ethyl acetate (3×100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1 to 1/1) to give the title compound **1e** (1.47 g, 73%).

MS m/z (ESI): 353 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.0 Hz, 1H), 6.17 (d, *J* = 5.8 Hz, 1H), 3.77 (d, *J* = 12.3 Hz, 1H), 3.57 (t, *J* = 10.9 Hz, 1H), 3.53 - 3.39 (m, 3H), 3.35 (d, *J* = 11.4 Hz, 1H), 3.32 - 3.24 (m, 2H), 1.45 (s, 9H), 1.15 (d, *J* = 6.5 Hz, 6H).

5 Step 5. 4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine hydrochloride (1f)

To a 30-mL microwave reaction vessel were **1e** (353 mg, 1 mmol), 1-methyl-1H-pyrazol-4-amine (102 mg, 1.05 mmol), pTsOH (4 mg, 0.02 mmol) and isopropanol (25 mL). The vessel was sealed and heated in a microwave reactor to 100°C for 1 h. After cooling to 10 room temperature, the mixture was added with a solution of HCl (33% in ethanol, 2 mL) and then heated in a microwave reactor at 80°C for 30 min. The synthesis was repeated for another three batches following the same procedure as described above. Four batches were combined and filtered. The filter cake was collected to give the title compound **1f** (1 g, 54%) as an HCl salt.

15 MS m/z (ESI): 314 [M+1]

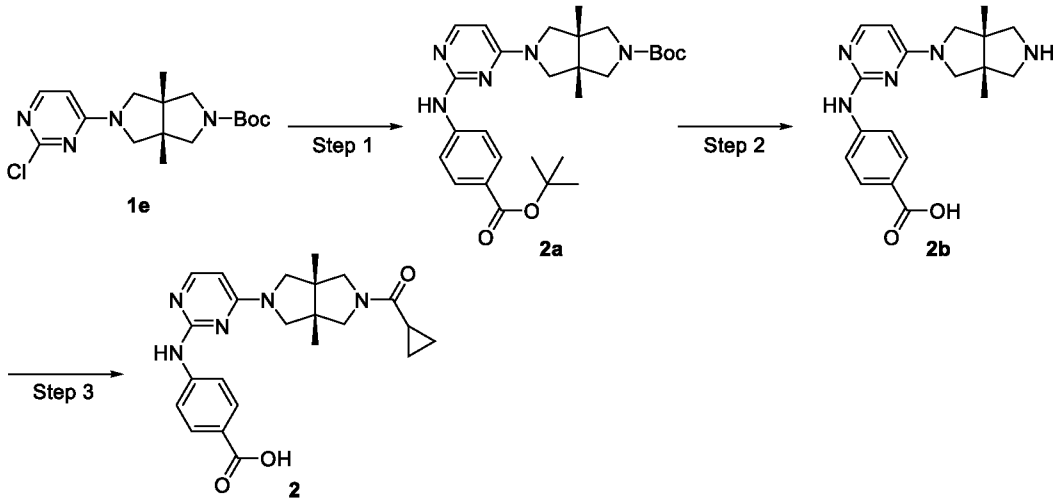
Step 6. Cyclopropyl((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (1)

To a solution of **1f** (46 mg, 0.1 mmol) and TEA (50 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0°C was added cyclopropanecarbonyl chloride (11 mg, 0.1 mmol). The mixture was stirred at 20 0°C for 20 min, then quenched with water (20 mL), and extracted with CH_2Cl_2 (2×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **1** (23 mg, solid, 61%).

MS m/z (ESI): 382 [M+1]

25 ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (d, *J* = 6.3 Hz, 2H), 7.60 (s, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 3.90 (d, *J* = 10.0 Hz, 2H), 3.89 (s, 3H), 3.76 (d, *J* = 10.8 Hz, 2H), 3.61 (d, *J* = 12.4 Hz, 2H), 3.48 (d, *J* = 12.3 Hz, 2H), 1.84 - 1.78 (m,1H), 1.26 (s, 3H), 1.23 (s, 3H), 0.96 - 0.82 (m, 4H).

30 **Example 2. 4-((4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)pyrimidine-2-yl)amino)benzoic acid**



Step 1. Tert-butyl (3aR,6aS)-5-(2-((4-(tert-butoxycarbonyl)phenyl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (2a)

To a 10-mL microwave reaction vessel were added **1e** (100 mg, 0.283 mmol), tert-butyl 4-aminobenzoate (55 mg, 0.283 mmol), pTsOH (5 mg, 0.0283 mmol) and isopropanol (4 mL). The vessel was stirred in a microwave reactor at 100°C for 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1 to 1/2) to give the title compound **2a** (102 mg, 71%).

MS m/z (ESI): 510 [M+1]

Step 2. 4-((4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)benzoic acid (2b)

To a solution of **2a** (30 mg, 0.06 mmol) in ethanol (2 mL) was added an HCl solution (33% in ethanol, 2 mL). The mixture was stirred at room temperature for 2 h and then concentrated to dryness under vacuum to give the title compound **2b** (36 mg). The crude product was used directly in next step without further purification.

MS m/z (ESI): 354 [M+1]

Step 3. 4-((4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)benzoic acid (2)

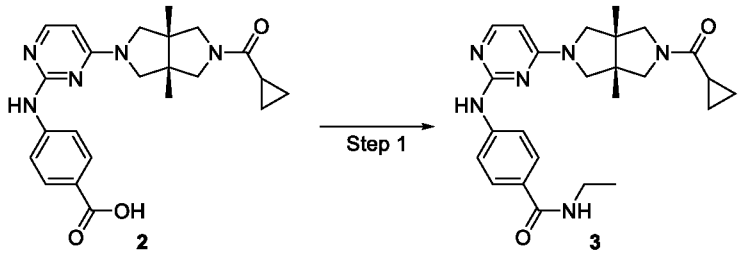
To a solution of **2b** (36 mg, crude) and TEA (30 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added cyclopropanecarbonyl chloride (6 mg, 0.06 mmol). The mixture was stirred for 10 min and then quenched with water (0.5 mL). The mixture was concentrated to dryness and the residue was dissolved in THF (2 mL). The resulting mixture was added with a 20% sodium chloride aqueous solution (2 mL) and stirred at room temperature for 2 h. The mixture was adjusted to pH = 3 ~ 4 with 1 N HCl and extracted with ethyl acetate (3×20 mL). The

combined organic phase was dried over anhydrous sodium sulfate, filtered, concentrate to dryness under vacuum, and purified by prep-HPLC to give the title compound **2** (20 mg, solid, 79%).

MS m/z (ESI): 422 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (dd, *J* = 10.3, 7.5 Hz, 3H), 7.81 (d, *J* = 8.7 Hz, 2H), 6.07 (d, *J* = 6.1 Hz, 1H), 3.92 (d, *J* = 10.9 Hz, 2H), 3.76 (d, *J* = 10.8 Hz, 2H), 3.62 (d, *J* = 12.4 Hz, 2H), 3.49 (d, *J* = 12.4 Hz, 2H), 1.84 - 1.77 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 0.95 - 0.84 (m, 4H).

Example 3. 4-((4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-N-ethylbenzamide

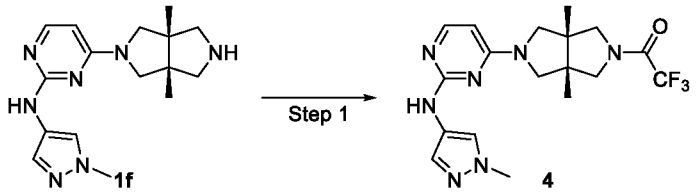


To solution of **2** (56 mg, 0.133 mmol) in CH_2Cl_2 (10 mL) were added DIEA (59 mg, 0.153 mmol) and HATU (58 mg, 0.153 mmol). The mixture was stirred at room temperature for 5 min, and then added with 3 drops of ethylamine aqueous solution (65%-70% wt.). The mixture was stirred at room temperature for 30 min, concentrated and purified by prep-HPLC to give the title compound **3** (3.3 mg, solid, 6%).

MS m/z (ESI): 449 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, *J* = 6.1 Hz, 1H), 7.84 - 7.77 (m, 4H), 6.04 (d, *J* = 6.1 Hz, 1H), 3.90 (d, *J* = 11.1 Hz, 2H), 3.76 (d, *J* = 10.9 Hz, 2H), 3.62 (d, *J* = 12.4 Hz, 2H), 3.48 (d, *J* = 12.5 Hz, 2H), 3.43 (q, *J* = 14.5, 7.3 Hz, 2H), 1.85 - 1.77 (m, 1H), 1.28 - 1.19 (m, 9H), 0.95 - 0.83 (m, 4H).

Example 4. 1-((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2,2,2-trifluoroethan-1-one hydrochloride



To a mixture of **1f** (69 mg, 0.15 mmol) and DIEA (116 mg, 0.9 mmol) in CH_2Cl_2 (2 mL) was added a solution of trifluoroacetic anhydride (32 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 20 min, concentrated and purified by prep-HPLC to give the title compound **4** (36.4 mg, solid, 54%) as an HCl salt.

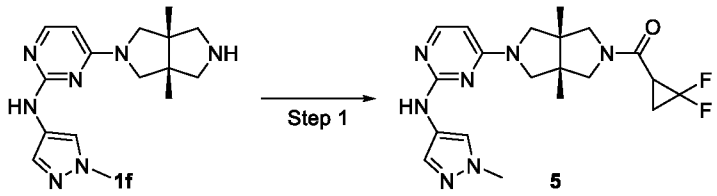
MS m/z (ESI): 410 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (s, 1H), 7.74 (s, 1H), 7.65 (s, 1H), 6.31 (dd, *J* = 7.4, 5.0 Hz, 1H), 4.00 - 3.73 (m, 9H), 3.70 - 3.61 (m, 2H), 1.27 (s, 6H).

Example 6 was prepared according to the procedure for Example 4 except that ethyl chloroformate was used instead of trifluoroacetic anhydride.

Example	Acyl chloride or anhydride	^{1}H NMR	MS m/z (ESI)
ethyl (3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**6**)	ethyl chloroformate	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 6.0 Hz, 1H), 7.64 (s, 1H), 7.58 (s, 1H), 5.75 (d, *J* = 6.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.76 (s, 1H), 3.63 - 3.25 (m, 7H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 6H).	386 [M+1]

Example 5. (2,2-Difluorocyclopropyl)((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride

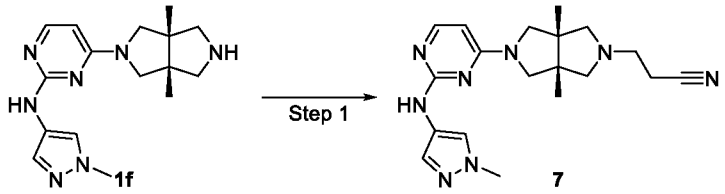


To a mixture of **1f** (69 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) were added DIEA (116 mg, 0.9 mmol), HATU (57 mg, 0.15 mmol) and 2,2-difluorocyclopropane-1-carboxylic acid (19 mg, 0.15 mmol). The mixture was stirred at room temperature for 20 min, followed by concentration and purification by prep-HPLC to give the title compound **5** (32.8 mg, solid, 52%) as an HCl salt.

MS m/z (ESI): 418 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (t, *J* = 4.0 Hz, 2H), 7.59 (s, 1H), 5.92 (d, *J* = 6.1 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 4H), 3.78 (q, *J* = 11.0 Hz, 2H), 3.66 (d, *J* = 11.9 Hz, 3H), 3.52 (d, *J* = 12.5 Hz, 2H), 2.89 - 2.79 (m, 1H), 2.09 - 2.01 (m, 1H), 1.85 - 1.74 (m, 1H), 1.28 - 1.19 (m, 6H).

Example 7. 3-((3aR,6aS)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propanenitrile

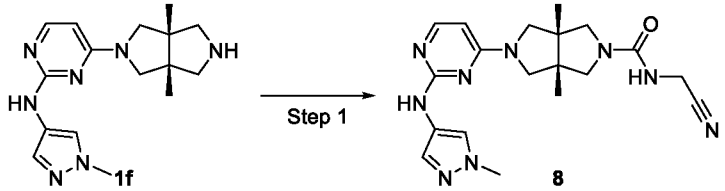


To a mixture of **1f** (69 mg, 0.15 mmol) in MeCN (5 mL) were added 3-bromopropanenitrile (20 mg, 0.15 mmol) and DIEA (116 mg, 0.9 mmol). The mixture was stirred for 20 h, and then heated to 90°C for 24 h (LCMS showed that only trace amount of desired product was generated). The reaction mixture was transferred to a 15-mL sealed tube and heated to 120°C for 72 h. After cooling to room temperature, the reaction mixture was concentrated to dryness under vacuum and purified by prep-HPLC to give the title compound **7** (3.2 mg, solid, 4%).

MS m/z (ESI): 367 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, *J* = 5.6 Hz, 2H), 7.61 (s, 1H), 5.92 (d, *J* = 6.1 Hz, 1H), 3.88 (s, 3H), 3.77 (dd, *J* = 19.3, 12.2 Hz, 2H), 3.48 - 3.39 (m, 2H), 2.97 (d, *J* = 9.3 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 2.61 (dd, *J* = 12.8, 8.0 Hz, 4H), 1.20 (s, 6H).

Example 8. (3aR,6aS)-N-(cyanomethyl)-3a,6a-dimethyl-5-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide



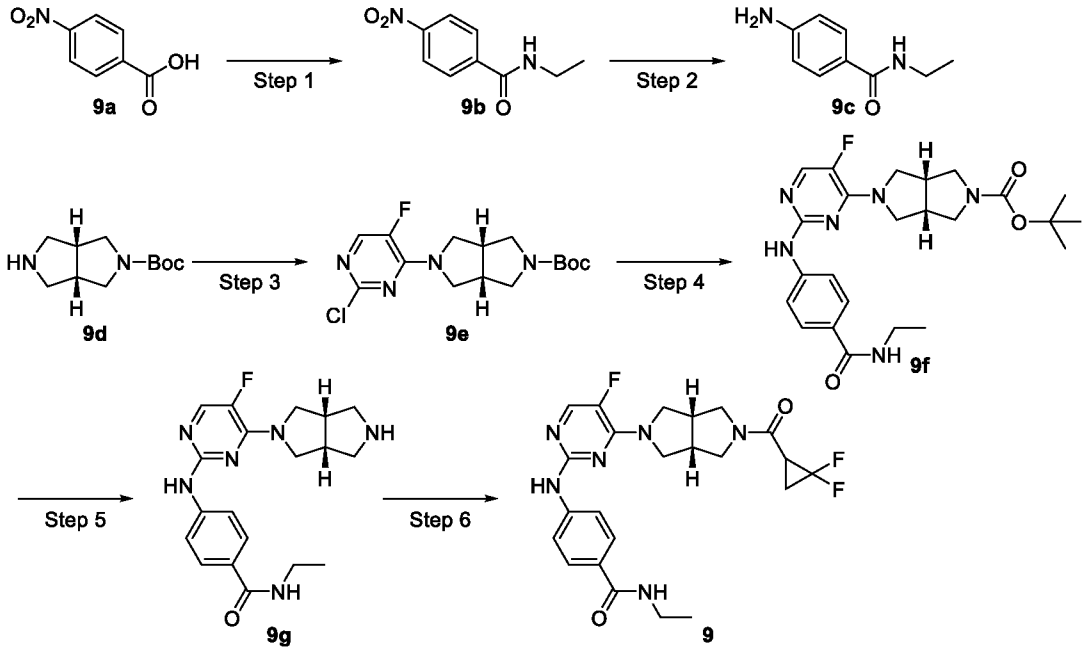
To a solution of 2-aminoacetonitrile (14 mg, 0.24 mmol) in DMF (3 mL) was added N,N'-carbonyldiimidazole (49 mg, 0.3 mmol). The resulting mixture was heated to 65°C and stirred for 2 h, and then added with **1f** (69 mg, 0.15 mmol). The mixture was stirred at 65°C for another 2 h and concentrated under vacuum. The residue was dispersed in a saturated

sodium hydrogen carbonate aqueous solution (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, concentrated and purified by prep-HPLC to give the title compound **8** (19.2 mg, solid, 32%).

MS m/z (ESI): 396 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 8.0 Hz, 2H), 7.57 (s, 1H), 5.88 (d, J = 6.0 Hz, 1H), 4.09 (s, 2H), 3.85 (s, 3H), 3.76 (s, 1H), 3.59 (s, 1H), 3.51 (d, J = 9.9 Hz, 3H), 3.37 (d, J = 10.3 Hz, 3H), 1.19 (s, 6H).

Example 9. 4-((4-((3aR,6aS)-5-(2,2-difluorocyclopropane-1-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoropyrimidin-2-yl)amino)-N-ethylbenzamide



Step 1. N-ethyl-4-nitrobenzamide (9b)

To solution of 4-nitrobenzoic acid (5 g, 30 mmol) in CH_2Cl_2 (100 mL) was added oxalyl chloride (7.6 g, 60 mmol) dropwise, followed by DMF (0.1 mL). The mixture was stirred at for 30 min and then concentrated to dryness under vacuum. The residue was dissolved in THF (50 mL) and added with an aqueous solution of ethylamine (60 to 70% wt., 10 mL) dropwise. The mixture was stirred at room temperature for 30 min, poured into water (200 mL), and extracted with ethyl acetate (2×100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate =1/1 to 0/100) to give the title compound **9b** (5.13 g, 88%).

MS m/z (ESI): 195 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 - 8.23 (m, 2H), 7.98 - 7.85 (m, 2H), 6.16 (s, 1H), 3.54 (qd, *J* = 7.3, 5.7 Hz, 2H), 1.29 (t, *J* = 7.3 Hz, 3H).

Step 2. 4-amino-N-ethylbenzamide (9c)

5 To a mixture of water (40 mL), acetic acid (4 mL), ammonium chloride (14.13 g, 264.2 mmol), ethanol (100 mL) and **9b** (5.13 g, 26.42 mmol) was added zinc powder (8.64 g, 132 mmol) in batches. The mixture was stirred for 1 h and added with zinc powder (8.64 g, 132 mmol) in batches again. The resulting mixture was stirred at 60°C for 1 h. After cooling to room temperature, the mixture was filtered through a pad of celite. The filtrate was 10 concentrated to dryness under vacuum and the residue was dispersed in a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and extracted with ethyl acetate (4×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1 to 0/100) to give the title compound **9c** (3.25 g, 75%).

15 MS m/z (ESI): 165 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (t, *J* = 5.2 Hz, 1H), 7.55 (dd, *J* = 9.0, 2.2 Hz, 2H), 6.52 (dd, *J* = 9.0, 2.2 Hz, 2H), 5.54 (s, 2H), 3.26 - 3.16 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H).

Step 3. Tert-butyl (3aR,6aS)-5-(2-chloro-5-fluoropyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (9e)

20 To a solution of **9d** (900 mg, 4.24 mmol) in MeCN (50 mL) were added 2,4-dichloro-5-fluoropyrimidine (708 mg, 4.24 mmol) and DIEA (1.64 g, 12.72 mmol). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give the title compound **9e** (1.13 g, 78%).

25 MS m/z (ESI): 343 [M+1]

Step 4. Tert-butyl (3aR,6aS)-5-(2-((4-(ethylcarbamoyl)phenyl)amino)-5-fluoropyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (9f)

To a 10-mL microwave vessel containing **9e** (68 mg, 0.2 mmol), 4-amino-N-ethylbenzamide (33 mg, 0.2 mmol), KOtBu (48 mg, 0.5 mmol), and 1,4-dioxane (3 mL) 30 under nitrogen was added RuPhos-Pd-G2 (7 mg, 0.01 mmol). The vessel was then heated in a microwave reactor at 120°C for 1 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, concentrated and purified by silica gel column chromatography (dichloromethane/methanol = 10/1 to 5/1) to give the title

product **9f** (56 mg, 63%).

MS m/z (ESI): 471 [M+1]

Step 5. N-ethyl-4-((5-fluoro-4-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)benzamide hydrochloride (9g)

To a solution of **9f** (56 mg, 0.112 mmol) in ethanol (2 mL) was added a solution of HCl (33% in ethanol, 2 mL). The mixture was stirred for 14 h and then concentrated to dryness under vacuum to give the title compound **9g** (57 mg). The crude product was used directly in the next step without further purification.

MS m/z (ESI): 371 [M+1]

Step 6. 4-((4-((3aR,6aS)-5-(2,2-difluorocyclopropane-1-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)-5-fluoropyrimidine-2-yl)amino)-N-ethylbenzamide (9)

To a mixture of **9g** (57 mg, 0.112 mmol) in CH_2Cl_2 (5 mL) were added DIEA (91 mg, 0.696 mmol), 2,2-difluorocyclopropane-1-carboxylic acid (15 mg, 0.12 mmol) and HATU (46 mg, 0.12 mmol). The mixture was stirred for 1 h and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **9** (21 mg, solid, 40%).

MS m/z (ESI): 475 [M+1]

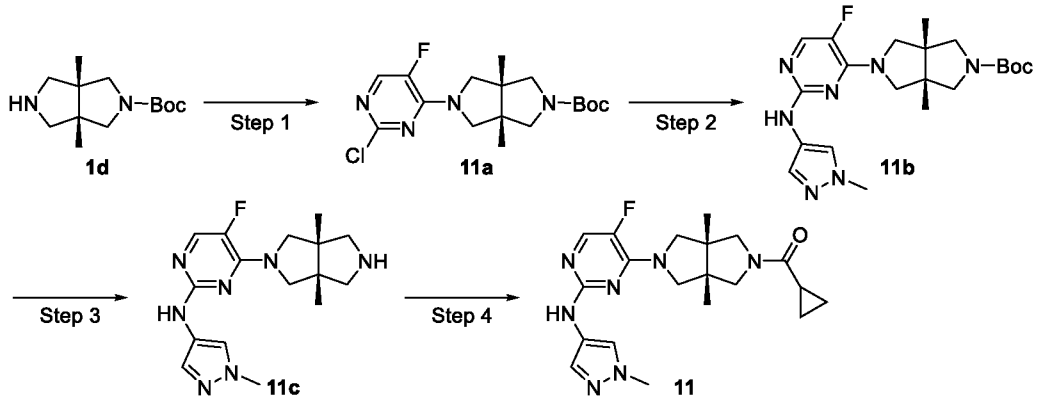
^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, *J* = 5.8 Hz, 1H), 7.77 - 7.70 (m, 4H), 4.09 - 3.90 (m, 3H), 3.82 - 3.56 (m, 4H), 3.52 - 3.43 (m, 1H), 3.40 (q, *J* = 7.2 Hz, 2H), 3.22 - 3.05 (m, 2H), 2.88 - 2.77 (m, 1H), 2.08 - 1.97 (m, 1H), 1.83 - 1.70 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).

Example 10 was prepared according to the procedure for Example 9 except that **1d** was used instead of **9d**.

Example	Amine	^{1}H NMR	MS m/z (ESI)
4-((4-((3aR,6aS)-5-(2,2-Difluorocyclopropane-1-carbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoropyrimidin-2-yl)amino)-N-ethylbenzamide (**10**)	**1d**	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, *J* = 5.8 Hz, 1H), 7.80 - 7.68 (m, 4H), 3.94 - 3.58 (m, 7H), 3.49 (d, *J* = 11.4 Hz, 1H), 3.40 (q, *J* = 7.3 Hz, 2H), 2.87 - 2.76 (m, 1H), 2.07 - 1.98 (m, 1H), 1.83 - 1.70 (m, 1H), 1.27 - 1.09 (m, 9H).	503 [M+1]

Example 11. Cyclopropyl((3aR,6aS)-5-(5-fluoro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-

yl)methanone



Step 1. Tert-butyl (3aR,6aS)-5-(2-chloro-5-fluoropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (11a)

To a solution of 2,4-dichloro-5-fluoropyrimidine (680 mg, 4 mmol) and **1d** (1.96 g, crude product, about 50% purity) in MeCN (40 mL) was added TEA (1.55 g, 12 mmol). The mixture was heated to 90°C and stirred for 18 h. After cooling to room temperature, the mixture was added with saturated ammonium chloride aqueous solution (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 7/3) to give the title compound **11a** (245 mg, 17%).

MS m/z (ESI): 371 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 4.9 Hz, 1H), 3.83 (s, 2H), 3.67 (s, 2H), 3.46 (s, 2H), 3.33 (s, 2H), 1.46 (s, 9H), 1.15 (s, 6H).

Step 2. Tert-butyl (3aR,6aS)-5-(5-fluoro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (11b)

To a 30-mL microwave vessel were added **11a** (245 mg, 0.66 mmol), 1-methyl-1H-pyrazol-4-amine (64 mg, 0.66 mmol), NaOtBu (159 mg, 1.65 mmol), 1,4-dioxane (8 mL) and RuPhos-Pd-G2 (24 mg, 0.033 mmol), and the reaction mixture was heated to 120°C in a microwave reactor for 1 h under nitrogen. After cooling to room temperature, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate = 100/0 to 0/100) to give the title compound **11b** (147 mg, 52%).

MS m/z (ESI): 432 [M+1]

Step 3. 4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine hydrochloride (11c)

To a solution of **11b** (147 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). The mixture was stirred for 18 h and then concentrated to dryness under vacuum. The residue was dissolved in CH_2Cl_2 (10 mL) and added with a solution of HCl in ethanol (9 M, 1 mL). The resulting mixture was concentrated to dryness to give the title compound **11c** as an HCl salt (160 mg, 98%).

MS m/z (ESI): 332 [M+1]

Step 4. Cyclopropyl((3aR,6aS)-5-(5-fluoro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidine-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)methanone (11)

To a mixture of **11c** (160 mg, 0.34 mmol) and TEA (243 mg, 2.4 mol) in CH_2Cl_2 (10 mL) at 0°C was added cyclopropanecarbonyl chloride (42 mg, 0.4 mmol). The mixture was stirred at 0°C for 30 min, diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by prep-HPLC to give the title compound **11** (12.5 mg, solid, 9%).

MS m/z (ESI): 400 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 5.7 Hz, 1H), 7.61 (s, 1H), 7.53 (s, 1H), 6.80 (s, 1H), 3.87 (s, 3H), 3.81 (dd, J = 20.0, 10.7 Hz, 3H), 3.64 (t, J = 11.8 Hz, 4H), 3.48 (d, J = 12.4 Hz, 1H), 1.60 - 1.52 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 1.05 - 0.96 (m, 2H), 0.83 - 0.73 (m, 2H).

Example 13 was synthesized according to the procedure for Example 11 except that in step 3, 2-(4-amino-1H-pyrazol-1-yl)ethan-1-ol was used instead of 1-methyl-1H-pyrazol-4-amine.

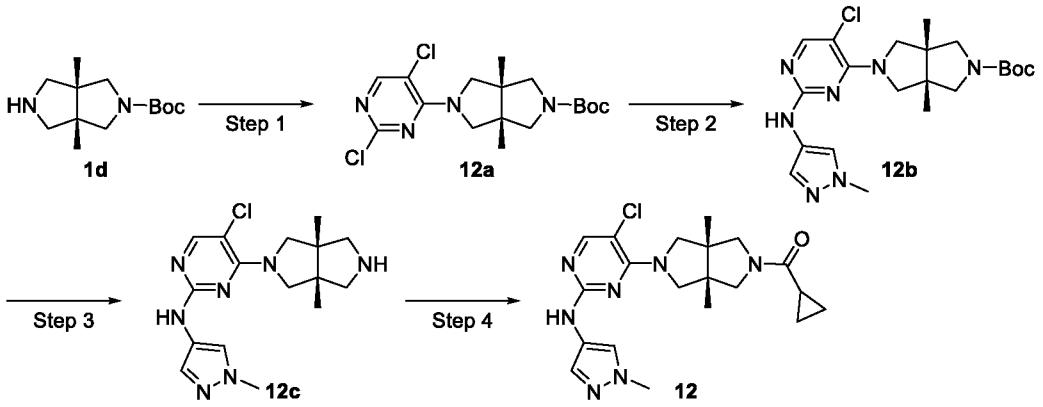
Example	Compound replacing 1-methyl-1H-pyrazol-4-amine	^{1}H NMR	MS m/z (ESI)
cyclopropyl((3aR,6aS)-5-(5-fluoro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-	2-(4-amino-1H-pyrazol-1-yl) ethan-1-ol	^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.73 (d, J = 5.9 Hz, 1H), 7.52 (s, 1H), 4.17 (t, J = 5.2 Hz, 2H), 3.93 - 3.80 (m, 5H), 3.74 - 3.70 (m, 3H), 3.59 (d, J = 12.4 Hz, 1H), 3.44 (d, J = 12.4 Hz, 1H), 1.81 - 1.75 (m, 1H), 1.22 (s, 3H), 1.19 (s, 3H),	430 [M+1]

yl)methanone (**13**)		0.92 - 0.87 (m, 2H), 0.87 - 0.80 (m, 2H).	

Example 15 and Example 24 were synthesized according to the procedure for Example 11 except that in step 1, different compounds were used instead of 2,4-dichloro-5-fluoropyrimidine.

Example	Compound replacing 2,4-dichloro-5-fluoropyrimidine	^{1}H NMR	MS m/z (ESI)
4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidine-5-carbonitrile (**15**)	2,4-dichloropyrimidine-5-carbonitrile	^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.83 (d, *J* = 6.6 Hz, 1H), 7.65 (d, *J* = 12.0 Hz, 1H), 3.85 - 3.74 (m, 4H), 3.72 - 3.58 (m, 3H), 3.58 - 3.44 (m, 3H), 3.34 (dd, *J* = 12.4, 4.2 Hz, 1H), 1.71 - 1.65 (m, 1H), 1.12(d, *J* = 7.4 Hz, 3H), 1.09(d, *J* = 8.0 Hz, 3H), 0.81 - 0.78 (m, 2H), 0.76 - 0.69 (m, 2H).	407 [M+1]
Cyclopropyl((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (**24**)	2,4-dichloro-5-methylpyrimidine	^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (s, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 3.95 - 3.87 (m, 3H), 3.86 (s, 3H), 3.80 - 3.70 (m, 3H), 3.61 (d, *J* = 12.4 Hz, 1H), 3.44 (d, *J* = 12.4 Hz, 1H), 2.28 (s, 3H), 1.83 - 1.77 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 0.94 - 0.89 (m, 2H), 0.87 - 0.83 (m, 2H).	396 [M+1]

Example 12. ((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (12)



Step 1. Tert-butyl (3aR,6aS)-5-(2,5-dichloropyrimidin-4-yl)-3a,6a-

dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (12a)

To a solution of 2,4,5-trichloropyrimidine (183 mg, 1 mmol) and **1d** (770 mg, crude product, about 1 mmol) in MeCN (40 mL) was added DIEA (388 mg, 3 mmol). The mixture was heated to 90°C and stirred for 24 h. After cooling to room temperature, the reaction mixture was added with saturated ammonium chloride aqueous solution (50 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 7/3) to give the title compound **12a** (90 mg, 23%).

MS m/z (ESI): 387 [M+1]

Step 2. Tert-butyl (3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (12b)

To a 30-mL microwave vessel were added **12a** (90 mg, 0.23 mmol), 1-methyl-1H-pyrazol-4-amine (23 mg, 0.23 mmol), 1,4-dioxane (5 mL), NaOtBu (49 mg, 0.506 mmol) and RuPhos-Pd-G2 (9 mg, 0.0115 mmol). The reaction mixture was heated to 110°C in a microwave reactor for 1 h under nitrogen. After cooling to room temperature, the mixture was filtered through a pad of celite. The filtrate was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate = 100/0 to 0/100) to give the title compound **12b** (61 mg, 59%).

MS m/z (ESI): 448 [M+1]

Step 3. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine hydrochloride (12c)

To a solution of **12b** (61 mg, 0.136 mmol) in CH_2Cl_2 (5 mL) was added TFA (2 mL). The mixture was stirred for 20 h and then concentrated to dryness under vacuum. The residue was dissolved in a mixture of methanol (2 mL) and water (10 mL) and added with a solution of HCl (9 M in ethanol, 0.2 mL). The mixture was concentrated to dryness again to give the title compound **12c** (67 mg, 100%) as an HCl salt.

MS m/z (ESI): 348 [M+1]

Step 4. ((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (12)

To a mixture of **12c** (67 mg, 0.136 mmol) and TEA (55 mg, 0.544 mol) in CH_2Cl_2 (20 mL) at 0°C was added cyclopropanecarbonyl chloride (14 mg, 0.136 mmol). The mixture was stirred at 0°C for 30 min and then washed with saturated ammonium chloride solution (20

mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **12** (1.9 mg, solid, 3%).

MS m/z (ESI): 416 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.75 (s, 1H), 7.53 (s, 1H), 3.97 (dd, *J* = 15.1, 11.8 Hz, 2H), 3.90 - 3.78 (m, 6H), 3.71 (d, *J* = 10.8 Hz, 1H), 3.59 (d, *J* = 12.4 Hz, 1H), 3.42 (d, *J* = 12.4 Hz, 1H), 1.78 (dd, *J* = 8.7, 3.9 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 0.92 - 0.87 (m, 2H), 0.86 - 0.82 (m, 2H).

Examples 19, 34, 37, 41 and 96 were synthesized according to the procedure for Example 12 except that in step 4, different compounds were used instead of cyclopropanecarbonyl chloride.

Example	Compound replacing cyclopropanecarbonyl chloride	^{1}H NMR	MS m/z (ESI)
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-one (**19**)	acetic chloride	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 4.02 - 3.94 (m, 2H), 3.86 (s, 3H), 3.86 - 3.80 (m, 2H), 3.71 (d, *J* = 11.0 Hz, 1H), 3.59 (d, *J* = 12.5 Hz, 1H), 3.55 (d, *J* = 11.0 Hz, 1H), 3.43 (d, *J* = 12.4 Hz, 1H), 2.08 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H).	390 [M+1]
5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**34**)	methanesulfonyl chloride	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.78 (s, 1H), 7.55 (s, 1H), 4.03 (d, *J* = 11.7 Hz, 2H), 3.87 (s, 3H), 3.81 (d, *J* = 11.7 Hz, 2H), 3.52 (d, *J* = 10.1 Hz, 2H), 3.36 (d, *J* = 10.1 Hz, 2H), 2.96 (s, 3H), 1.21 (s, 6H).	426 [M+1]
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-methoxyethan-1-one (**37**)	2-methoxyacetyl chloride	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 4.11 (s, 2H), 3.98 (dd, *J* = 11.7, 4.6 Hz, 2H), 3.86 (s, 3H), 3.83 (dd, *J* = 11.7, 1.7 Hz, 2H), 3.65 (dd, *J* = 11.6, 9.2 Hz, 2H), 3.49 (dd, *J* = 11.6, 9.4 Hz, 2H), 3.42 (s, 3H), 1.20 (d, *J* = 1.3 Hz, 6H).	420 [M+1]
5-chloro-4-((3aR,6aS)-5-(ethylsulfonyl)-3a,6a-	ethanesulfonyl chloride	^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.79 (s, 1H),	440 [M+1]

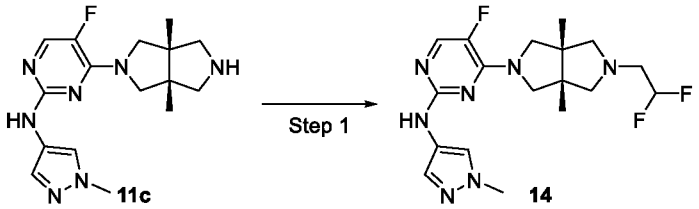
dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**41**)		7.55 (s, 1H), 4.04 (d, *J* = 11.7 Hz, 2H), 3.87 (s, 3H), 3.80 (d, *J* = 11.7 Hz, 2H), 3.55 (d, *J* = 10.0 Hz, 2H), 3.38 (d, *J* = 10.0 Hz, 2H), 3.14 (q, *J* = 7.4 Hz, 2H), 1.34 (t, *J* = 7.4 Hz, 3H), 1.21 (s, 6H).	
5-chloro-4-((3aR,6aS)-5-(cyclopropylsulfonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**96**)	cyclopropanesulfonyl chloride	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.08 (s, 1H), 7.90 (s, 1H), 7.70 (s, 1H), 7.45 (s, 1H), 3.93 (d, *J* = 11.5 Hz, 2H), 3.78 (s, 3H), 3.69 (d, *J* = 11.5 Hz, 2H), 3.48 (d, *J* = 10.1 Hz, 2H), 3.30 (d, *J* = 10.2 Hz, 2H), 2.77 (s, 1H), 1.12 (s, 6H), 0.94 (dd, *J* = 8.1, 5.2 Hz, 4H).	452 [M+1]

Example 23, 30 and 32 were synthesized according to the procedure for Example 12 except that in step 2, different compounds were used instead of 1-methyl-1H-pyrazol-4-amine.

Example	Compound replacing 1-methyl-1H-pyrazol-4-amine	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone hydrochloride (**23**)	1H-pyrazol-4-amine	^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 2H), 7.96 (s, 1H), 4.31 (d, *J* = 52.8 Hz, 2H), 4.05 – 3.80 (m, 3H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.62 (s, 1H), 3.47 (d, *J* = 12.6 Hz, 1H), 1.83 - 1.77 (m, 1H), 1.26 (s, 3H), 1.22 (s, 3H), 0.97 - 0.89 (m, 2H), 0.89 - 0.85 (m, 2H).	402 [M+1]
((3aR,6aS)-5-(5-chloro-2-((1-(difluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**30**)	1-(difluoromethyl)-1H-pyrazol-4-amine	^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.41 (t, *J* = 60.0 Hz, 1H), 4.05 - 3.95 (m, 2H), 3.87 (td, *J* = 11.2, 7.5 Hz, 3H), 3.74 (d, *J* = 10.8 Hz, 1H), 3.61 (d, *J* = 12.4 Hz, 1H), 3.45 (d, *J* = 12.4 Hz, 1H), 1.83 - 1.77 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.94 - 0.90 (m, 2H), 0.88 - 0.84 (m, 2H).	452 [M+1]
((3aR,6aS)-5-(5-chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-	2-(4-amino-1H-pyrazol-1-yl)ethan-1-ol	^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (s, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.31 - 4.15 (m, 3H), 4.02 –	446 [M+1]

yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone hydrochloride (**32**)		3.80 (m, 4H), 3.74 (d, *J* = 10.9 Hz, 1H), 3.65 (d, *J* = 12.4 Hz, 1H), 3.57 (d, *J* = 13.3 Hz, 1H), 3.47 (d, *J* = 12.9 Hz, 1H), 1.80 (s, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 0.96 - 0.80 (m, 4H).	

Example 14. 4-((3aR,6aS)-5-(2,2-difluoroethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-fluoro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

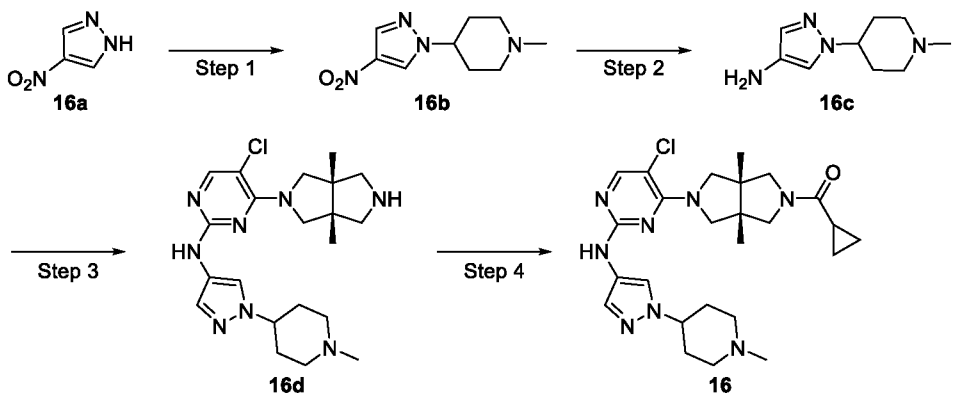


To a solution of **11c** (135 mg, 0.255 mmol) in DMF (2 mL) were added DIEA (132 mg, 1.02 mmol) and 1,1-difluoro-2-iodoethane (49 mg, 0.255 mmol), and the mixture was stirred at 70°C for 24 h. After cooling to room temperature, the mixture was transferred to a 15-mL sealed tube, and then added with DIEA (132 mg, 1.02 mmol) and 1,1-difluoro-2-iodoethane (98 mg, 0.51 mmol). The mixture was stirred in the sealed tube at 80°C for 72 h. After cooling to room temperature, the mixture was purified by prep-HPLC to give the title compound **14** (16.9 mg, solid, 17%).

MS m/z (ESI): 396 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.74 (d, *J* = 6.2 Hz, 1H), 7.55 (s, 1H), 5.89 (tt, *J* = 56.1, 4.3 Hz, 1H), 3.96 (dd, *J* = 11.7, 1.9 Hz, 2H), 3.87 (s, 3H), 3.58 (dd, *J* = 11.6, 1.2 Hz, 2H), 2.99 (d, *J* = 9.5 Hz, 2H), 2.89 (td, *J* = 15.3, 4.3 Hz, 2H), 2.66 (d, *J* = 9.5 Hz, 2H), 1.17 (s, 6H).

Example 16. ((3aR,6aS)-5-(5-Chloro-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone



Step 1. 1-Methyl-4-(4-nitro-1H-pyrazol-1-yl)piperidine (16b)

To a mixture of 4-nitro-1H-pyrazol **16a** (1.13 g, 10 mmol), 1-methyl piperidin-4-ol (1.15 g, 10 mmol), and triphenylphosphine (3.15 g, 12 mmol) in THF (25 mL) at 0°C under nitrogen was added diisopropyl azodicarboxylate (2.63 g, 13 mmol) dropwise. After stirring for 4 h, the mixture was diluted with water (100 mL) and adjusted to pH = 1 by addition of 6 N HCl. The resulting mixture was washed with ethyl acetate (2×50 mL). The aqueous layer was added with LiOH solid to adjust to pH = 10 and then extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/0 to 94/6) to give the title compound **16b** (800 mg, 38%).

MS m/z (ESI): 211 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.08 (s, 1H), 4.19 - 4.11 (m, 1H), 3.04 - 2.96 (m, 2H), 2.35 (s, 3H), 2.24 - 2.12 (m, 4H), 2.10 - 2.00 (m, 2H).

Step 2. 1-(1-Methylpiperidin-4-yl)-1H-pyrazol-4-amine (16c)

To a solution of **16b** (800 mg, 3.8 mmol) in MeOH (10 mL) was added 10% Pd/C (400 mg). The mixture was stirred under hydrogen for 2 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **16c** (688 mg, 100%). The crude product was used directly in the next step without further purification.

MS m/z (ESI): 181 [M+1]

Step 3. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)pyrimidin-2-amine (16d)

To a 10-mL microwave vessel were added **12a** (39 mg, 0.1 mmol), **16c** (18 mg, 0.1 mmol), pTsOH (38 mg, 0.2 mmol) and isopropanol (2 mL). The mixture was stirred in a microwave reactor at 100°C for 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum to give the title compound **16d** (60 mg). The crude

product was used directly in the next step without further purification.

MS m/z (ESI): 431 [M+1]

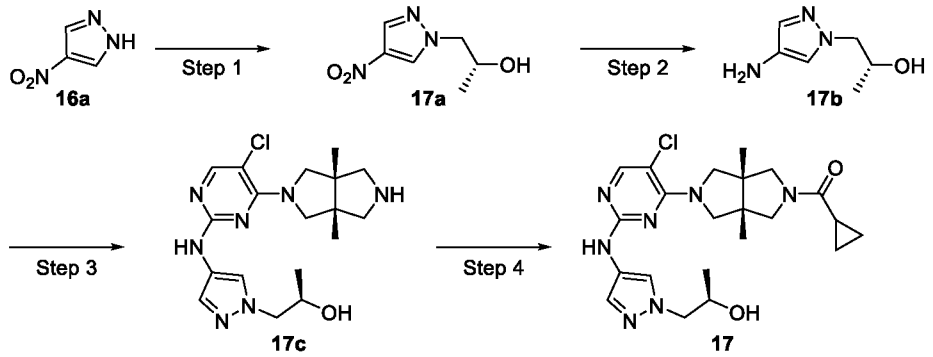
Step 4. ((3aR,6aS)-5-(5-chloro-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (16)

To a solution of **16d** (60 mg) and TEA (51 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added a solution of cyclopropanecarbonyl chloride (11 mg, 0.1 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **16** (22.3 mg, solid, 45% over two steps).

MS m/z (ESI): 499 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 7.85 (s, 1H), 7.56 (s, 1H), 4.19 - 4.11 (m, 1H), 4.19 - 4.11 (dd, J = 18.7, 11.6 Hz, 2H), 3.89 - 3.83 (m, 3H), 3.73 (d, J = 10.8 Hz, 1H), 3.62 (d, J = 12.4 Hz, 1H), 3.44 (d, J = 12.4 Hz, 1H), 3.03 (d, J = 12.5 Hz, 2H), 2.37 (s, 3H), 2.29 (t, J = 11.7 Hz, 2H), 2.16 (d, J = 11.6 Hz, 2H), 2.07 (dd, J = 16.7, 8.0 Hz, 2H), 1.84 - 1.76 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.94 - 0.89 (m, 2H), 0.88 - 0.82 (m, 2H).

Example 17. ((3aR,6aS)-5-(5-Chloro-2-((1-((R)-2-hydroxypropyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone



Step 1. (R)-1-(4-nitro-1H-pyrazol-1-yl)propan-2-ol (17a)

To a solution of 4-nitro-1H-pyrazol **16a** (2.26 g, 20 mmol) and (R)-2-methyloxirane (3.48 g, 60 mmol) in DMF (15 mL) was added cesium carbonate (13 g, 40 mmol). The mixture was stirred in a sealed tube at 100°C for 4 h. After cooling to room temperature, the mixture was poured into water (100 mL) and extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with water (3×100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 7/3), followed by

purification by prep-HPLC to give the title compound **17a** (1.2 g, 35%).

MS m/z (ESI): 172 [M+1]

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.77 (s, 1H), 8.26 (s, 1H), 5.03 (d, *J* = 4.8 Hz, 1H), 4.17 - 4.09 (m, 1H), 4.06 - 3.97 (m, 2H), 1.08 (d, *J* = 6.0 Hz, 3H).

Step 2. (R)-1-(4-amino-1H-pyrazol-1-yl)propan-2-ol (17b)

To a solution of **17a** (1.2 g, 7 mmol) in MeOH (20 mL) was added 10% Pd/C (120 mg). The mixture was stirred under hydrogen for 16 h and then filtered. The filtrate was concentrated to dryness and the residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/0 to 19/1) to give the title compound **17b** (848 mg, 86%).

MS m/z (ESI): 142 [M+1]

Step 3. (R)-1-(4-((5-chloro-4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)propan-2-ol (17c)

To a 10-mL microwave vessel was added **12a** (39 mg, 0.1 mmol), **17b** (15 mg, 0.1 mmol), pTsOH (38 mg, 0.2 mmol) and isopropanol (2 mL). The vessel was stirred in a microwave reactor at 100°C for 1 h. After cooling to room temperature, the mixture was concentrated to dryness to give the title compound **17c** (60 mg). The crude product was used directly in next step without further purification.

MS m/z (ESI): 392 [M+1]

Step 4. ((3aR,6aS)-5-(5-chloro-2-((1-((R)-2-hydroxypropyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (17)

To a solution of **17c** (60 mg, crude) and TEA (51 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was add a solution of cyclopropanecarbonyl chloride (11 mg, 0.1 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **17** (20.1 mg, solid, 44% over two steps).

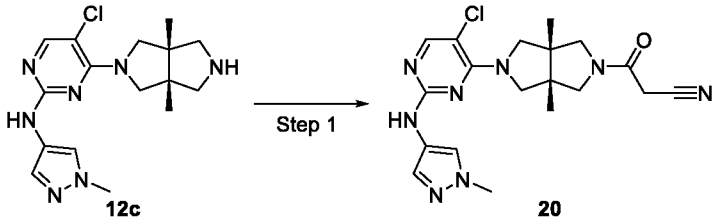
MS m/z (ESI): 460 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 7.84 (s, 1H), 7.54 (s, 1H), 4.13 - 3.97 (m, 5H), 3.91 - 3.83 (m, 3H), 3.72 (d, *J* = 10.8 Hz, 1H), 3.61 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.44 (dd, *J* = 12.4, 1.7 Hz, 1H), 1.83 - 1.77 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.94 - 0.89 (m, 2H), 0.88 - 0.82 (m, 2H).

Example 18 was synthesized according to the procedure for Example 12 except that in step 1, (S)-2-methyloxirane was used instead of (R)-2-methyloxirane.

Example	Compound replacing (R)-2-methyloxirane	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(5-chloro-2-((1-((S)-2-hydroxypropyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**18**)	(S)-2-methyloxirane	^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 7.84 (s, 1H), 7.54 (s, 1H), 4.14 - 3.95 (m, 5H), 3.92 - 3.82 (m, 3H), 3.72 (d, *J* = 10.8 Hz, 1H), 3.61 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.44 (dd, *J* = 12.4, 1.4 Hz, 1H), 1.83 - 1.77 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.94 - 0.88 (m, 2H), 0.89 - 0.81 (m, 2H).	460 [M+1]

Example 20. 3-((3aR,6aS)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



A mixture of **12c** (35 mg, 0.1 mmol), 2-cyanoacetic acid (9 mg, 0.1 mmol), DIEA (39 mg, 0.3 mmol), and HATU (46 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) was stirred for 30 min. The mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **20** (10.5 mg, solid, 25%).

MS m/z (ESI): 415 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 3.99 (t, *J* = 10.8 Hz, 2H), 3.86 (s, 3H), 3.84 (d, *J* = 11.8 Hz, 2H), 3.66 (dd, *J* = 18.8, 11.6 Hz, 2H), 3.50 (dd, *J* = 19.0, 11.6 Hz, 2H), 1.21 (s, 3H), 1.20 (s, 3H).

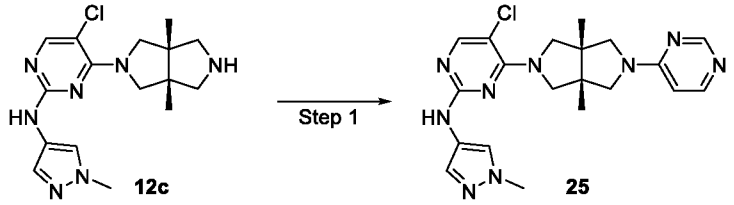
Examples 21, 22, 35, 36, 39, 42, 43, 44, 45, 46, 47, 48 and 52 were synthesized according to the procedure for Example 20 except that in Step 1, different compounds were used instead of 2-cyanoacetic acid.

Example	Compound replacing 2-cyanoacetic acid	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((R)-2,2-difluorocyclopropyl)methanone (**21**)	(R)-2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.54 (d, *J* = 9.5 Hz, 1H), 4.08 - 3.71 (m, 5H), 3.86 (d, *J* = 2.6 Hz, 3H), 3.68 - 3.56 (m, 2H), 3.48 (dd, *J* = 12.5, 2.6 Hz, 1H), 2.89 - 2.79 (m, 1H), 2.08 - 2.00 (m, 1H), 1.85 - 1.73 (m, 1H), 1.23 (d, *J* = 2.1 Hz, 3H), 1.21 (d, *J* = 4.9 Hz, 3H).	452 [M+1]
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone (**22**)	(S)-2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.54 (d, *J* = 9.4 Hz, 1H), 4.08 - 3.70 (m, 5H),3.86 (d, *J* = 2.6 Hz, 3H), 3.68 - 3.57 (m, 2H), 3.49 (dd, *J* = 12.5, 2.5 Hz, 1H), 2.89 - 2.78 (m, 1H), 2.05 - 2.00 (m, 1H), 1.84 - 1.73 (m, 1H), 1.23 (d, *J* = 2.2 Hz, 3H), 1.21 (d, *J* = 4.9 Hz, 3H).	452 [M+1]
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-hydroxyethan-1-one (**35**)	2-hydroxy acetic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 4.18 (s, 2H), 3.98 (dd, *J* = 11.7, 4.7 Hz, 2H), 3.86 (s, 3H), 3.84 (d, *J* = 11.8 Hz, 2H), 3.63 (t, *J* = 11.4 Hz, 2H), 3.47 (dd, *J* = 14.6, 11.7 Hz, 2H), 1.20 (s, 3H), 1.20 (s, 3H).	406 [M+1]
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (**36**)	propionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 4.01 - 3.93 (m, 2H), 3.86 (s, 3H), 3.83 (dd, *J* = 11.6, 4.9 Hz, 2H), 3.69 (d, *J* = 11.0 Hz, 1H), 3.60 (d, *J* = 12.4 Hz, 1H), 3.53 (d, *J* = 11.0 Hz, 1H), 3.44 (d, *J* = 12.4 Hz, 1H), 2.37 (q, *J* = 7.5 Hz, 2H), 1.21 (s, 3H), 1.19 (s, 3H), 1.13 (t, *J* = 7.5 Hz, 3H).	404 [M+1]
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrol	oxetane-3-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 4.86 - 4.81 (m, 4H), 4.15 (dd, *J* = 15.3, 7.7 Hz, 1H), 3.96 (dd, *J* = 11.7, 3.4 Hz, 2H), 3.86 (s, 3H), 3.82 (dd, *J* = 11.7,	432 [M+1]

o[3,4-c]pyrrol-2(1H)-yl)(oxetan-3-yl)methanone (**39**)		2.5 Hz, 2H), 3.64 (d, *J* = 12.5 Hz, 1H), 3.51 (d, *J* = 10.8 Hz, 1H), 3.47 (d, *J* = 12.5 Hz, 1H), 3.36 (d, *J* = 4.3 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H).	
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)cyclopropane-1-carbonitrile (**42**)	1-cyanocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 1H), 7.66 (s, 1H), 7.42 (s, 1H), 3.99 - 3.84 (m, 3H), 3.80 - 3.69 (m, 3H), 3.75 (s, 3H), 3.52 (d, *J* = 12.7 Hz, 1H), 3.37 (d, *J* = 12.7 Hz,1H), 1.55 - 1.43 (m, 4H), 1.13 (s, 3H), 1.10 (s, 3H).	441 [M+1]
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(1-hydroxycyclopropyl)methanone (**43**)	1-hydroxycyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 1H), 7.65 (s, 1H), 7.43 (s, 1H), 3.96 (d, *J* = 12.1 Hz, 1H), 3.89 (d, *J* = 11.6 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 1H), 3.79 - 3.68 (m, 3H), 3.74 (s, 3H), 3.51 (d, *J* = 12.6 Hz, 1H), 3.35 (d, *J* = 12.6 Hz, 1H), 1.09 (s, 6H), 1.04 - 0.99 (m, 2H), 0.82 - 0.79 (m, 2H).	432 [M+1]
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-hydroxy-2-methylpropan-1-one (**44**)	2-hydroxy-2-methylpropionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.77 (s, 1H), 7.54 (s, 1H), 4.06 (d, *J* = 12.2 Hz, 1H), 4.01 (d, *J* = 11.6 Hz, 1H), 3.95 (d, *J* = 11.7 Hz, 1H), 3.88-3.78 (m, 3H), 3.86 (s, 3H), 3.63 (d, *J* = 12.8 Hz, 1H), 3.47 (d, *J* = 12.8 Hz, 1H), 1.42 (d, *J* = 1.7 Hz, 6H), 1.19 (d, *J* = 1.9 Hz, 6H).	434 [M+1]
3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2,2-dimethyl-3-oxopropanenitrile (**45**)	2-cyano-2-methylpropionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.78 (s, 1H), 7.52 (s, 1H), 4.10 - 3.96 (m, 3H), 3.91 - 3.79 (m, 3H), 3.86 (s, 3H), 3.68 (d, *J* = 12.9 Hz, 1H), 3.53 (d, *J* = 12.8 Hz, 1H), 1.62 (d, *J* = 3.8 Hz, 6H), 1.23 (d, *J* = 9.2 Hz, 6H).	443 [M+1]
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-	isoxazole-5-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (d, *J* = 1.9 Hz, 1H), 7.85 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 7.00 (d, *J* = 1.9 Hz, 1H), 4.05 (dd, *J* = 18.9, 11.7 Hz, 3H), 3.93 - 3.84 (m, 3H), 3.85 (s, 3H), 3.81 (d, *J* = 13.1 Hz, 1H), 3.68	443 [M+1]

yl)(isoxazol-5-yl)methanone (**46**)		(d, J = 13.1 Hz, 1H), 1.25 (d, J = 7.2 Hz, 6H).	
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(pyridin-2-yl)methanone (**47**)	picolinic acid	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.97 (td, J = 7.8, 1.7 Hz, 1H), 7.85 (s, 1H), 7.81 - 7.78 (m, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 7.54 - 7.51 (m, 1H), 4.11 (d, J = 11.6 Hz, 1H), 3.97 (d, J = 11.7 Hz, 1H), 3.93 - 3.77 (m, 4H), 3.85 (s, 3H), 3.72 (d, J = 11.9 Hz, 1H), 3.67 (d, J = 12.9 Hz, 1H), 1.27 (s, 3H), 1.17 (s, 3H).	453 [M+1]
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3,3-trifluoropropan-1-one hydrochloride (**48**)	3,3,3-trifluoropropionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1H), 7.85 (s, 1H), 7.64 (s, 1H), 4.36 (s, 1H), 4.23 (d, J = 11.4 Hz, 1H), 3.94 (s, 3H), 3.87 - 3.72 (m, 2H), 3.64 (dd, J = 26.0, 9.5 Hz, 2H), 3.54 - 3.38 (m, 4H), 1.23 (d, J = 4.5 Hz, 6H).	458 [M+1]
1-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3-difluoropropan-1-one (**52**)	3,3-difluoropropionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (s, 1H), 7.82 (s, 1H), 7.60 (s, 1H), 6.24 (tt, J = 56.0, 4.7 Hz, 1H), 4.12 (s, 2H), 4.00 (s, 2H), 3.93 (s, 3H), 3.76 (d, J = 10.9 Hz, 1H), 3.60 (t, J = 12.9 Hz, 2H), 3.49 (d, J = 12.4 Hz, 1H), 3.03 (td, J = 16.0, 4.7 Hz, 2H), 1.22 (d, J = 4.9 Hz, 6H).	440 [M+1]

Example 25. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



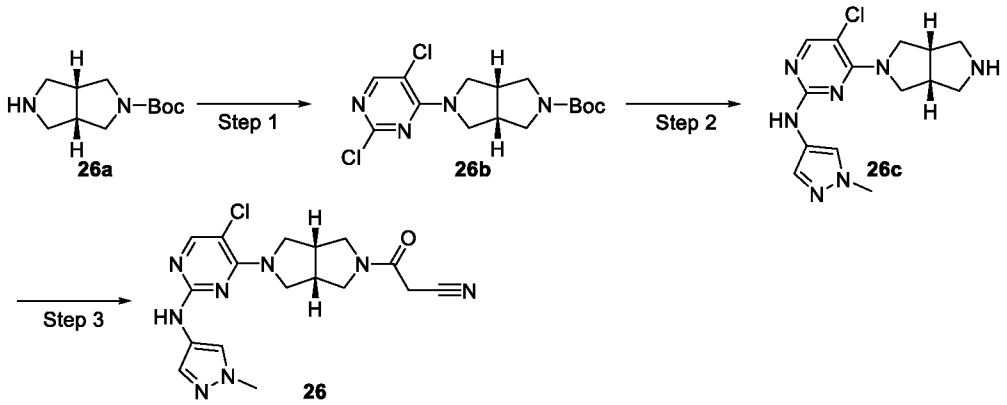
A mixture of **12c** (100 mg, 0.26 mmol), 4-chloropyrimidine hydrochloride (59 mg, 0.39 mmol), and DIEA (336 mg, 2.6 mmol) in MeCN (4 mL) was heated to 80°C and stirred for 8 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **25** (65.1 mg, solid,

58%).

MS m/z (ESI): 426 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.46 (s, 1H), 8.14 (d, J = 6.1, 1H), 7.89 (s, 1H), 7.69 (s, 1H), 7.43 (s, 1H), 6.46 (dd, J = 6.1, 1.0, 1H), 3.88 (s, 2H), 3.76 (s, 3H), 3.74 (s, 2H), 3.67 (s, 2H), 3.52 (s, 2H), 1.15 (s, 6H).

Example 26. 3-((3aR,6aS)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. Tert-butyl (3aR,6aS)-5-(2,5-dichloropyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (26b)

To a solution of 2,4,5-trichloropyrimidine (182mg, 1 mmol) in MeCN (10 mL) were added **26a** (212 mg, 1 mmol) and potassium carbonate (207 mg, 1.5 mmol). The mixture was stirred at 80°C for 3 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 3/1) to give the title compound **26b** (300 mg, 84%).

MS m/z (ESI): 359 [M+1]

Step 2. 5-Chloro-4-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (26c)

To a mixture of **26b** (300 mg, 0.84 mmol) and 1-methyl-1H-pyrazol-4-amine hydrochloride (81.3 mg, 0.84 mmol) in isopropanol (50 mL) was added pTsOH (318 mg, 1.68 mmol). The mixture was heated to 100°C in a microwave reactor for 2 h. After cooling to room temperature, the precipitate was collected by filtration to give the title compound **26c** (200 mg, 75%).

MS m/z (ESI): 320 [M+1]

Step 3. 3-((3aR,6aS)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (26)

To mixture of **26c** (100 mg, 0.313 mmol), 2-cyanoacetic acid (26.6 mg, 0.313 mmol) and TEA (47.5 mg, 0.47 mmol) in DMF (5 mL) was added HATU (178.6 mg, 0.47 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **26** (61.9 mg, solid, 50%).

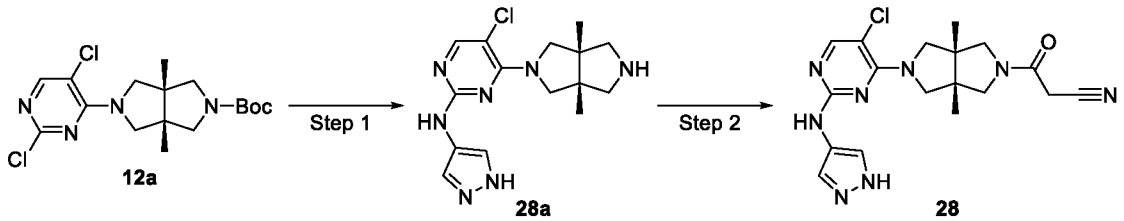
MS m/z (ESI): 387 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.78 (s, 1H), 7.54 (s, 1H), 4.19 - 4.11 (m, 2H), 3.93 - 3.72 (m, 9H), 3.52 - 3.45 (m, 2H), 3.18 - 3.12 (m, 1H), 3.09 - 3.03 (m, 1H).

Examples 27 was synthesized according to the procedure for Example 26 except that in step 3, (S)-2,2-difluorocyclopropane-1-carboxylic acid was used instead of 2-cyanoacetic acid.

Example	Compound replacing 2-cyanoacetic acid	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone (**27**)	(S)-2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.79 (s, 1H), 7.53 (d, *J* = 5.1 Hz, 1H), 4.20 - 4.10 (m, 2H), 4.05 - 3.90 (m, 2H), 3.90 - 3.83 (m, 3H), 3.82 - 3.75 (m, 2H), 3.73 - 3.60 (m, 1H), 3.53 - 3.42 (m, 1H), 3.20 - 3.05 (m, 2H), 2.89 - 2.81 (m, 1H), 2.09 - 2.00 (m, 1H), 1.84 - 1.74 (m, 1H).	424 [M+1]

Example 28. 3-((3aR,6aS)-5-(2-((1H-Pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. 5-chloro-4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)-N-(1H-pyrazol-4-yl)pyrimidine-2-amine (28a)

To a 30-mL microwave vessel were added **12a** (161 mg, 0.42 mmol), 1H-pyrazol-4-amine (35 mg, 0.42 mmol), pTsOH (160 mg, 0.84 mmol) and isopropanol (10 mL). The mixture was heated to 100°C in a microwave reactor for 1 h. The mixture was cooled to room temperature and concentrated to dryness under vacuum to give the title compound **28a** (260 mg). The crude product is used directly in the next step without purification.

MS m/z (ESI): 334 [M+1]

Step 2. 3-((3aR,6aS)-5-(2-((1H-Pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (28)

To a mixture of **28a** (130 mg, crude, 0.21 mmol), 2-cyanoacetic acid (18 mg, 0.21 mmol) and DIEA (82 mg, 0.63 mmol) in DMF (5 mL) was added HATU (80 mg, 0.21 mmol). The mixture was stirred for 1 h and then purified by prep-HPLC to give the title compound **28** (7.6 mg, solid, 9%).

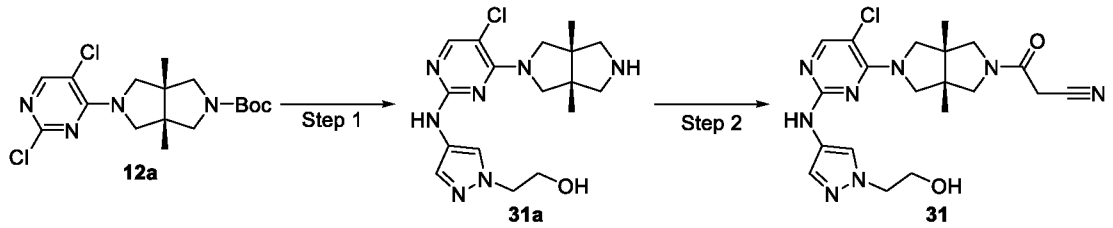
MS m/z (ESI): 401 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 2H), 7.65 (s, 1H), 4.02 (d, *J* = 11.8 Hz, 1H), 3.98 (d, *J* = 11.8 Hz, 1H), 3.85 (dd, *J* = 11.6, 2.8 Hz, 2H), 3.66 (t, *J* = 12.1 Hz, 2H), 3.53 (d, *J* = 10.7 Hz, 1H), 3.47 (d, *J* = 12.5 Hz, 1H), 1.21 (s, 3H), 1.20 (s, 3H).

Example 29 was synthesized according to the procedure for Example 28 except that in step 2, (S)-2,2-difluorocyclopropane-1-carboxylic acid was used instead of 2-cyanoacetic acid.

Example	Compound replacing 2-cyanoacetic acid	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone (**29**)	(S)-2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 2H), 7.64 (s, 1H), 4.16 - 4.03 (m, 1H), 4.02 - 3.94 (m, 1H), 3.92 - 3.81 (m, 2H), 3.76 (q, *J* = 10.9 Hz, 1H), 3.69 - 3.54 (m, 2H), 3.49 (d, *J* = 12.6 Hz, 1H), 2.88 - 2.78 (m, 1H), 2.08 - 1.99 (m, 1H), 1.84 - 1.73 (m, 1H), 1.23 (s, 3H), 1.21 (d, *J* = 3.6 Hz, 3H).	438 [M+1]

Example 31. 3-((3aR,6aS)-5-(5-Chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. 2-(4-((5-Chloro-4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)ethan-1-ol (31a)

To a 30-mL microwave vessel were added **12a** (330 mg, 0.852 mmol), 2-(4-amino-1H-pyrazol-1-yl)ethan-1-ol (108 mg, 0.852 mmol), pTsOH (324 mg, 1.704 mmol) and isopropanol (10 mL). The mixture was heated to 100°C in a microwave reactor for 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **31a** (210 mg, 65%).

MS m/z (ESI): 378 [M+1]

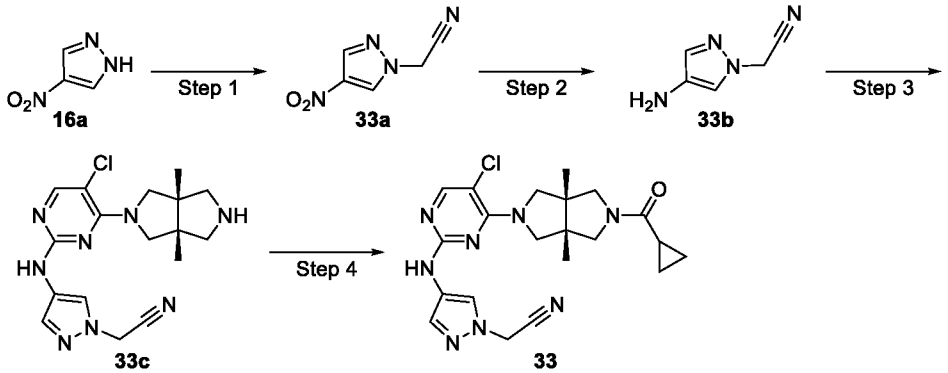
Step 2. 3-((3aR,6aS)-5-(5-Chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (31)

To a mixture of **31a** (100 mg, 0.26 mmol), 2-cyanoacetic acid (23 mg, 0.26 mmol) and DIEA (101 mg, 0.87 mmol) in CH_2Cl_2 (10 mL) was added HATU (101 mg, 0.26 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **31** (18.6 mg, solid, 16%).

MS m/z (ESI): 445 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (s, 1H), 7.84 (s, 1H), 7.53 (s, 1H), 4.20 (t, *J* = 5.2 Hz, 2H), 4.02 (d, *J* = 5.8 Hz, 1H), 3.99 (d, *J* = 5.7 Hz, 1H), 3.92 - 3.81 (m, 4H), 3.68 (d, *J* = 10.7 Hz, 1H), 3.63 (d, *J* = 12.5 Hz, 1H), 3.52 (d, *J* = 10.7 Hz, 1H), 3.48 (d, *J* = 12.5 Hz, 1H), 1.21 (s, 3H), 1.20 (s, 3H).

Example 33. 2-(4-((5-Chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)acetonitrile



Step 1. 2-(4-Nitro-1H-pyrazol-1-yl)acetonitrile (33a)

To a solution of 4-nitro-1H-pyrazol 1**6a** (1.13 g, 10 mmol) in DMF (12 mL) was added cesium carbonate (9.75 g, 30 mmol). After cooling to 0°C, the mixture was added with 2-bromoacetonitrile (2.4 g, 20 mmol) dropwise. The mixture was stirred for 1 h, diluted with

water (150 mL) and extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with water (3×100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 1/1) to give the title compound **33a** (960 mg, 63%).

MS m/z (ESI): 153 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.16 (s, 1H), 5.15 (s, 2H).

Step 2. 2-(4-Amino-1H-pyrazol-1-yl)acetonitrile (33b)

A mixture of **33a** (940 mg, 6.18 mmol), ammonium chloride (6.6 g, 123.6 mmol), ethanol (40 mL) and water (10 mL) was heated to 60°C, and then added with zinc powder (4 g, 61.8 mmol) in batches. The mixture was stirred at 60°C for 10 min, cooled to room temperature and filtered. The filtrate was diluted with water (80 mL) and extracted with ethyl acetate (3×100 mL). The combined organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/0 to 19/1) to give the title compound **33b** (130 mg, 17%).

MS m/z (ESI): 123 [M+1]

Step 3. 2-(4-((5-Chloro-4-((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)acetonitrile (33c)

To a 10-mL microwave flask were added **12a** (155 mg, 0.4 mmol), **33b** (49 mg, 0.4 mmol), pTsOH (16 mg, 0.08 mmol) and isopropanol (4 mL). The mixture was stirred in a microwave reactor at 100°C for 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum to give the title compound **33c**. The crude product is used directly in the next step without purification.

MS m/z (ESI): 373 [M+1]

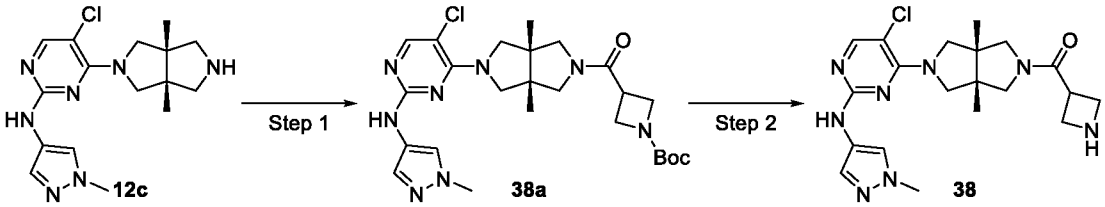
Step 4. 2-(4-((5-Chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)acetonitrile (33)

To a mixture of **33c** (crude, 0.4 mmol) in CH_2Cl_2 (20 mL) were added TEA (121 mg, 1.2 mmol) and a solution of cyclopropanecarbonyl chloride (42 mg, 0.4 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound 2 **33** (81 mg, solid, 46% over two steps).

MS m/z (ESI): 441 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.87 (s, 1H), 7.63 (s, 1H), 5.29 (s, 2H), 4.06 - 3.96 (m, 2H), 3.95 - 3.82 (m, 3H), 3.72 (d, *J* = 10.8 Hz, 1H), 3.62 (d, *J* = 12.4 Hz, 1H), 3.45 (d, *J* = 12.4 Hz, 1H), 1.83 - 1.77 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 0.94 - 0.88 (m, 2H), 0.88 - 0.82 (m, 2H).

Example 38. Azetidin-3-yl((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



Step 1. Tert-butyl 3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)azetidine-1-carboxylate (38a)

To a mixture of **12c** (35 mg, 0.1 mmol), 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (21 mg, 0.1 mmol) and DIEA (39 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added HATU (38 mg, 0.1 mmol). After stirring at room temperature for 30 min, the mixture was diluted with saturated ammonium chloride solution (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum to give the title compound **38a**. This crude product is used directly in the next step without purification.

MS m/z (ESI): 531 [M+1]

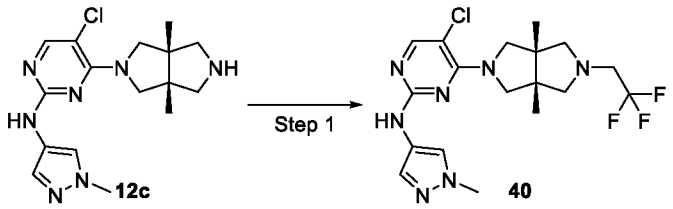
Step 2. Azetidin-3-yl((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (38)

To a solution of **38a** (crude, about 0.1 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL). The mixture was stirred for 30 min and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **38** (19.9 mg, solid, 46% over two steps.

MS m/z (ESI): 431 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 4.05 - 3.93 (m, 4H), 3.90 - 3.78 (m, 8H), 3.63 (d, *J* = 12.5 Hz, 1H), 3.57 (d, *J* = 10.8 Hz, 1H), 3.46 (d, *J* = 12.5 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 1.19 (s, 6H).

Example 40. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(2,2,2-trifluoroethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

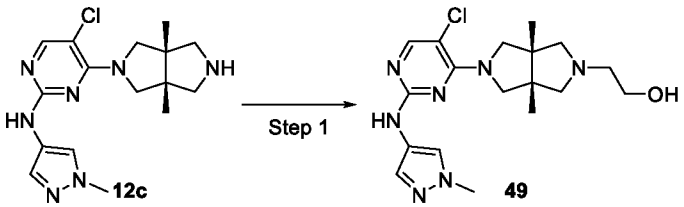


To a mixture of **12c** (50 mg, 0.14 mmol) in 1,4-dioxane (4 mL) were added DIEA (54 mg, 0.42 mmol) and 2,2,2-trifluoroethyltrifluoromethanesulfonate (65 mg, 0.28 mmol). The mixture was stirred in a sealed tube at 100°C for 2 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **40** (7.3 mg, solid, 12%).

MS m/z (ESI): 430 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.77 (s, 1H), 7.56 (s, 1H), 4.06 (d, J = 11.5 Hz, 2H), 3.86 (s, 3H), 3.69 (d, J = 11.5 Hz, 2H), 3.22 (q, J = 9.8 Hz, 2H), 3.04 (d, J = 9.3 Hz, 2H), 2.79 (d, J = 9.3 Hz, 2H), 1.16 (s, 6H).

Example 49. 2-((3aR,6aS)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-ol



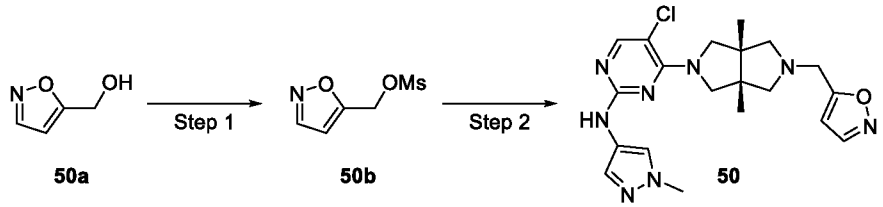
A mixture of **12c** (35 mg, 0.1 mmol), 2-bromoethanol (15 mg, 0.12 mmol) and potassium carbonate (42 mg, 0.3 mmol) in MeCN (5 mL) was heated to reflux for 20 h while stirring. After cooling to room temperature, the mixture was concentrated to dryness under vacuum. The residue was dissolved in DMSO (5 mL) and then added with 2-bromoethanol (0.2 mL) and cesium carbonate (98 mg, 0.3 mmol). The mixture was heated to 100°C for 2 h. After cooling to room temperature, the mixture was filtered and the filtrate was purified by prep-HPLC to give the title compound **49** (16.7 mg, solid, 43%).

MS m/z (ESI): 392 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.77 (s, 1H), 7.56 (s, 1H), 4.12 (d, J = 11.5

Hz, 2H), 3.87 (s, 3H), 3.65 (dd, J = 8.7, 5.1 Hz, 4H), 2.93 (d, J = 9.6 Hz, 2H), 2.70 - 2.61 (m, 4H), 1.17 (s, 6H).

Example 50. 5-Chloro-4-((3aR,6aS)-5-(isoxazol-5-ylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



Step 1. Isoxazole-5-yl-methylmethanesulfonate (50b)

To a solution of isoxazole-5-ylmethanol **50a** (76 mg, 0.77 mmol) in CH_2Cl_2 (10 mL) at 0°C were added TEA (390 mg, 3.85 mmol) and methyl sulfonyl chloride (93 mg, 0.81 mmol). After stirring at room temperature for 1 h, the resulting solution was used directly in the next step.

MS m/z (ESI): 178 [M+1]

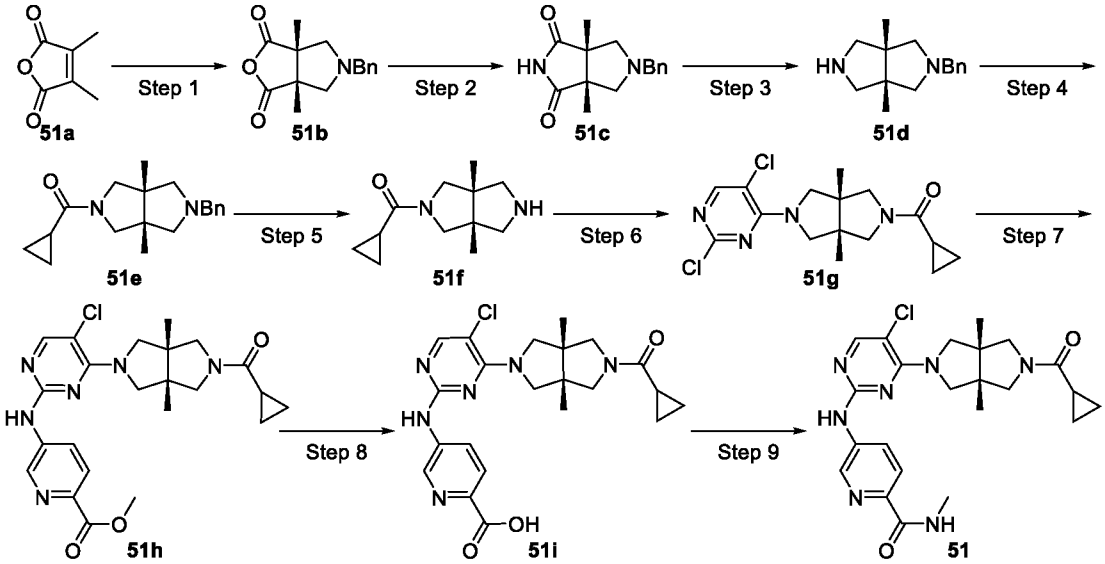
Step 2. 5-Chloro-4-((3aR,6aS)-5-(isoxazol-5-ylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (50)

To a mixture of **12c** (70 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added the solution obtained from Step 1 dropwise. The mixture was stirred for 2 h and concentrated to dryness under vacuum. The residue was dissolved in DMSO (2 mL) and added with cesium carbonate (195 mg, 0.6 mmol). The mixture was heated to 50°C and then cooled to room temperature immediately. The mixture was then filtered and the filtrate was purified by prep-HPLC to give the title compound **50** (7.7 mg, solid, 9%).

MS m/z (ESI): 429 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (d, J = 1.4 Hz, 1H), 7.84 (s, 1H), 7.76 (s, 1H), 7.56 (s, 1H), 6.32 (d, J = 1.1 Hz, 1H), 4.08 (d, J = 11.5 Hz, 2H), 3.87 (s, 2H), 3.87 (s, 3H), 3.62 (d, J = 11.4 Hz, 2H), 2.94 (d, J = 9.4 Hz, 2H), 2.66 (d, J = 9.4 Hz, 2H), 1.15 (s, 6H).

Example 51. 5-((5-Chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-N-methylpicolinamide



Step 1. (3aR,6aS)-5-Benzyl-3a,6a-dimethyltetrahydro-1H-furo[3,4-c]pyrrole-1,3(3aH)-dione (51b)

To a solution of 3,4-dimethylfuran-2,5-dione **51a** (6 g, 47.6 mmol) in CH_2Cl_2 (120 mL) was added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (14.8 g, 61.9 mmol). After cooling to 0°C, the mixture was added with a solution of TFA (543 mg, 4.76 mmol) in CH_2Cl_2 (30 mL) dropwise under nitrogen. The resulting mixture was stirred for 3 h and then concentrated to dryness under vacuum to give the title compound **51b** (17 g). The crude product was used directly in the next step without further purification.

MS m/z (ESI): 260 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.18 (m, 5H), 3.53 (s, 2H), 3.46 (d, J = 10.2 Hz, 2H), 2.18 (d, J = 10.1 Hz, 2H), 1.28 (s, 6H).

Step 2. (3aR,6aS)-5-Benzyl-3a,6a-dimethyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (51c)

To a solution of **51b** (17 g, crude product, 47.6 mmol) in THF (60 mL) was added ammonium hydroxide (60 mL). The mixture was heated in a sealed tube at 100°C for 4 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum. The residue was diluted with water (150 mL) and extracted with CH_2Cl_2 (3×150 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 1/4) to give the title compound **51c** (7 g, 57% over two steps).

MS m/z (ESI): 259 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 7.35 - 7.12 (m, 5H), 3.48 (s, 2H), 3.12

(d, J = 9.7 Hz, 2H), 2.03 (d, J = 9.6 Hz, 2H), 1.09 (s, 6H).

Step 3. (3aR,6aS)-2-Benzyl-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (51d)

To a solution of **51c** (2.67 g, 10.34 mmol) in THF (30 mL) was added LAH (1.18 g, 31 mmol) in batches. The mixture was heated to reflux for 2 h while stirring. After cooling to 0°C, the mixture was added with water (8 mL), 20% sodium hydroxide aqueous solution (16 mL) and water (8 mL). The mixture was stirred for 10 min and filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **51d** (2.44 g, 100%).

MS m/z (ESI): 231 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 - 7.17 (m, 5H), 3.45 (s, 2H), 2.61 (d, J = 8.8 Hz, 2H), 2.46 (d, J = 8.7 Hz, 2H), 2.24 (dd, J = 10.6, 8.9 Hz, 4H), 0.97 (s, 6H).

Step 4. ((3aR,6aS)-5-Benzyl-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (51e)

To a solution of **51d** (2.44 g, 10.34 mmol) in CH_2Cl_2 (40 mL) were added TEA (3.14 g, 31 mmol) and cyclopropanecarbonyl chloride (1.08 g, 10.34 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 1/4) to give the title compound **51e** (1.59 g, 52%).

MS m/z (ESI): 299 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.27 (m, 4H), 7.25 - 7.20 (m, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.75 (d, J = 12.1 Hz, 1H), 3.59 (q, J = 13.3 Hz, 2H), 3.46 (d, J = 10.4 Hz, 1H), 3.34 (d, J = 12.1 Hz, 1H), 2.81 (d, J = 9.3 Hz, 1H), 2.77 (d, J = 9.2 Hz, 1H), 2.37 (d, J = 9.1 Hz, 2H), 1.59 (tt, J = 8.0, 4.7 Hz, 1H), 1.09 (s, 3H), 1.05 (s, 3H), 1.03 - 0.95 (m, 2H), 0.79 - 0.68 (m, 2H).

Step 5. Cyclopropyl((3aR,6aS)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (51f)

To a solution of **51e** (1.59 g, 5.38 mmol) in ethanol (30 mL) was added 10% Pd/C (320 mg). The mixture was stirred under hydrogen for 18 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **51f** (1.11 g, 100%).

MS m/z (ESI): 209 [M+1]

Step 6. Cyclopropyl((3aR,6aS)-5-(2,5-dichloropyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (51g)

To a solution of **51f** (1.11 g, 5.33 mmol) in MeCN (20 mL) were added DIEA (2.07 g, 16 mmol) and 2,4,5-trichloropyrimidine (977 mg, 5.33 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by silica gel

column chromatography (petroleum ether/ethyl acetate = 100/0 to 3/7) to give the title compound **51g** (1.59 g, 86%).

MS m/z (ESI): 355 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 3.96 (s, 2H), 3.87 - 3.72 (m, 3H), 3.62 (d, *J* = 7.0 Hz, 2H), 3.48 (d, *J* = 12.3 Hz, 1H), 1.60 - 1.51 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H), 1.03 - 1.00 (m, 2H), 0.82 - 0.75 (m, 2H).

Step 7. Methyl 5-((5-chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)picolinate (51h)

A mixture of **51g** (355 mg, 4.74 mmol), methyl 5-aminopicolinate (167 mg, 1.1 mmol), cesium carbonate (975 mg, 3 mmol), tris(dibenzylideneacetone)dipalladium (92 mg, 0.1 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (116 mg, 0.2 mmol) in 1,4-dioxane (15 mL) was heated in a microwave reactor to 100°C for 1 h under nitrogen. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/0 to 9/1) to give the title compound **51h** (88 mg, 19%).

MS m/z (ESI): 471 [M+1]

Step 8. 5-((5-Chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)picolinic acid (51i)

To a mixture of **51h** (88 mg, 0.19 mmol) in THF (2 mL) and MeOH (2 mL) was added 1 N NaOH (4 mL). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The reside was added with water (10 mL) and washed with ethyl acetate (20 mL). The aqueous layer was adjusted to pH = 3 by addition of 1 N HCl and extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum to give the title compound **51i** (30 mg, 35%).

MS m/z (ESI): 457 [M+1]

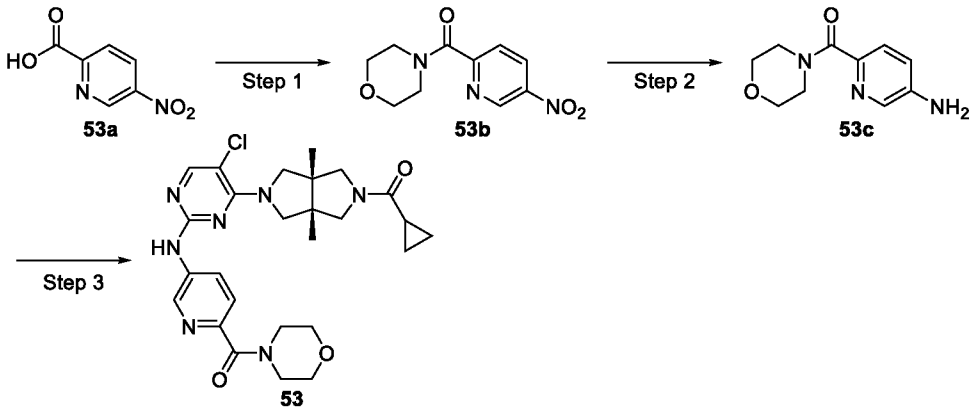
Step 9. 5-((5-Chloro-4-((3aR,6aS)-5-(cyclopropanecarbonyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)amino)-N-methylpicolinamide (51)

To a solution of **51i** (30 mg, 0.066 mmol) in CH_2Cl_2 (10 mL) were added DIEA (74 mg, 0.57 mmol), HATU (72 mg, 0.19 mmol) and a methylamine solution (2 M in THF, 0.05 mL, 1 mmol) sequentially. The resulting mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **51** (8.2 mg, solid, 27%).

MS m/z (ESI): 470 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.77 (d, *J* = 2.3 Hz, 1H), 8.17 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.88 (d, *J* = 10.1 Hz, 2H), 3.91 (t, *J* = 12.2 Hz, 2H), 3.82 - 3.73 (m, 3H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.50 (d, *J* = 12.5 Hz, 1H), 3.34 (d, *J* = 12.4 Hz, 1H), 2.85 (s, 3H), 1.72 - 1.66 (m, 1H), 1.13 (s, 3H), 1.09 (s, 3H), 0.82 - 0.77 (m, 2H), 0.77 - 0.71 (m, 2H).

Example 53. ((3aR,6aS)-5-(5-Chloro-2-((6-(morpholine-4-carbonyl)pyridin-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone



Step 1. Morpholino(5-nitropyridin-2-yl)methanone (53b)

To a solution of 5-nitropicolinic acid **53a** (505 mg, 3 mmol) in CH_2Cl_2 (30 mL) were added morpholine (262 mg, 3 mmol), DIEA (1.16 g, 9 mmol) and HATU (1.14 g, 3 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate = 100/0 to 1/4) to give the title compound **53b** (880 mg, contaminated with DIEA and tetramethylurea).

MS m/z (ESI): 238 [M+1]

Step 2. (5-Aminopyridin-2-yl)(morpholino)methanone (53c)

To a solution of **53b** (880 mg, about 3 mmol) in MeOH (20 mL) was added 10% Pd/C (200 mg). The mixture was stirred under hydrogen for 2 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **53c** (740 mg, contaminated with DIEA and tetramethylurea).

MS m/z (ESI): 208 [M+1]

Step 3. ((3aR,6aS)-5-(5-Chloro-2-((6-(morpholine-4-carbonyl)pyridin-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (53)

To a mixture of **51g** (71 mg, 0.2 mmol) and **53c** (42 mg, 0.2 mmol) in 1,4-dioxane (2

mL) were added NaOEt (30 mg, 0.44 mmol) and RuPhos-Pd-G2 (8 mg, 0.01 mmol). The mixture was heated to 100°C in a microwave reactor under nitrogen for 1 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/0 to 9/1) and then prep-HPLC to give the title compound **53** (11.4 mg, solid, 11%).

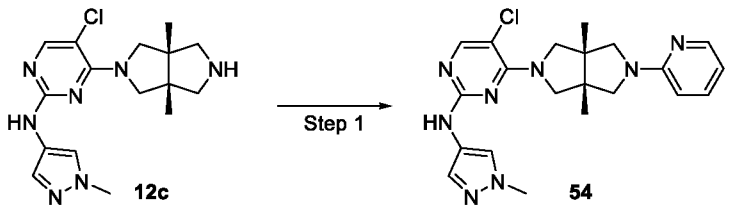
MS m/z (ESI): 526 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (d, *J* = 2.4 Hz, 1H), 8.29 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.99 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 4.02 (t, *J* = 11.0 Hz, 2H), 3.95 - 3.58 (m, 13H), 3.46 (d, *J* = 12.4 Hz, 1H), 1.81 (ddd, *J* = 12.8, 7.9, 4.7 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.92 (dt, *J* = 5.4, 3.8 Hz, 2H), 0.89 - 0.81 (m, 2H).

Example 59 was synthesized according to the procedure for Example 53 except that in step 1, 1-methylpiperazine was used instead of morpholine.

Example	Compound replacing morpholine	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(5-chloro-2-((6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**59**)	1-methyl piperazine	^{1}H NMR (400 MHz, CD_3OD) δ 8.91 (d, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.98 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 4.02 (t, *J* = 10.8 Hz, 2H), 3.89 (dd, *J* = 19.1, 11.1 Hz, 3H), 3.82 (s, 2H), 3.73 (d, *J* = 10.8 Hz, 1H), 3.64 (s, 2H), 3.61 (d, *J* = 12.5 Hz, 1H), 3.46 (d, *J* = 12.4 Hz, 1H), 2.53 (d, *J* = 35.9 Hz, 4H), 2.35 (s, 3H), 1.84 - 1.78 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.94 - 0.89 (m, 2H), 0.89 - 0.82 (m, 2H).	539 [M+1]

Example 54. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(pyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



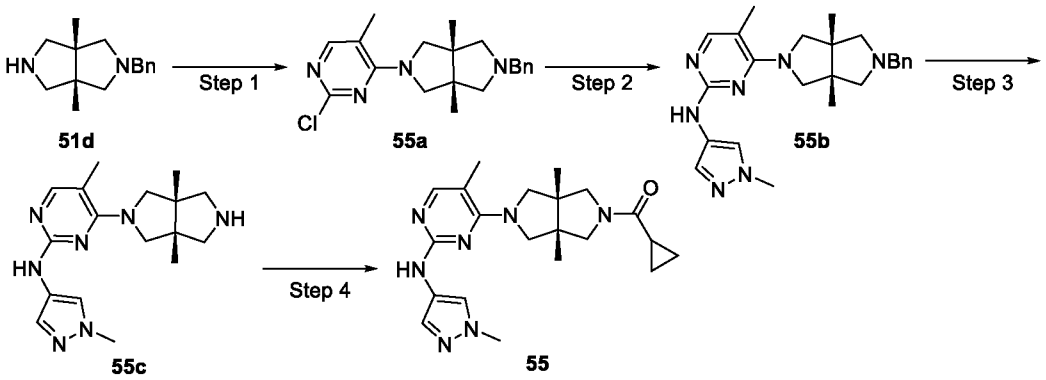
A mixture of **12c** (100 mg, 0.26 mmol), 2-bromopyridine (62 mg, 0.39 mmol), DBU (4

mL) was heated to 140°C and stirred for 16 h. After cooling to room temperature, the mixture was added with water (4 mL) and extracted with ethyl acetate (3×5 mL). The combined organic phase was washed with water (10 mL) and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **54** (36.4 mg, solid, 33%).

MS m/z (ESI): 425 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.04 (d, J = 3.7 Hz, 1H), 7.89 (s, 1H), 7.69 (s, 1H), 7.47 (s, 1H), 7.43 (s, 1H), 6.54 (d, J = 1.6 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 3.89 (d, J = 11.4 Hz, 2H), 3.75 (s, 3H), 3.75 - 3.71 (m, 2H), 3.56 (d, J = 10.9 Hz, 2H), 3.38 (d, J = 10.8 Hz, 2H), 1.15 (s, 6H).

Example 55. 4-((3aR,6aS)-3a,6a-Dimethyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



Step 1. (3aR,6aS)-2-Benzyl-5-(2-chloro-5-methylpyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (55a)

To a solution of **51d** (2.02 g, 8.8 mmol) in MeCN (20 mL) were added 2,4-dichloro-5-methylpyrimidine (1.63 g, 10 mmol) and DIEA (3.88 g, 30 mmol). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 45/55) to give the title compound **55a** (1.45 g, 46%).

MS m/z (ESI): 357 [M+1]

Step 2. 4-((3aR,6aS)-5-Benzyl-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (55b)

To a mixture of **55a** (1.45 g, 4.1 mmol) and 1-methyl-1H-pyrazol-4-amine hydrochloride (4.1 g, 1 mmol) in isopropanol (40 mL) was added pTsOH (78 mg, 0.41 mmol). The mixture was stirred at 100°C for 18 h. After cooling to room temperature, the mixture was added with MeOH (20 mL), followed by TEA (0.5 mL). The mixture was stirred for another 5 min and

concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 19/1) to give the title compound **55b** (540 mg, 32%).

MS m/z (ESI): 418 [M+1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 7.51 (s, 1H), 7.30 (dd, *J* = 6.6, 3.5 Hz, 4H), 7.25 - 7.20 (m, 1H), 6.86 (s, 1H), 3.85 (d, *J* = 10.8 Hz, 2H), 3.85 (s, 3H), 3.60 (s, 2H), 3.48 (d, *J* = 10.8 Hz, 2H), 2.80 (d, *J* = 9.3 Hz, 2H), 2.41 (d, *J* = 9.3 Hz, 2H), 2.20 (s, 3H), 1.10 (s, 6H).

Step 3. 4-((3aR,6aS)-3a,6a-Dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (55c)

To a solution of **55b** (540 mg, 1.29 mmol) in MeOH (30 mL) was added 10% Pd/C (300 mg). The mixture was stirred under hydrogen at 36°C for 16 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **55c** (340 mg, 81%).

MS m/z (ESI): 328 [M+1]

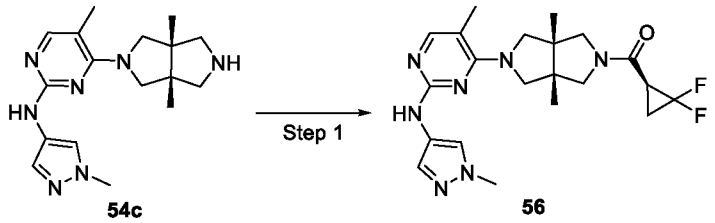
Step 4. 4-((3aR,6aS)-3a,6a-Dimethyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (55)

To a solution of **55c** (33 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added TEA (30 mg, 0.3 mmol), followed by a solution of MsCl (12 mg, 0.1 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **55** (18.7 mg, solid, 46%).

MS m/z (ESI): 406 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.50 (s, 1H), 7.44 (s, 1H), 3.82 (d, *J* = 11.2 Hz, 2H), 3.74 (s, 3H), 3.60 (d, *J* = 11.2 Hz, 2H), 3.40 (d, *J* = 10.1 Hz, 2H), 3.23 (d, *J* = 10.1 Hz, 2H), 2.83 (s, 3H), 2.15 (s, 3H), 1.09 (s, 6H).

Example 56. ((S)-2,2-difluorocyclopropyl)((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



To a solution of **54c** (33 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added (S)-2,2-

difluorocyclopropane-1-carboxylic acid (13 mg, 0.1 mmol) and DIEA (39 mg, 0.3 mmol), followed by HATU (38 mg, 0.1 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **56** (21.3 mg, solid, 49%).

MS m/z (ESI): 432 [M+1]

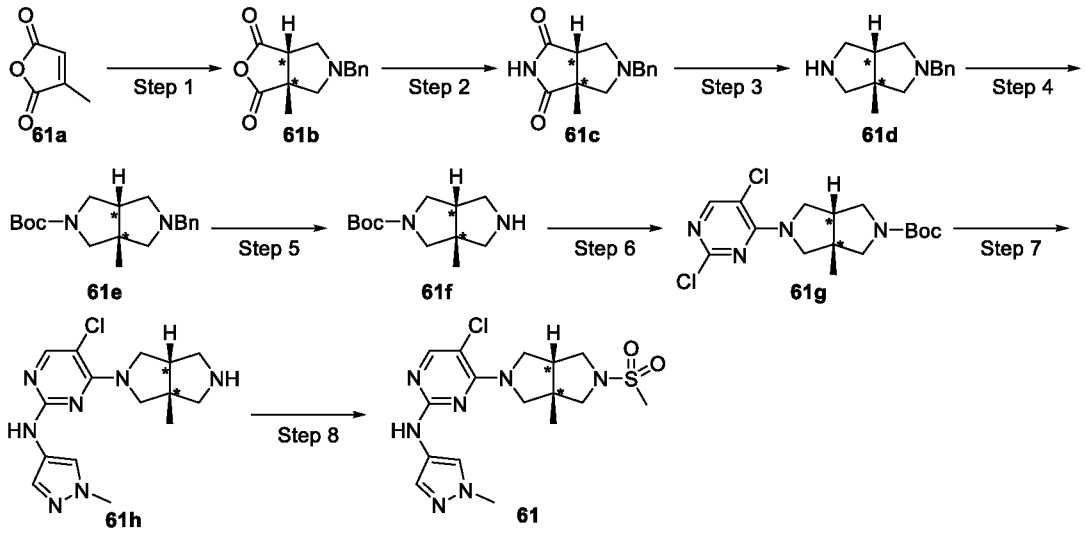
^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, *J* = 3.1 Hz, 1H), 7.62 (s, 1H), 7.54 (d, *J* = 11.0 Hz, 1H), 3.98 - 3.88 (m, 2H), 3.86 (d, *J* = 2.7 Hz, 3H), 3.82 - 3.71 (m, 3H), 3.68 - 3.56 (m, 2H), 3.48 (dd, *J* = 12.6, 2.7 Hz, 1H), 2.89 - 2.79 (m, 1H), 2.28 (d, *J* = 5.7 Hz, 3H), 2.08 - 2.00 (m, 1H), 1.85 - 1.73 (m, 1H), 1.24 (d, *J* = 3.4 Hz, 2H), 1.21 (d, *J* = 3.9 Hz, 3H).

Example 57, 58 and 60 were synthesized according to the procedure for Example 56 except that in step 1, different compounds were used instead of (S)-2,2-difluorocyclopropane-1-carboxylic acid.

Example	Compound replacing cyclo(S)-2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR	MS m/z (ESI)
3-((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (**57**)	2-cyanoacetic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (s, 1H), 7.62 (s, 1H), 7.55 (s, 1H), 3.92 (dd, *J* = 11.2, 2.9 Hz, 2H), 3.86 (s, 3H), 3.75 (d, *J* = 11.2 Hz, 2H), 3.68 (d, *J* = 10.7 Hz, 1H), 3.64 (d, *J* = 12.5 Hz, 1H), 3.52 (d, *J* = 10.7 Hz, 1H), 3.47 (d, *J* = 12.4 Hz, 1H), 2.28 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H).	395 [M+1]
((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(isoxazol-5-yl)methanone (**58**)	isoxazole-5-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d, *J* = 1.8 Hz, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 7.43 (s, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 3.96 (d, *J* = 11.6 Hz, 1H), 3.87 (d, *J* = 11.3 Hz, 1H), 3.83 (d, *J* = 11.4 Hz, 1H), 3.79 (d, *J* = 11.6 Hz, 1H), 3.73 (s, 3H), 3.72 - 3.63 (m, 3H), 3.55 (d, *J* = 13.1 Hz, 1H), 2.16 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H).	423 [M+1]
1-((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-	3,3,3-trifluoro propionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.62 (s, 1H), 7.47 (s, 1H), 4.28 - 4.16 (m, 1H), 4.13 - 4.02 (m, 1H), 3.99 - 3.85 (m, 1H), 3.93 (s, 3H), 3.84 - 3.56 (m, 4H),	428 [M+1]

yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3,3,3-trifluoropropan-1-one hydrochloride (**60**)		3.53 - 3.39 (m, 3H), 2.38 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H).	

Example 61. Cis-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine



Step 1. Cis-5-benzyl-3a-methyltetrahydro-1H-furo[3,4-c]pyrrole-1,3(3aH)-dione (61b)

To a solution of 3-methylfuran-2,5-dione (5.33 g, 47.6 mmol) and N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (14.8 g, 61.9 mmol) in CH_2Cl_2 (170 mL) was added trifluoroacetic acid (543 mg, 4.76 mmol). The mixture was stirred for 3 h and then concentrated to dryness under vacuum to give the title compound **61b** (11.62 g). The crude product was used directly in the next step without further purification

MS m/z (ESI): 246 [M+1]

Step 2. Cis-5-benzyl-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (61c)

To a solution of **61b** (11.66 g, about 47.6 mmol) in THF (60 mL) was added ammonium hydroxide (60 mL). The mixture was heated in a sealed tube at 100°C for 5 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was dissolved in CH_2Cl_2 (200 mL). The resulting mixture was washed with water (20 mL) and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/1 to 1/1) to give the title compound **61c** (8 g, 68%).

MS m/z (ESI): 245 [M+1]

Step 3. Cis-2-benzyl-3a-methyloctahydropyrrolo[3,4-c]pyrrole (61d)

To a solution of **61c** (8 g, 32. 8 mmol) in THF (100 mL) was added LAH (3.73 g, 98.36 mmol). The mixture was heated to 70°C and stirred for 3 h. After cooling to 0°C, the mixture was added with water (10 mL), a 20% NaOH solution (20 mL) and water (10 mL) sequentially. The mixture was stirred for 10 min and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound (8 g). The crude product was used directly in the next step without further purification.

MS m/z (ESI): 217 [M+1]

Step 4. Tert-butyl cis-5-benzyl-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (61e)

To a solution of **61d** (8 g, crude) and TEA (7.48 g, 74.07 mmol) in CH_2Cl_2 (100 mL) was added di-tert-butyl dicarbonate (8.07 g, 37.03 mmol). The mixture was stirred for 3 h and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/1 to 7/3) to give the title compound **61e** (10 g, 96% over two steps).

MS m/z (ESI): 317 [M+1]

Step 5. Tert-butyl cis-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (61f)

To a solution of **61e** (10 g, 31.64 mmol) in MeOH (100 mL) was added 10% Pd/C (1 g). The mixture was stirred under hydrogen for 18 h and then filtered. The filtrated was concentrated to dryness under vacuum to give the title compound **61f** (7 g, 97%).

MS m/z (ESI): 227 [M+1]

Step 6. Tert-butyl cis-5-(2,5-dichloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (61g)

To a solution of 2,4,5-trichloropyrimidine (546 mg, 3 mmol) in MeCN (10 mL) were added **61f** (678 mg, 3 mmol) and potassium carbonate (828 mg, 6 mmol). The mixture was heated to 80°C and stirred for 3 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 9/1) to give the title compound **61g** (850 mg, 76%).

MS m/z (ESI): 373 [M+1]

Step 7. Cis-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine hydrochloride (61h)

To a mixture of **61g** (850 mg, 2.28 mmol) and 1-methyl-1H-pyrazol-4-amine

hydrochloride (221 mg, 2.28 mmol) in isopropanol (10 mL) was added pTsOH (868 mg, 4.57 mmol). The mixture was heated in a microwave reactor at 100°C for 2 h. After cooling to room temperature, the precipitate was collected by filtration to give the title compound **61h** (200 mg, 75%) as an HCl salt.

5 MS m/z (ESI): 334 [M+1]

Step 8. Cis-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methyl-5-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine (61)

To a mixture of **61h** (33.3 mg, 0.1 mmol) and TEA (20.2 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added MsCl (11.4 mg, 0.1 mmol). The mixture was stirred for 1 h and concentrated 10 to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **61** (15.4 mg, solid, 37%).

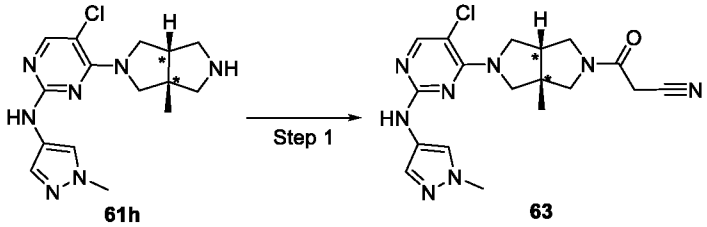
MS m/z (ESI): 412 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 1H), 7.66 (s, 1H), 7.43 (s, 1H), 4.06 - 4.01 (m, 1H), 3.88 (d, J = 11.5 Hz, 1H), 3.76 - 3.64 (m, 6H), 3.61 - 3.56 (m, 1H), 3.35 (d, *J* = 9.9 Hz, 15 2H), 2.83 (s, 3H), 2.56 - 2.51 (m, 1H), 1.22 (s, 3H).

Example 62 was synthesized according to the procedure for Example 61 except that in step 8, cyclopropanecarbonyl chloride was used instead of MsCl.

Example	Compound replacing methanesulfonyl chloride	^{1}H NMR	MS m/z (ESI)
cis-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**62**)	cyclopropanecarbonyl chloride	^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 1H), 7.66 (s, 1H), 7.43 (s, 1H), 4.11 - 3.92 (m, 2H), 3.88 - 3.80 (m, 1H), 3.76 - 3.66 (m, 6H), 3.61 - 3.55 (m, 1H), 3.35 - 3.29 (m, 1H), 2.61 - 2.48 (m, 1H), 1.73 - 1.66(m, 1H), 1.21 (d, *J* = 11.8 Hz, 3H), 0.82 - 0.71 (m, 4H).	402 [M+1]

20 **Example 63. Cis-3-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile**



To a solution of **61h** (66.6 mg, 0.2 mmol), HATU (152 mg, 0.4 mmol) and TEA (40.4 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) was added 2-cyanoacetic acid (17 mg, 0.2 mmol). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **63** (12.4 mg, solid, 16%).

MS m/z (ESI): 401 [M+1]

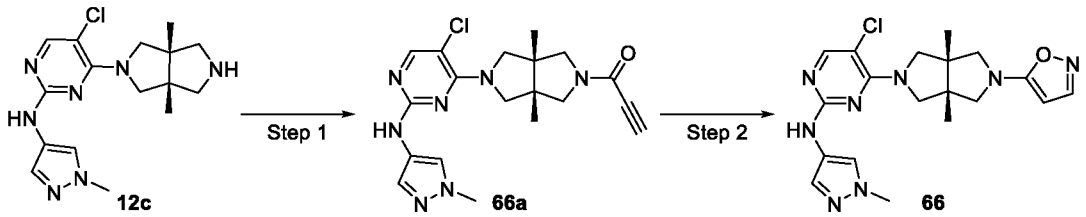
^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.78 (s, 1H), 7.54 (s, 1H), 4.20 - 4.15 (m, 1H), 4.00 - 3.92 (m, 1H), 3.88 - 3.79 (m, 6H), 3.66 - 3.61 (m, 1H), 3.52 - 3.45 (m, 2H), 2.71 - 2.62 (m, 1H), 1.32 (d, *J* = 4.0 Hz, 3H).

Example 64, 65 and 68 were synthesized according to the procedure for Example 63 except that in step 1, different compounds were used instead of 2-cyanoacetic acid.

Example	Compound replacing 2-cyanoacetic acid	^{1}H NMR	MS m/z (ESI)
cis-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(isoxazol-5-yl)methanone (**64**)	isoxazole-5-carboxlic acid	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (d, *J* = 1.7 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.54 (s, 1H), 7.00 (t, *J* = 1.6 Hz, 1H), 4.31 - 4.14 (m, 2H), 4.06 - 3.97 (m, 2H), 3.94 - 3.79 (m, 6H), 3.68 - 3.62 (m, 1H), 2.78 - 2.68 (m, 1H), 1.36 (d, *J* = 7.9 Hz, 3H).	429 [M+1]
cis-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone (**65**)	(S) -2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.78 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 4.23 - 4.14 (m, 1H), 4.11 - 4.00 (m, 1H), 3.99 - 3.91 (m, 1H), 3.90 - 3.78 (m, 5H), 3.76 - 3.67 (m, 1H), 3.64 - 3.55 (m, 1H), 3.52 - 3.44 (m, 1H), 2.89 - 2.81 (m, 1H), 2.75 - 2.64 (m, 1H), 2.08 - 2.00 (m, 1H), 1.83 - 1.74 (m, 1H), 1.34 (dd, *J* = 9.0, 4.6 Hz, 3H).	438 [M+1]
cis-1-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-	3,3,3-trifluoropropionic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.99 - 7.79 (m, 2H), 7.63 (s, 1H), 4.68 - 4.46 (m, 1H) 4.35 - 4.13 (m, 2H), 4.00 - 3.70 (m, 5H), 3.67	444 [M+1]

methylhexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)-3,3,3-trifluoropropan-1-one (**68**)		- 3.38 (m, 5H), 2.80 - 2.65(m, 1H), 1.34 (d, *J* = 3.9 Hz, 3H).	

Example 66. 5-Chloro-4-((3aR,6aS)-5-(isoxazol-5-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



Step 1. 01-((3aR,6aS)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)prop-2-yn-1-one (66a)

To a mixture of **12c** (139 mg, 0.4 mmol) in CH_2Cl_2 (20 mL) were added propiolic acid (28 mg, 0.4 mmol), DIEA (155 mg, 1.2 mmol) and HATU (152 mg, 0.4 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 100/0 to 19/1) to give the title compound **66a** (90 mg, 56%).

MS m/z (ESI): 400 [M+1]

Step 2. 5-Chloro-4-((3aR,6aS)-5-(isoxazol-5-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (66)

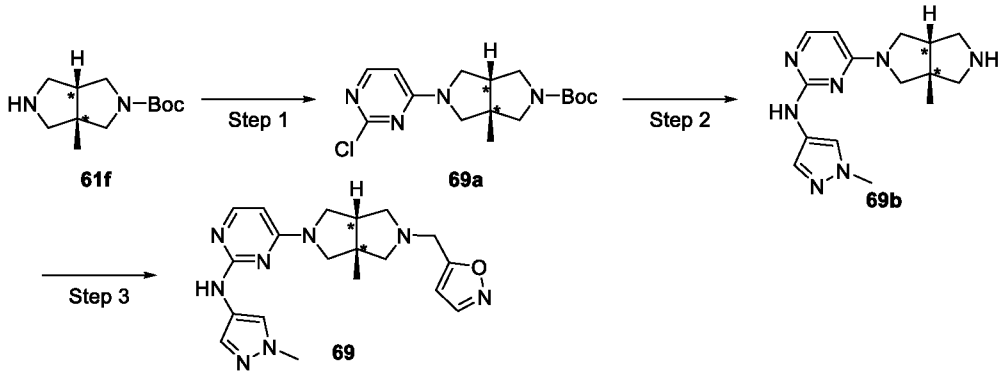
To a solution of **66a** (90 mg, 0.225 mmol) in THF (2 mL) were added water (2 mL), ammonium chloride (60 mg, 1.125 mmol) and sodium azide (73 mg, 1.125 mmol). The mixture was stirred for 18 h, and then heated to 70°C and stirred for another 2 h. After cooling to room temperature, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (2×20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **66** (12.1 mg, solid, 13%).

MS m/z (ESI): 415 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, *J* = 2.1 Hz, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 5.00 (d, *J* = 2.1 Hz, 1H), 4.01 (d, *J* = 11.6 Hz, 2H), 3.86 (d, *J* = 11.5 Hz, 2H), 3.85 (s, 3H), 3.62 (d, *J* = 10.3 Hz, 2H), 3.47 (d, *J* = 10.3 Hz, 2H), 1.24 (s, 6H).

Example 69. Cis-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-

c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



Step 1. Tert-butyl cis-5-(2-chloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (69a)

To a solution of 2,4-dichloropyrimidine (444 mg, 3 mmol) in MeCN (10 mL) were added **61f** (678 mg, 3 mmol) and potassium carbonate (621 mg, 4.5 mmol). The mixture was stirred at 80°C for 3 h and then cooled to room temperature. The mixture was filtered, and the filtrate was concentrated to dryness under vacuum to give the title compound **69a** (700 mg, 69%).

MS m/z (ESI): 339 [M+1]

Step 2. Cis-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine (69b)

To a mixture of **69a** (700 mg, 2.07 mmol) and 1-methyl-1H-pyrazol-4-amine hydrochloride (200 mg, 2.07 mmol) in isopropanol (15 mL) was added pTsOH (787 mg, 4.14 mmol). The mixture was stirred at 100°C for 18 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1 to 4/1) to give the title compound **69b** (300 mg, 48%).

MS m/z (ESI): 300 [M+1]

Step 3. Cis-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (69)

Compound **69** was synthesized according to Step 2 in Example 50 except that **69b** was used instead of **12c**.

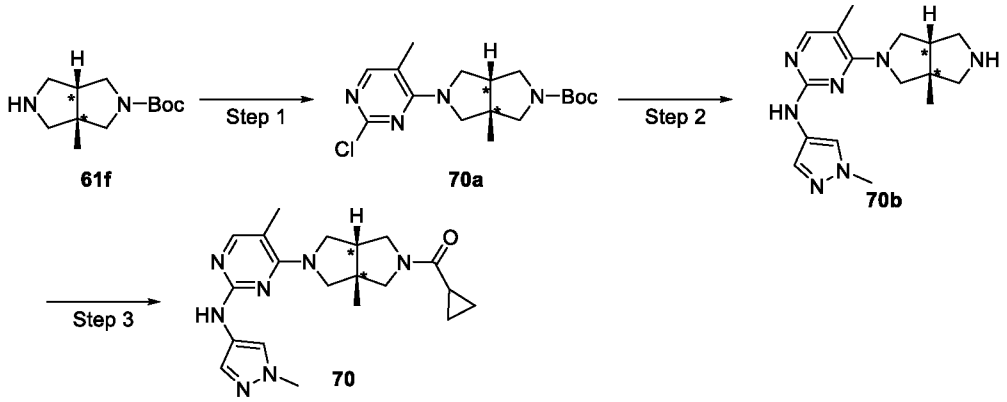
MS m/z (ESI): 381 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (d, J = 1.8 Hz, 1H), 7.83 - 7.80 (m, 2H), 7.58 (s, 1H), 6.35 (d, J = 1.8 Hz, 1H), 5.92 (d, J = 6.1 Hz, 1H), 3.87 (s, 5H), 3.82 (s, 2H), 3.63 (s, 1H), 3.52 (s, 1H), 2.98 (dd, J = 9.4, 7.8 Hz, 1H), 2.84 (d, J = 9.2 Hz, 1H), 2.69 (dd, J = 9.5, 4.6 Hz, 1H), 2.58 (d, J = 9.3 Hz, 1H), 2.55 - 2.49 (m, 1H), 1.32 (s, 3H).

Example 73 and 74 were synthesized according to Step 2 in Example 50 except that different chemicals were used instead of **12c**.

Example	Compounds replacing **12c**	^{1}H NMR	MS m/z (ESI)
cis-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**73**)	cis-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine hydrochloride **70b**	^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (d, *J* = 1.8 Hz, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.56 (s, 1H), 6.35 (d, *J* = 1.8 Hz, 1H), 3.93 (dd, *J* = 11.3, 7.9 Hz, 1H), 3.87 (s, 2H), 3.86 (s, 3H), 3.83 (d, *J* = 10.8 Hz, 1H), 3.69 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.53 (d, *J* = 10.9 Hz, 1H), 3.00 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.80 (d, *J* = 9.3 Hz, 1H), 2.66 (dd, *J* = 9.4, 4.9 Hz, 1H), 2.60 (d, *J* = 9.2 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.23 (s, 3H), 1.31 (s, 3H).	395 [M+1]
cis-5-chloro-4-(5-(isoxazol-5-ylmethyl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**74**)	cis-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine hydrochloride **61h**	^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (d, *J* = 1.7 Hz, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.55 (s, 1H), 6.35 (d, *J* = 1.7 Hz, 1H), 4.05 (dd, *J* = 11.7, 8.0 Hz, 1H), 3.98 (d, *J* = 11.3 Hz, 1H), 3.87 (s, 2H), 3.87 (s, 2H), 3.84 (dd, *J* = 11.8, 3.7 Hz, 1H), 3.67 (d, *J* = 11.3 Hz, 1H), 2.99 (dd, *J* = 9.8, 8.1 Hz, 1H), 2.81 (d, *J* = 9.2 Hz, 1H), 2.67 (dd, *J* = 9.5, 4.8 Hz, 1H), 2.59 (d, *J* = 9.3 Hz, 1H), 2.46 (ddd, *J* = 12.1, 7.9, 4.1 Hz, 1H), 1.30 (s, 3H).	415 [M+1]

Example 70. Cis-cyclopropyl(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



Step 1. Tert-butyl cis-5-(2-chloro-5-methylpyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (70a)

To a solution of 2,4-dichloro-5-methylpyrimidine (324mg, 2mmol) in MeCN (10 mL) were added **61f** (452 mg, 2 mmol) and potassium carbonate (552 mg, 4 mmol). The mixture was stirred at 80°C for 3 h and then cooled to room temperature. The mixture was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 7/3) to give the title compound **70a** (600 mg, 85%).

MS m/z (ESI): 353 [M+1]

Step 2. Cis-5-methyl-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine hydrochloride (70b)

To a mixture of **70a** (600 mg, 1.7 mmol) and 1-methyl-1H-pyrazol-4-amine hydrochloride (165 mg, 1.7 mmol) in isopropanol (15 mL) was added pTsOH (646 mg, 3.4 mmol). The mixture was heated at 100°C in a microwave reactor for 1 h. After cooling to room temperature, the mixture was filtered, and the filtrate concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1 to 67/33) to give the title compound **70b** as an HCl salt (400 mg, 75%).

MS m/z (ESI): 314 [M+1]

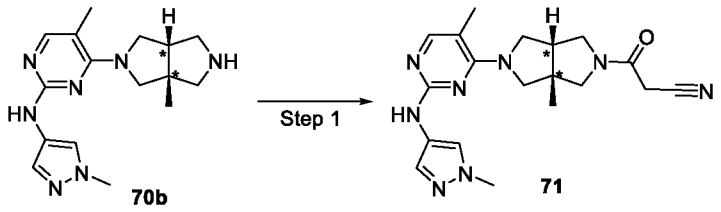
Step 3. Cis-cyclopropyl(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (70)

To a mixture of **70b** (62.6 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) were added TEA (30.3 mg, 0.3 mmol) and cyclopropanecarbonyl chloride (20.8 mg, 0.2 mmol). The mixture was stirred at room temperature for 1 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **70** (7.3 mg, solid, 10%).

MS m/z (ESI): 382 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (s, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 4.05 - 3.92 (m, 2H), 3.81 - 3.71 (m, 4H), 3.69 - 3.48 (m, 4H), 3.36 - 3.29 (m, 1H), 2.60 - 2.47 (m, 1H), 2.17 (s, 3H), 1.74 - 1.66 (m, 1H), 1.22 (d, J = 12.1 Hz, 3H), 0.84 - 0.66 (m, 4H).

Example 71. Cis-3-(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



To a mixture of **70b** (62.6 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) were added 2-cyanoacetic acid (17 mg, 0.2 mmol), TEA (40.4 mg, 0.4 mmol) and HATU (114 mg, 0.3 mmol). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **71** (9.4 mg, solid, 10%).

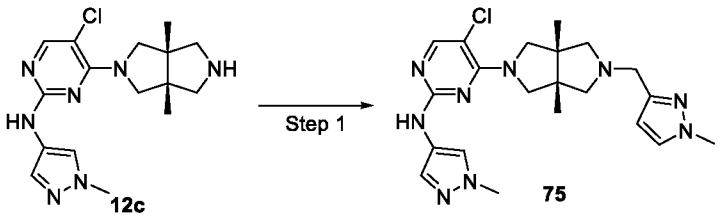
MS m/z (ESI): 382 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.50 (s, 1H), 7.43 (s, 1H), 4.01 - 3.93 (m, 1H), 3.83 - 3.56 (m, 8H), 3.54 - 3.49(m, 1H), 3.43 - 3.27 (m, 3H), 2.59 - 2.49 (m, 1H), 2.15 (d, *J* = 12.8 Hz, 3H), 1.22 (dd, *J* = 10.7, 3.4 Hz, 3H).

Example 72 was synthesized according to the procedure for Example 71 except that in step 1, (S)-2,2-difluorocyclopropane-1-carboxylic acid was used instead of 2-cyanoacetic acid.

Example	Compound replacing 2-cyanoacetic acid	^{1}H NMR	MS m/z (ESI)
cis-((S)-2,2-difluorocyclopropyl)(3a-methyl-5-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (**72**)	(S)-2,2-difluorocyclopropane-1-carboxylic acid	^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (d, *J* = 2.4 Hz, 1H), 7.62 (s, 1H), 7.57 - 7.50 (m, 1H), 4.14 - 4.08 (m, 1H), 3.90 - 3.42 (m, 10H), 2.89 - 2.81 (m, 1H), 2.73 - 2.63 (m, 1H), 2.28 (d, *J* = 5.8 Hz, 3H), 2.07 - 2.01 (m, 1H), 1.83 - 1.75 (m, 1H), 1.38 - 1.29 (m, 3H).	418 [M+1]

Example 75. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((1-methyl-1H-pyrazol-3-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine hydrochloride



To a mixture of **12c** (35 mg, 0.1 mmol) in DMF (4 mL) were added cesium carbonate (98 mg, 0.3 mmol) and 33-(chloromethyl)-1-methyl-1H-pyrazole (14 mg, 0.11 mmol). The mixture was stirred for 20 h and then filtered. The filtrate was purified directly by prep-HPLC to give the title compound **75** as an HCl salt (3.4 mg, solid, 8%).

MS m/z (ESI): 442 [M+1]

^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (t, *J* = 31.0 Hz, 2H), 7.74 - 7.56 (m, 2H), 6.56 (d, *J*

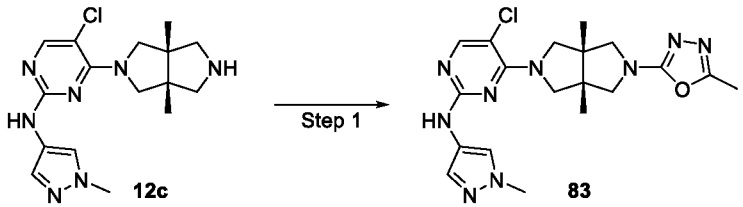
= 5.3 Hz, 1H), 4.45 (d, *J* = 6.5 Hz, 2H), 4.15 - 3.85 (m, 6H), 3.81 (d, *J* = 12.8 Hz, 2H), 3.71 (d, *J* = 11.8 Hz, 2H), 3.60 (d, *J* = 11.9 Hz, 2H), 3.54 - 3.48 (m, 2H), 1.28 (s, 3H), 1.22 (s, 3H).

Example 76, 77, 78, 79, 80, 81 and 82 were synthesized according to the procedure for Example 75 except that in step, different compounds were used instead of 1,3-(chloromethyl)-1-methyl-1H-pyrazole.

Example	Compound replacing 3-(chloromethyl)-1-methyl-1H-pyrazole	^{1}H NMR	MS m/z (ESI)
5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((1-methyl-1H-pyrazol-4-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine hydrochloride (**76**)	(1-methyl-1H-pyrazol-4-yl)methyl methanesulfonate	^{1}H NMR (400 MHz, CD_3OD) δ 8.29 - 7.59 (m, 5H), 4.92 (s, 2H), 4.50-4.40 (m, 3H), 4.02-3.91 (m, 6H), 3.78 (d, *J* = 11.0 Hz, 2H), 3.64 - 3.53 (m, 2H), 3.43 -3.35 (m, 1H), 1.29 (s, 6H).	442 [M+1]
5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((1-methyl-1H-1,2,4-triazol-3-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**77**)	3-(chloromethyl)-1-methyl-1H-1,2,4-triazole	^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.44 (s, 1H), 3.95 (d, *J* = 11.7 Hz, 4H), 3.79 (s, 3H), 3.75 (s, 3H), 3.50 (d, *J* = 11.5 Hz, 2H), 3.25 (s, 2H), 2.97 (s, 2H), 1.08 (s, 6H).	443 [M+1]
5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((3-methylisoxazol-5-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**78**)	(3-methylisoxazol-5-yl)methyl methanesulfonate	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.56 (s, 1H), 6.17 (s, 1H), 4.09 (d, *J* = 11.5 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 2H), 3.62 (d, *J* = 11.5 Hz, 2H), 2.94 (d, *J* = 9.5 Hz, 2H), 2.65 (d, *J* = 9.5 Hz, 2H), 2.24 (s, 3H), 1.15 (s, 6H).	443 [M+1]
4-((3aR,6aS)-5-((1H-pyrazol-4-yl)methyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**79**)	4-(chloromethyl)-1H-pyrazole	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.65 - 7.48 (m, 3H), 4.08 (d, *J* = 11.5 Hz, 2H), 3.86 (s, 3H), 3.67 - 3.56 (m, 4H), 2.92 - 2.85 (m, 2H), 2.63 (d, *J* = 9.9 Hz, 2H), 1.15 (s, 6H).	428 [M+1]
5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((2-methyloxazol-5-yl)methyl)hexahydropyrrol	2-(chloromethyl)-5-methyl-1,3,4-	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 4.08 (d, *J* = 11.5 Hz, 2H), 3.93 (s, 3H), 3.87	444 [M+1]

o[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**80**)	oxadiazole	(brs, 2H), 3.64 (d, *J* = 11.5 Hz, 2H), 2.98 (d, *J* = 9.4 Hz, 2H), 2.70 (d, *J* = 9.4 Hz, 2H), 2.51 (s, 3H), 1.16 (s, 6H).	
4-((3aR,6aS)-5-((1H-pyrazol-3-yl)methyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-chloro-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**81**)	3-(chloromethyl)-1H-pyrazole	^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.76 (s, 1H), 7.59 (s, 1H), 7.55 (s, 1H), 6.29 (s, 1H), 4.05 (d, *J* = 11.4 Hz, 2H), 3.86 (s, 3H), 3.73 (s, 2H), 3.61 (d, *J* = 11.3 Hz, 2H), 2.90 (s, 2H), 2.62 (s, 2H), 1.14 (s, 6H).	428 [M+1]
5-chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**82**)	5-(chloromethyl)-3-methyl-1,2,4-oxadiazole	^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.77 (s, 1H), 7.55 (s, 1H), 4.08 (d, *J* = 11.5 Hz, 2H), 4.00 (s, 2H), 3.87 (s, 3H), 3.65 (d, *J* = 11.5 Hz, 2H), 3.02 (d, *J* = 9.3 Hz, 2H), 2.75 (d, *J* = 9.3 Hz, 2H), 2.35 (s, 3H), 1.16 (s, 6H).	444 [M+1]

Example 83. 5-Chloro-4-((3aR,6aS)-3a,6a-dimethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine

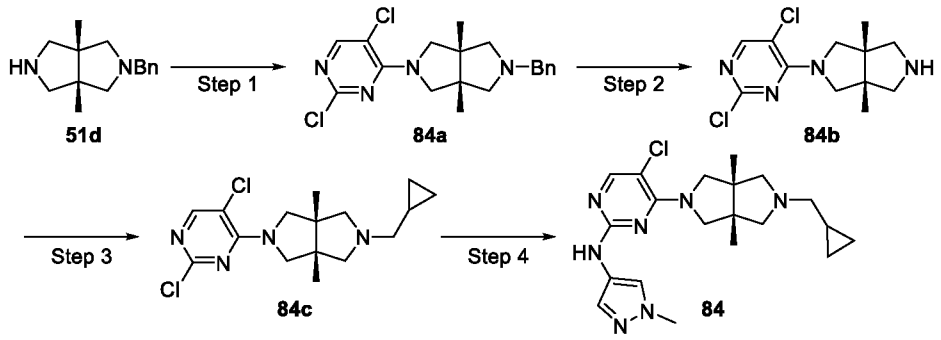


To a mixture of **12c** (80 mg, 0.208 mmol) in DMF (3 mL) were added 5-methyl-1,3,4-oxadiazol-2(3H)-one (21 mg, 0.208 mmol) and DIEA (161 mg, 1.25 mmol). The mixture was stirred at for 5 min and then added with (benzotriazol1yloxy)tris(dimethylamino)phosphonium hexafluophosphate (101 mg, 0.229 mmol). The resulting mixture was heated to 50°C and stirred for 12 h. After cooling to room temperature, the mixture was added with water (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic phase was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **83** (8.5 mg, solid, 10%).

MS m/z (ESI): 430 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.70 (s, 1H), 7.44 (s, 1H), 3.92 (d, *J* = 11.6 Hz, 2H), 3.77 (s, 3H), 3.73 (d, *J* = 11.3 Hz, 2H), 3.57 (d, *J* = 10.4 Hz, 2H), 3.40 (d, *J* = 10.4 Hz, 2H), 2.31 (s, 3H), 1.14 (s, 6H).

Example 84. 5-Chloro-4-((3aR,6aS)-5-(cyclopropylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



Step 1. (3aR,6aS)-2-benzyl-5-(2,5-dichloropyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (84a)

To a solution of **51d** (400 mg, 1.74 mmol) in MeCN (10 mL) were added potassium carbonate (720 mg, 5.22 mmol) and 2,4,5-trichloropyrimidine (410 mg, 2.26 mmol). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 3/2) to give the title compound **84a** (200 mg, 31%).

MS m/z (ESI): 377 [M+1]

Step 2. (3aR,6aS)-2-(2,5-dichloropyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (84b)

To a solution of **84a** (0.2 g, 0.53 mmol) in CH_2Cl_2 (10 mL) was added 1-chloroethyl chloroformate (226 mg, 1.59 mmol). The mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and then added with MeOH (10 mL). The mixture was heated to reflux for another 2 h and then cooled to room temperature. The mixture was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 9/1) to give the title compound **84b** (140 mg, 92%).

MS m/z (ESI): 287 [M+1]

Step 3. (3aR,6aS)-2-(cyclopropylmethyl)-5-(2,5-dichloropyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (84c)

A mixture of (bromomethyl)cyclopropane (56.3 mg, 0.42 mmol), **84b** (60 mg, 0.21 mmol), potassium carbonate (87 mg, 0.63 mmol) in MeCN (4 mL) was heated to 50°C and stirred for 16 h. After cooling to room temperature, the mixture was concentrated to dryness

under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 2/3) to give the title compound **84c** (50 mg, 70%).

MS m/z (ESI): 341 [M+1]

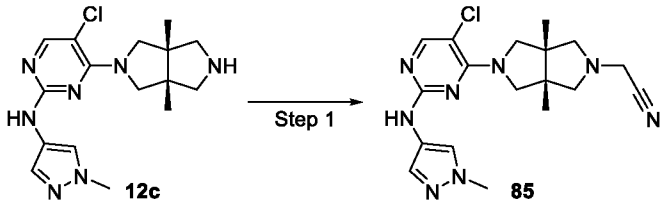
Step 4. 5-Chloro-4-((3aR,6aS)-5-(cyclopropylmethyl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (84)

A mixture of **84c** (50 mg, 0.147 mmol), 1-methyl-1H-pyrazol-4-amine (21 mg, 0.122 mmol) and pTsOH (55 mg, 0.284 mmol) in isopropanol (2 mL) was heated to 100°C and stirred for 4 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **84** (16.4 mg, solid, 28%).

MS m/z (ESI): 402 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.70 (s, 1H), 7.45 (s, 1H), 3.98 (d, J = 10.9 Hz, 2H), 3.77 (s, 3H), 3.56 (d, J = 11.2 Hz, 2H), 2.82 (s, 2H), 2.32 (d, J = 63.4 Hz, 4H), 1.07 (s, 6H), 0.79 (s, 1H), 0.41 (d, J = 6.1 Hz, 2H), 0.05 (s, 2H).

Example 85. 2-((3aR,6aS)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetonitrile



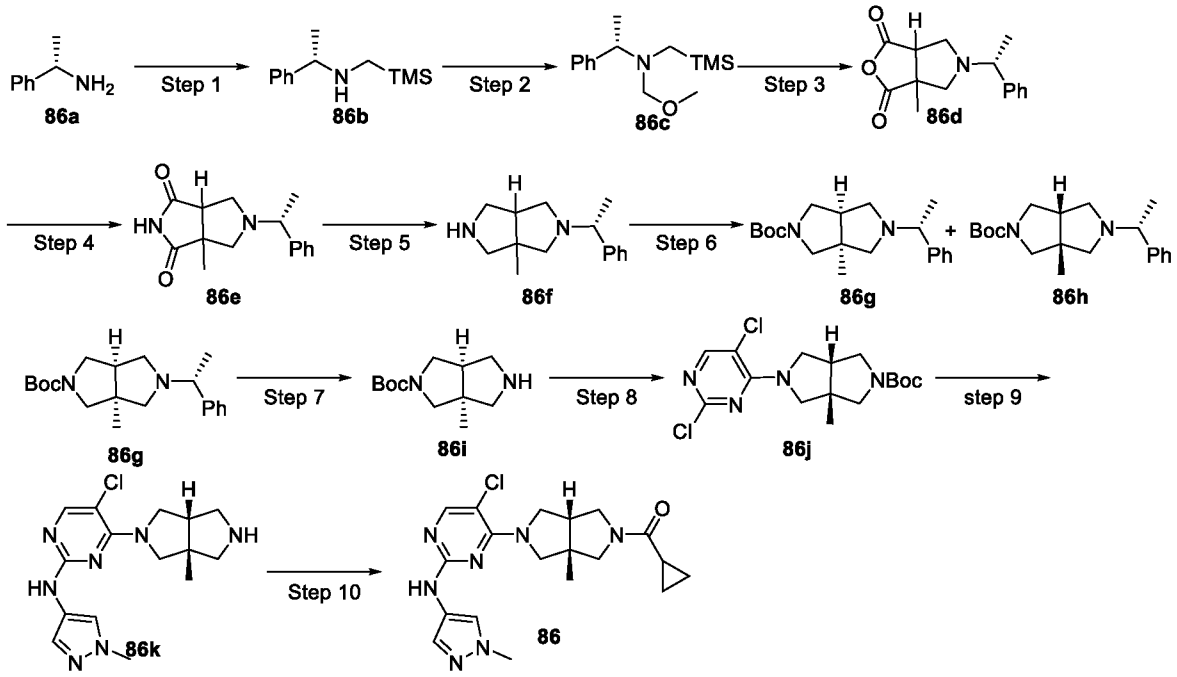
A mixture of **12c** (42 mg, 0.115 mmol), 2-bromoacetonitrile (30 mg, 0.23 mmol), TEA (50 mg, 0.46 mmol) in THF (1 mL) was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **85** (16 mg, solid, 34%).

MS m/z (ESI): 402 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 4.00 (d, J = 11.3 Hz, 2H), 3.80 (s, 2H), 3.77 (s, 3H), 3.56 (d, J = 11.3 Hz, 2H), 2.85 (d, J = 9.2 Hz, 2H), 2.55 (d, J = 9.3 Hz, 2H), 1.09 (s, 6H).

Example 86. ((3aS,6aR)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-

yl)(cyclopropyl)methanone



Step 1. (S)-1-Phenyl-N-((trimethylsilyl)methyl)ethan-1-amine (86b)

A mixture of (chloromethyl)trimethylsilane (20.24 g, 165 mmol), **86a** (20 g, 165 mmol) and TEA (20 g, 165 mmol) was heated to reflux for 16 h. After cooling to room temperature, the mixture was added with n-heptane (500 mL), stirred and filtered. The filtrate was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/20) to give the title compound **86b** (26 g, 76%).

MS m/z (ESI): 208 [M+1]

Step 2. (S)-N-(methoxymethyl)-1-phenyl-N-((trimethylsilyl)methyl)ethan-1-amine (86c)

To a 37% formaldehyde aqueous solution (6.6 g, 81.49 mmol) at 0°C was added **86b** (13.0 g, 62.68 mmol). The mixture was stirred at 0°C for 0.5 h and then added with MeOH (3.4 g, 106.56 mmol) and potassium carbonate (8.7 g, 62.68 mmol). The mixture was stirred at 0°C for another 2 h, added with water (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by distillation to give the title compound **86c** (6.816 g, 43%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.35 - 7.30 (m, 4H), 7.23 (s, 1H), 4.18 (d, *J* = 9.3 Hz, 1H), 3.99 (d, *J* = 9.3 Hz, 1H), 3.90 (d, *J* = 6.8 Hz, 1H), 3.14 (s, 3H), 2.06 (q, *J* = 14.4 Hz, 2H), 1.33 (d, *J* = 6.8 Hz, 3H), 0.00 (s,9H).

Step 3. Cis-3a-methyl-5-((R)-1-phenylethyl)tetrahydro-1H-furo[3,4-c]pyrrole-1,3(3aH)-dione (86d)

To a solution of **86c** (6.62 g, 26.34 mmol) in CH_2Cl_2 (25 mL) at 0°C was added a solution of 3-methylfuran-2,5-dione (2.95 g, 26.34 mmol) in CH_2Cl_2 (10 mL), followed by addition of a solution of TFA (0.3 g, 2.63 mmol) in CH_2Cl_2 (5 mL) dropwise. The resulting mixture was stirred for 6 h and then concentrated to dryness under vacuum to give the title compound **86d** (6.83 g). The crude product was used directly in the next step without further purification.

MS m/z (ESI): 260 [M+1]

Step 4. Cis- 3a-methyl-5-((R)-1-phenylethyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (86e)

To a solution of **86d** (6.83 g, 26.34 mmol) in THF (30 mL) was added ammonium hydroxide (30 mL). The resulting mixture was heated to 100°C in sealed tube and stirred for 3 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/2) to give the title compound **86e** (4.30 g, 63%).

MS m/z (ESI): 259 [M+1]

Step 5. Cis-3a-methyl-2-((R)-1-phenylethyl)octahydropyrrolo[3,4-c]pyrrole (86f)

To a solution of **86e** (4.3 g, 16.65 mmol) in THF (80 mL) at 0°C was added LAH (1.90 g, 49.95 mmol) in batches. The mixture was heated to 70°C and stirred for 2 h. After cooling to 0°C, the mixture was quenched with saturated sodium sulfate solution (20 mL) and filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **86f** (3.62 g, 94%).

MS m/z (ESI): 231 [M+1]

Step 6. Tert-butyl (3aS,6aR)-3a-methyl-5-((R)-1-phenylethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (86g) and tert-butyl (3aR,6aS)-3a-methyl-5-((R)-1-phenylethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (86h)

To a solution of **86f** (3.62 g, 15.73 mmol) in CH_2Cl_2 (40 mL) at 0°C were added TEA (3.18 g, 31.46 mmol) and a solution of di-tert-butyl pyrocarbonate (4.12 g, 18.88 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h, added with water (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography(petroleum ether/ethyl acetate = 20/1) to give the title compound **86g** (1.89 g) and **86h** (1.65 g), as well as a mixture of **86g** and **86h** (1.04 g). The total yield of

86g and **86h** was 88%.

Tert-butyl (3aS,6aR)-3a-methyl-5-((R)-1-phenylethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate **86g**:

MS m/z (ESI): 331 [M+1]

5 ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (d, J = 4.5 Hz, 4H), 7.21 (d, J = 4.2 Hz, 1H), 3.57 - 3.48 (m,1H), 3.25 (d, J = 10.8 Hz, 1H), 3.22 - 3.14 (m, 2H), 3.06 (d, J = 10.8 Hz, 1H), 2.54 (dd, J = 5.5, 3.8 Hz, 2H), 2.35 (d, J = 9.1 Hz, 1H), 2.18 (s, 1H), 2.12 (d, J = 9.1 Hz, 1H), 1.40 (s, 9H), 1.24 (d, J = 6.5 Hz, 3H), 1.08 (s, 3H).

Tert-butyl (3aR,6aS)-3a-methyl-5-((R)-1-phenylethyl)hexahydropyrrolo[3,4-c]pyrrole-
10 2(1H)-carboxylate **86h**:

MS m/z (ESI): 331 [M+1]

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.29 (d, J = 4.4 Hz, 4H), 7.21 (d, J = 4.3 Hz, 1H), 3.49 - 3.41 (m, 1H), 3.34 (d, J = 10.9 Hz, 1H), 3.20 (d, J = 6.6 Hz, 1H), 3.10 (dd, J = 11.3, 3.5 Hz, 1H), 3.06 (d, J = 11.0 Hz, 1H), 2.65 (s, 1H), 2.57 (d, J = 8.9 Hz, 1H), 2.18 (d, J = 3.5
15 Hz, 1H), 2.16 (s, 2H), 1.39 (s, 9H), 1.24 (d, J = 6.5 Hz, 3H), 1.11 (s, 3H).

Step 7. Tert-butyl (3aS,6aR)-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (86i)

To a solution of **86g** (1.89 g, 5.72 mmol) in MeOH (50 mL) was added 10% Pd/C (0.19 g). Twhe mixture was stirred under hydrogen for 12 h and then concentrated to dryness under
20 vacuum to give the title compound **86i** (1.30 g, 100%).

MS m/z (ESI): 227 [M+1]

Step 8. Tert-butyl (3aS,6aR)-5-(2,5-dichloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (86j)

To a solution of **86i** (1.3 g, 5.73 mmol) in MeCN (40 mL) were added DIEA (1.48 g,
25 11.46 mmol) and 2,4,5-trichloropyrimidine (1.05 g, 5.73 mmol). The mixture was stirred for 2 h and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7/3) to give the title compound **86j** (1.83 g, 86%).

MS m/z (ESI): 373 [M+1]

30 Step 9. 5-Chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-((3aR,6aS)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine (86k)

To a solution of **86j** (1.83 g, 4.91 mmol) in isopropanol (30 mL) were added 1-methyl-1H-pyrazol-4-amine hydrochloride (656 mg, 4.91 mmol) and pTsOH (93 mg, 0.49 mmol). The mixture was heated to 100°C and stirred for 12 h. After cooling to room temperature, the

reaction mixture was filtered and the filter cake was collected to give the title compound **86k** (1.28 g, 82%) as an HCl salt.

MS m/z (ESI): 334 [M+1]

Step 10. ((3aS,6aR)-5-(5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (86)

To a solution of **86k** (100 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) were added cyclopropanecarboxylic acid (23 mg, 0.27 mmol) and DIEA (175 mg, 1.35 mmol). The mixture was stirred for 10 min and then added with HATU (205 mg, 0.54 mmol). The mixture was stirred for another 2 h, added with water (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic phase was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **86** (64.3 mg, solid, 59%).

MS m/z (ESI): 402 [M+1]

Specific rotation $[\alpha]_D^{20}$ = -9.2°×dm^2/kg

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 4.04 (s, 1H), 3.95 (dd, J = 10.7, 7.7 Hz, 1H), 3.88 - 3.80 (m, 1H), 3.78 (s, 3H), 3.75 - 3.69 (m, 1H), 3.65 (dd, J = 13.6, 6.6 Hz, 1H), 3.58 (dd, J = 12.7, 8.0 Hz, 1H), 3.44 (d, J = 12.2 Hz, 1H), 3.28 (s, 1H), 2.69 - 2.60 (m, 1H), 1.73 (dd, J= 13.0, 6.2 Hz, 1H), 1.23 (d, J = 12.9 Hz, 3H), 0.77 - 0.66 (m, 4H).

Example 87, 88, 89, 90 and 91 were synthesized according to the procedure for Example 86 except that in Step 7, different compounds were used instead of **86g**, and in Step 10, different compounds were used instead of cyclopropanecarboxylic acid.

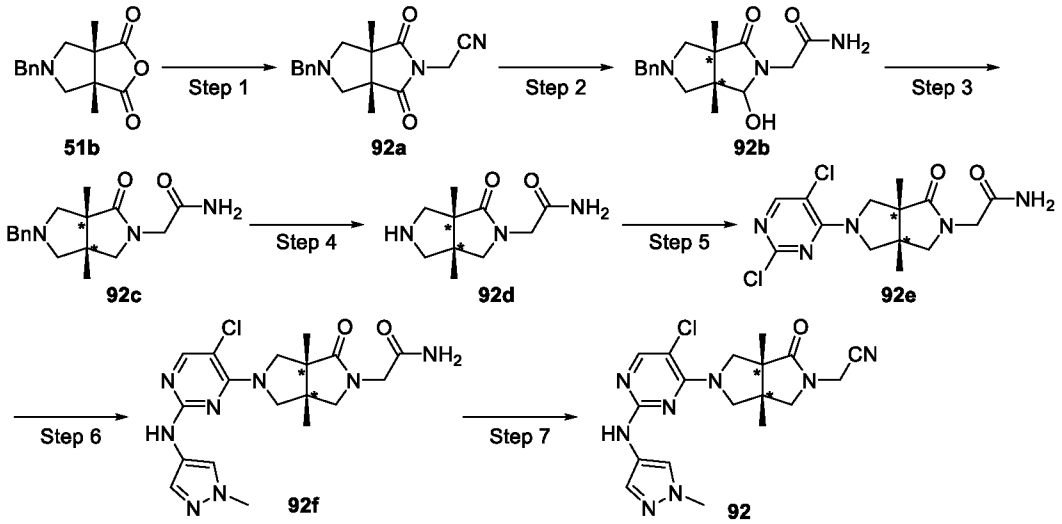
Example	Compound replacing **86g**	Compound replacing cyclopropanecarboxylic acid
87	**86h**	cyclopropanecarboxylic acid
88	**86g**	2-cyanoacetic acid
89	**86h**	2-cyanoacetic acid
90	**86g**	(S)-2,2-difluorocyclopropane-1-carboxylic acid
91	**86h**	(S)-2,2-difluorocyclopropane-1-carboxylic acid

The characterization data of Example 87, 88, 89, 90 and 91 are shown below

Example	^{1}H NMR	MS m/z (ESI)	$[\alpha]_D^{20}$ (°×dm^2/kg)
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 4.04 (s, 1H), 3.95 (d, J = 3.0 Hz, 1H), 3.83 (s, 1H), 3.78 (s, 3H), 3.75 - 3.69 (m, 1H),	402 [M+1]	+9.1

methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**87**)	3.68 - 3.61 (m, 1H), 3.61 - 3.54 (m, 1H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.29 - 3.23 (m, 1H), 2.66 (d, *J* = 11.2 Hz, 1H), 1.73 (dd, *J* = 13.2, 6.4 Hz, 1H), 1.23(d, *J* = 12.9 Hz, 3H), 0.77 - 0.66 (m, 4H).		
3-((3aS,6aR)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (**88**)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 4.03 (d, *J* = 5.3 Hz, 1H), 3.92 (d, *J* = 3.1 Hz, 2H), 3.86 (d, *J* = 11.4 Hz, 1H),3.81 (d, *J* = 11.1 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 1H), 3.64 (dd, *J* = 12.1, 6.9 Hz, 1H), 3.49 (dd, *J* = 28.2, 11.3 Hz, 1H), 3.37 (s, 1H), 3.33 (d, *J* = 10.1 Hz, 1H), 2.61(s, 1H), 1.21 (d, *J* = 3.1 Hz, 3H).	401 [M+1]	-12
3-((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (**89**)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 4.03 (d, *J* = 4.9 Hz, 1H), 3.92 (d, *J* = 3.1 Hz, 2H), 3.84 (dd, *J* = 18.6, 11.3Hz, 1H), 3.78 (s, 3H), 3.71 (d, *J* = 7.8 Hz, 1H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.65 - 3.60 (m, 1H), 3.49 (dd, *J* = 28.1, 11.3 Hz, 1H), 3.37 (s, 1H), 3.33 (d, *J* = 10.7 Hz,1H), 2.61 (s, 1H), 1.25 - 1.18 (m, 3H).	401 [M+1]	+12
((3aS,6aR)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone (**90**)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 4.04 (s, 1H), 3.82 (s, 1H), 3.77 (d, *J* = 3.0 Hz, 3H), 3.72 (dd, *J*= 16.5, 5.8 Hz, 2H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.63 (s, 1H), 3.49 (d, *J* = 12.4 Hz, 1H), 3.34 (d, *J* = 5.4 Hz, 1H), 2.93 (dd, *J* = 15.4, 9.6 Hz, 1H), 2.67 (s, 1H), 1.89(dd, *J* = 21.7, 16.7 Hz, 2H), 1.23 (d, *J* = 16.9 Hz, 3H).	438 [M+1]	+27
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)((S)-2,2-difluorocyclopropyl)methanone (**91**)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.43 (d, *J* = 4.8 Hz, 1H), 4.06 (s, 1H), 3.89 (s, 1H), 3.85 - 3.79 (m, 1H), 3.77 (d, *J* = 3.6Hz, 3H), 3.73 - 3.62 (m, 2H), 3.47 (d, *J* = 12.4 Hz, 1H), 3.41 (d, *J* = 10.6 Hz, 1H), 3.38 - 3.31 (m, 1H), 2.93 (d, *J* = 10.1 Hz, 1H), 2.63 (dd, *J* = 23.4, 18.8 Hz,1H), 1.91 (s, 2H), 1.24 (d, *J* = 4.0 Hz, 3H).	438 [M+1]	+40

Example 92. Cis-2-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetonitrile



Step 1. 2-((3aR,6aS)-5-Benzyl-3a,6a-dimethyl-1,3-dioxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetonitrile (92a)

To a mixture of **51b** (1.5 g, 5.4 mmol) and 2-aminoacetonitrile (500 mg, 5.4 mmol) in 1,2-dichloroethane (6 mL) was added TEA (1.6 g, 16.2 mmol). The resulting solution was heated to 60°C and stirred for 12 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **92a** (1 g, 62%).

MS m/z (ESI): 298 [M+1]

Step 2. Cis-2-(5-benzyl-1-hydroxy-3a,6a-dimethyl-3-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetamide (92b)

To a solution of **92a** (800 mg, 2.7 mmol) in EtOH (10 mL) at 0°Cwas added sodium borohydride (260 mg, 6.7 mmol). The mixture was heated to reflux for 12 h. After cooling to room temperature, the residue was concentrated to dryness under vacuum. The residue was diluted with CH_2Cl_2 (10 mL) and filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **92b** (900 mg). The crude product was used directly in next step without further purification.

MS m/z (ESI): 318 [M+1]

Step 3. Cis-2-(5-Benzyl-3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetamide (92c)

To a solution of **92b** (900 mg, crude product) in TFA (8 mL) was added triethylsilane (4mL). The solution was heated to 120°C in a sealed tube and stirred for 48 h. After cooling

to room temperature, the solution was concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **92c** (130 mg, 16% over two steps).

MS m/z (ESI): 302 [M+1]

Step 4. Cis-2-(3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetamide (92d)

To a solution of **92c** (130 mg, 0.42 mmol) in MeOH (5 mL) was added 10% Pd/C (50 mg). The mixture was stirred under hydrogen for 3 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **92d** (90 mg, 100%).

MS m/z (ESI): 212 [M+1]

Step 5. Cis-2-(5-(2,5-dichloropyrimidin-4-yl)-3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetamide (92e)

A mixture of **92d** (90 mg, 0.42 mmol), 2,4,5-trichloropyrimidine (91 mg, 0.5 mmol) and DIEA (0.3 mL) in MeCN (2 mL) was heated to 50°C and stirred for 12 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **92e** (150 mg, 99%).

MS m/z (ESI): 358 [M+1]

Step 6. Cis-2-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetamide (92f)

A mixture of **92e** (100 mg, 0.26 mmol), 1-methyl-1H-pyrazol-4-amine hydrochloride (40 mg, 0.29 mmol) and pTsOH (6 mg, 0.026 mmol) in isopropanol (4 mL) was heated to 120°C and stirred for 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum to give the title compound **92f** (150 mg). The crude product was used directly in the next step without further purification.

MS m/z (ESI): 419 [M+1]

Step 7. Cis-2-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethyl-1-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetonitrile (92)

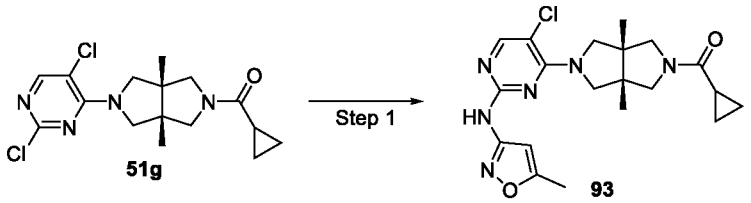
A mixture of **92f** (150 mg, crude product) in trichlorophosphorus oxide (2 mL) was heated to 100°C for 12 h while stirring. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and dissolved in MeCN (5 mL) to which was added slowly TEA until pH = 7. The mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **92** (15 mg, solid, 14% over two steps).

MS m/z (ESI): 401 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (brs, 1H), 7.91 (s, 1H), 7.70 (s, 1H), 7.44 (s, 1H),

4.44 (s, 2H), 4.15 (d, J = 11.4 Hz, 1H), 3.81 (d, J = 11.8 Hz, 1H), 3.78 (s, 3H), 3.70 (d, J = 11.8 Hz, 1H), 3.65 (d, J = 12.1 Hz, 1H), 3.43 (d, J = 10.0 Hz, 1H), 3.34 (d, J = 4.8 Hz, 1H), 1.18 (s, 3H), 1.09 (s, 3H).

Example 93. ((3aR,6aS)-5-(5-chloro-2-((5-methylisoxazol-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone



To a solution of **51g** (0.25 g, 0.71 mmol) and 5-methylisoxazol-3-amine (83 mg, 0.85 mmol) in isopropanol (6 mL) was added pTsOH (270 mg, 1.42 mmol). The mixture was stirred at 100°C for 18 h and then cooled to room temperature. The mixture was concentrated to dryness under vacuum and the residue was purified by prep-HPLC to give the title compound **93** (51.3 mg, solid, 17%).

MS m/z (ESI): 417 [M+1]

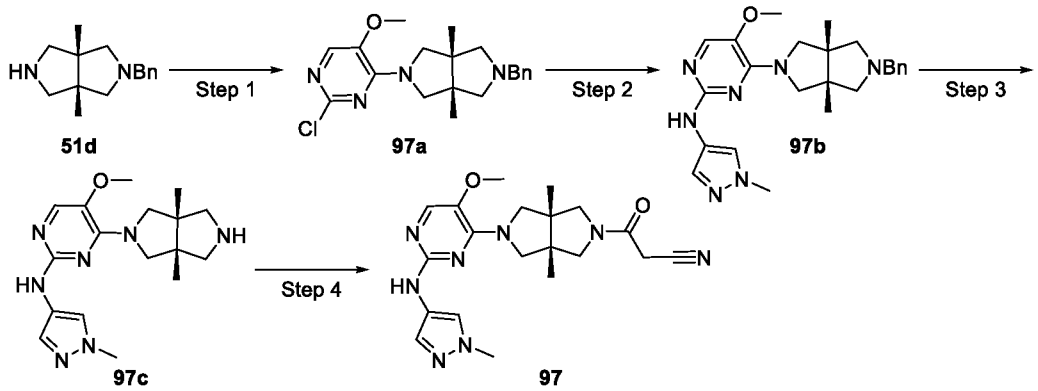
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.97 (s, 1H), 6.65 (s, 1H), 3.92 – 3.66 (m, 5H), 3.59 (d, J = 10.7 Hz, 1H), 3.47 (d, J = 12.3 Hz, 1H), 3.29 (d, J =12.5 Hz, 1H), 2.36 (s, 3H), 1.76 - 1.64 (m, 1H), 1.10 (d, J = 12.9 Hz, 6H), 0.77 - 0.65 (m, 4H).

Example 94 and 95 were synthesized according to the procedure for Example 93 except that in Step 1, different compounds were used instead of 5-methylisoxazol-3-amine.

Example	Compound replacing 5-methylisoxazole-3-amine	^{1}H NMR	MS m/z (ESI)
((3aR,6aS)-5-(5-chloro-2-((1-methyl-1H-pyrazol-3-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**94**)	1-methyl-1H-pyrazol-3-amine	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.90 (s, 1H), 7.51 (d, J = 2.1 Hz, 1H), 6.47 (d, J = 2.2 Hz, 1H), 3.92 - 3.65 (m, 8H), 3.59 (d, J = 10.7 Hz, 1H), 3.45 (d, J = 12.3 Hz, 1H), 3.31 (d, J = 4.9 Hz, 1H), 1.70 (dd, J = 12.0, 6.0 Hz, 1H), 1.10 (d, J = 13.2 Hz, 6H), 0.77 - 0.62 (m, 4H).	416 [M+1]
((3aR,6aS)-5-(2-((1H-pyrazol-3-yl)amino)-5-chloropyrimidin-4-yl)-3a,6a-	1H-pyrazol-3-amine	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 2.7 Hz, 1H), 8.12 (s, 1H), 5.78 (d, J = 2.7 Hz, 1H), 5.27 (s, 2H), 3.91 (t, J = 11.9 Hz,	402 [M+1]

dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(cyclopropyl)methanone (**95**)		2H), 3.78 (dd, *J* = 22.8, 10.7 Hz, 3H), 3.59 (d, *J* = 10.7 Hz, 1H), 3.47 (d, *J* = 12.3 Hz, 1H), 3.29 (d, *J* = 12.4 Hz, 1H), 1.71 (ddd, *J* = 12.7, 10.9, 6.9 Hz, 1H), 1.11 (d, *J* = 13.5 Hz, 6H), 0.71 (dd, *J* = 8.7, 4.8 Hz, 4H).	

Example 97. 3-((3aR,6aS)-5-(5-Methoxy-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. (3aR,6aS)-2-Benzyl-5-(2-chloro-5-methoxypyrimidin-4-yl)-3a,6a-dimethyloctahydropyrrolo[3,4-c]pyrrole (97a)

To a solution of **51d** (0.26 g, 1.13 mmol) in MeCN (10 mL) were added potassium carbonate (0.47 g, 3.39 mmol) and 2,4-dichloro-5-methoxypyrimidine (0.263 mg, 1.47 mmol). The mixture was stirred for 2 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100/0 to 0/100) to give the title compound **97a** (70 mg, 20%).

MS m/z (ESI): 373 [M+1]

Step 2. 4-((3aR,6aS)-5-Benzyl-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-methoxy-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (97b)

A mixture of **97a** (70 mg, 0.188 mmol), 1-methyl-1H-pyrazol-4-amine (27.3 mg, 0.182 mmol) and pTsOH (71.4 mg, 0.376 mmol) in n-butanol (5 mL) was stirred at 120°C for 8 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 9/1) to give the title compound **97b** (70 mg, 86%).

MS m/z (ESI): 434 [M+1]

Step 3. 4-((3aR,6aS)-3a,6a-Dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-

methoxy-N-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (97c)

To a solution of **97b** (70 mg, 0.16 mmol) in MeOH (5 mL) was added 10% Pd/C (34 mg, 0.32 mmol). The mixture was stirred under hydrogen for 3 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **97c** (50 mg, 91%).

MS m/z (ESI): 344 [M+1]

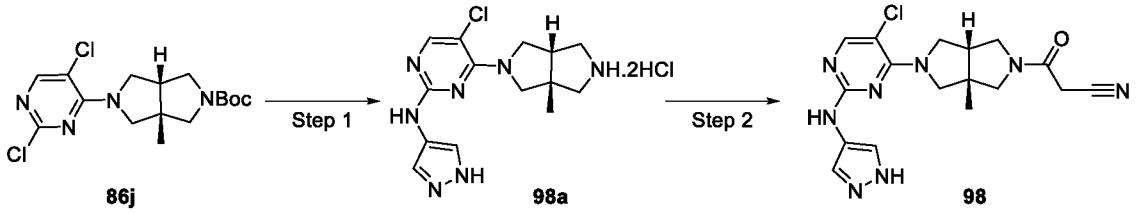
Step 4. 3-((3aR,6aS)-5-(5-Methoxy-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a,6a-dimethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (97)

To a mixture of **97c** (50 mg, 0.146 mmol), 2-cyanoacetic acid (25 mg, 0.292 mmol), DIEA (38 mg, 0.292 mmol) in DMF (1 mL) was added HATU (67 mg, 0.175 mmol). The mixture was stirred for 1 h and then purified by prep-HPLC to give the title compound **97** (31.9 mg, solid, 53%).

MS m/z (ESI): 411[M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.70 (s, 1H), 7.67 (s, 1H), 7.41 (s, 1H), 3.91 (d, J = 1.1 Hz, 2H), 3.82 - 3.71 (m, 5H), 3.66 (s, 3H), 3.63 - 3.52 (m, 3H), 3.47 (d, J = 12.2 Hz, 1H), 3.39 (d, J = 10.5 Hz, 1H), 3.31 (d, J = 5.3 Hz, 1H), 1.07 (t, J = 7.5 Hz, 6H).

Example 98. 3-((3aS,6aR)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. 5-Chloro-4-((3aR,6aS)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-(1H-pyrazol-4-yl)pyrimidin-2-amine dihydrochloride (98a)

To a solution of **86j** (4.00 g, 10.72 mmol) in EtOH (50 mL) were added 1H-pyrazol-4-amine (1.16 g, 13.94 mmol) and pTsOH monohydrate (0.21 g, 1.07 mmol). The mixture was heated to 70°C and stirred for 16 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum and added with a solution of HCl (10 N in ethanol, 50 mL). The mixture was heated to 50°C and stirred for another 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum, and added with a mixture of methanol and 2-methoxy-2-methylpropane (60 mL, 1/1 v/v). The resulting mixture was stirred for 30 min and then filtered. The filter cake was collected and dried to give the title compound **98a** (3.4 g, 81%) as an HCl salt.

MS m/z (ESI): 320 [M+1]

Step 2. 3-((3aS,6aR)-5-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile hemiformate (98)

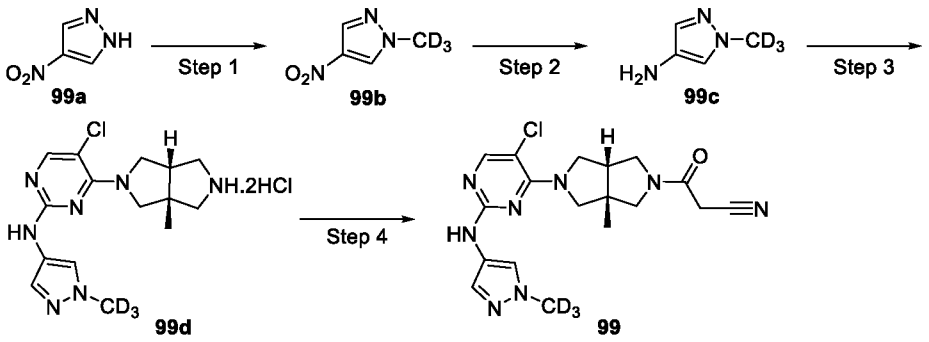
To a solution of **98a** (3.30 g, 8.40 mmol) in methanol (40 mL) were added ethyl cyanoacetate (1.90 g, 16.80 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.10 g, 33.60 mmol). The mixture was stirred for 5 h and concentrated to dryness under vacuum. The residue was purified by prep-HPLC to give the title compound **98** (1.04 g, solid, 30%) as a formic acid salt.

MS m/z (ESI): 387 [M+1]

Specific rotation $[\alpha]_D^{20}$ = -4.6°×dm^2/kg

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1.5H), 9.07 (s, 1H), 8.13 (s, 0.5H), 7.89 (s, 1H), 7.65 (s, 2H), 4.09 - 3.99 (m, 1H), 3.92 (d, J = 2.7 Hz, 2H), 3.84 (dd, J = 26.5, 11.3 Hz, 1H), 3.76 - 3.72 (m, 1H), 3.69 (d, J = 11.1 Hz, 1H), 3.64 (dd, J = 12.5, 7.3 Hz, 1H), 3.49 (dd, J = 22.9, 11.3 Hz, 1H), 3.38 (dd, J = 15.7, 7.9 Hz, 1H), 3.29 (d, J = 12.3 Hz, 1H), 2.57 (d, J = 33.9 Hz, 1H), 1.21 (d, J = 2.7 Hz, 3H).

Example 99. 3-((3aS,6aR)-5-(5-Chloro-2-((1-(methyl-d3)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. 1-(Methyl-d_3)-4-nitro-1H-pyrazole (99b)

To a solution of 4-nitro-1H-pyrazol **99a** (2.5 g, 22.11 mmol) in MeCN (20 mL) were added iodomethane-d_3 (3.85 g, 26.53 mmol) and potassium carbonate (4.58 g, 33.17 mmol). The mixture was heated to 70°C and stirred for 12 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum. The residue was added with water (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 4/1) to

give the title compound **99b** (2.50 g, 87%).

MS m/z (ESI): 131 [M+1]

Step 2. 1-(Methyl-d_3)-1H-pyrazol-4-amine (99c)

To a solution of **99b** (2.50 g, 19.2 mmol) in MeOH (30 mL) was added 10% Pd/C (0.5 g) . The mixture was stirred under hydrogen for 16 h and then filtered. The filtrate was concentrated to dryness under vacuum to give the title compound **99c** (1.92 g, 100%).

MS m/z (ESI): 101 [M+1]

Step 3. 5-Chloro-N-(1-(methyl-d_3)-1H-pyrazol-4-yl)-4-((3aR,6aS)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine dihydrochloride (99d)

To a solution of **86j** (3.00 g, 8.04 mmol) in EtOH (50 mL) were added **99c** (1.05 g, 10.45 mmol) and pTsOH monohydrate (0.15 g, 0.80 mmol). The mixture was heated to 70°C and stirred for 8 h. After cooling to room temperature, the mixture was added with an ethanol solution of HCl (10 N, 50 mL). The mixture was heated to 50°C again and stirred for 1 h. After cooling to room temperature, the mixture was concentrated to dryness under vacuum. The residue was added with a mixture of methanol and 2-methoxy-2-methylpropane (60 mL, 1/1 v/v). After stirring for 30 min, the mixture was filtered. The filter cake was collected and dried to give the title compound **99d** (3.3 g, 100%) as an HCl salt.

MS m/z (ESI): 337 [M+1]

Step 4. 3-((3aS,6aR)-5-(5-Chloro-2-((1-(methyl-d_3)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (99)

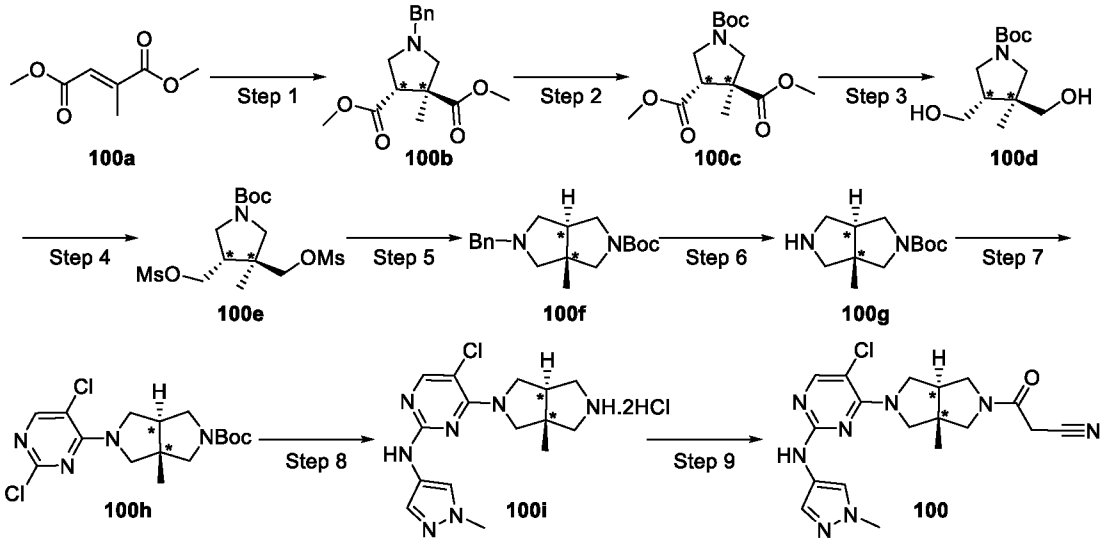
To a mixture of **99d** (3.30 g, 8.05 mmol) in MeCN (35 mL) were added ethyl cyanoacetate (1.82 g, 16.10 mmol) and DBU (4.90 g, 32.2 mmol). The mixture was heated to 30°C and stirred for 4 h. The mixture was concentrated to dryness under vacuum and then added with EtOH (20 mL). After stirring for 1 h, the mixture was filtered and the filter cake was collected to give the title compound **99** (2.60 g, solid, 80%).

MS m/z (ESI): 404 [M+1]

Specific rotation $[\alpha]_D^{20}$ = -7.2°×dm^2/kg

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 4.03 (dd, J = 11.2, 5.9 Hz, 1H), 3.93 (d, J = 3.0 Hz, 2H), 3.84 (dd, J = 18.6, 11.5 Hz, 1H), 3.73 (d, J = 10.2 Hz, 1H), 3.69 (s, 1H), 3.64 (dd, J = 12.1, 7.1 Hz, 1H), 3.49 (dd, J = 27.8, 11.2 Hz, 1H), 3.42 - 3.33 (m, 1H), 3.33 - 3.24 (m, 1H), 2.57 (d, J = 31.9 Hz, 1H), 1.20 (t, J = 8.1 Hz, 3H).

Example 100. Trans-3-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile



Step 1. Dimethyl trans-1-benzyl-3-methylpyrrolidine-3,4-dicarboxylate (100b)

To a mixture of dimethyl 2-methylfumarate **100a** (9.63 g, 60.89 mmol) and TFA (0.69 g, 6.09 mmol) in CH_2Cl_2 (10 mL) at 0°C was added slowly a solution of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (17.35 g, 73.07 mmol) in CH_2Cl_2 (200 mL). After addition, the resulting yellow solution was gradually warmed to room temperature within 16 h, and then added with a saturated sodium bicarbonate aqueous solution (200 mL) and CH_2Cl_2 (200 mL). The mixture was stirred for 15 min. The separated organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness under vacuum to give a residue which was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/3) to give the title compound **100b** (17.74 g, 100%).

MS m/z (ESI): 292 [M+1]

Step 2. 1-(Tert-butyl) 3,4-dimethyl trans-3-methylpyrrolidine-1,3,4-tricarboxylate (100c)

To a mixture of **100b** (17.74 g, 60.79 mmol) and di-tert-butyl pyrocarbonate (14.62 g, 66.67 mmol) in MeOH (200 mL) was added 10% Pd/C (1.8 g). The resulting mixture was heated to 50°C under hydrogen and stirred for 20 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give the title compound **100c** (18.00 g, 98%).

MS m/z (ESI): 202 [M+1-100]

Step 3. Tert-butyl trans-3,4-bis(hydroxymethyl)-3-methylpyrrolidine-1-carboxylate (100d)

To a solution of **100c** (18.00 g, 22.75 mmol) in THF (200 mL) at 0°Cwas add a solution of lithium borohydride (2M in THF, 65 mL, 131.41 mmol). After stirring for 30 min, the mixture was gradually warmed to room temperature and stirred for additional 16 h. The mixture was cooled to 0°C again and added slowly with 1 N HCl until the pH was 1. The resulting solution was extracted with CH_2Cl_2 (400 mL). The organic phase was washed with water and brine in sequence, dried it over anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give the title compound **100d** (14.00 g, 96%).

MS m/z (ESI): 190 [M+1-56]

Step 4. Tert-butyl trans-3-methyl-3,4-bis(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (100e)

To a solution of **100d** (14.00 g, 57.07 mmol) and DIEA (44.00 g, 342.41 mmol) in CH_2Cl_2 (200 mL) at 0°C was added MsCl (20.00 g, 171.21 mmol) dropwise. The mixture was stirred for 1 h and then added with a saturated ammonium chloride aqueous solution (100 mL) and CH_2Cl_2 (200 mL). The mixture was stirred for 10 min and allowed to stand. The separated organic layer was washed with saturated brine and saturated sodium bicarbonate solution in sequence, dried over anhydrous sodium sulfate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give the title compound **100e** (8.00 g, 35%).

MS m/z (ESI): 346 [M+1-56]

Step 5. Tert-butyl trans-5-benzyl-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (100f)

A mixture of **100e** (8.00 g, 19.93 mmol), TEA (12.10 g, 119.55 mmol) and benzylamine (8.54 g, 79.72 mmol) in toluene (100 mL) was heated to reflux for 16 h. After cooling to room temperature, the reaction mixture was added with 1 N NaOH (100 mL) and saturated brine. The mixture was stirred for 10 min and the separated organic phase was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated to dryness under vacuum and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give the title compound **100f** (3.00 g, 48%).

MS m/z (ESI): 317 [M+1]

Step 6. Tert-butyl trans-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate

(100g)

To a solution of **100f** (3.00 g, 9.48 mmol) in MeOH (100 mL) was added 20% Pd/C (0.6 g). The mixture was heated to 50°C under hydrogen and stirred for 12 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated to dryness under vacuum to give the title compound **100g** (2.15 g, 100%).

MS m/z (ESI): 227 [M+1]

Step 7. Tert-butyl trans-5-(2,5-dichloropyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (100h)

To a solution of **100g** (2.15 g, 9.50 mmol) in ethyl acetate (40 mL) at 0°C were added DIEA (1.47 g, 11.40 mmol) and 2,4,5-trichloropyrimidine (1.74 g, 9.50 mmol). The mixture was stirred for 1 h and then concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/3) to give the title compound **100h** (3.30 g, 93%).

MS m/z (ESI): 373 [M+1]

Step 8. Trans- 5-chloro-N-(1-methyl-1H-pyrazol-4-yl)-4-(3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-amine dihydrochloride (100i)

To a solution of **100h** (3.30 g, 8.84 mmol) in ethanol (40 mL) were added 1-methyl-1H-pyrazol-4-amine hydrochloride (1.54 g, 11.49 mmol) and pTsOH monohydrate (0.17 g, 0.88 mmol). The mixture was heat to 70°C and stirred for 16 h. After cooling to room temperature, the mixture was concentrated to dryness and added with a mixture of 2-methoxy-2-methylpropane and methanol (40 mL, 1/1 v/v). After stirring for 30 min, the mixture was filtered and the filter cake was collected to give the title compound **100i** (3.15 g, 88%) as an HCl salt.

MS m/z (ESI): 334 [M+1]

Step 9. Trans-3-(5-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3a-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-oxopropanenitrile (100)

A mixture of **100i** (2.00 g, 4.92 mmol) in acetonitrile (40 mL) were added ethyl 2-cyanoacetate (1.11 g, 9.84 mmol) and DBU (3.74 g, 24.60 mmol). The mixture was heated to 30°C and stirred for 2 h. The mixture was concentrated to dryness, added with ethanol (30 mL) and stirred at room temperature for 1 h. The mixture was filtered, and the filer cake was collected to give the title compound **100** (1.15 g, solid, 58%).

MS m/z (ESI): 401 [M+1]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.90 (s, 1H), 7.70 (s, 1H), 7.46 (s, 1H), 4.00 - 3.90 (m, 3H), 3.78 (s, 3H), 3.69 - 3.47 (m, 4H), 3.42 - 3.33 (m, 1H), 3.28 (dd, J = 11.9,

9.3 Hz, 1H), 3.09 (dd, J = 20.0, 10.8 Hz, 1H), 2.40 (dd, J = 24.7, 17.6 Hz, 1H), 0.94 (d, J = 8.8 Hz, 3H).

Example 101. Biological Experiments

5 **JAK2 Inhibition Assay**

The effect of the compounds of the present invention on the enzymatic activity of JAK2 was assessed by detecting the substrate phosphorylation level in a kinase reaction using the HTRF kinase assay detection kit (Cisbio, Cat. No. 62TK0PEC).

The experimental method is generally described below:

10 A reaction buffer contained the following components: an enzyme reaction buffer (1×), 5 mM $MgCl_2$, 1 mM DTT and 0.01% Brij35 from the kit. A JAK2 kinase solution contained a human recombinant JAK2 protein (Carna Biosciences, 08-045) diluted in the reaction buffer to 0.15 ng/μL. A substrate reaction solution contained 2.5 μM ATP and 0.25 μM of a biotinylated tyrosine kinase substrate from the kit in the reaction buffer. A detection solution

15 contained 0.1 ng/μL Eu^{3+}-labeled cage antibody (Cisbio, 61T66KLB) and 12.5 nM streptavidin-labeled XL665 (Cisbio, 610SAXLB) in the reaction buffer.

The test compound was dissolved in DMSO to 10 μM, followed by a serial 4-fold dilution with DMSO to a minimum concentration of 0.061 nM. Each concentration was further diluted 40-fold with the reaction buffer.

20 To a 384-well assay plate (Corning, 3674) were added 4 μL of compound solution and 2 μL of JAK2 kinase solution. The mixture was mixed and incubated at room temperature for 15 minutes, and then added with 4 μL of the substrate reaction solution. After further incubation at room temperature for 30 minutes, the reaction mixture was added with an equal volume of 10 μL detection solution and allowed to stand at room temperature for 30 minutes.

25 An Envision plate reader (Perkin Elmer) was then used to measure the progress of the reaction at 620 nm and 665 nm. The ratio of absorbances at 665 nm and 620 nm was positively correlated with the degree of substrate phosphorylation, therefore the activity of JAK2 kinase was detected. In the experiment, the group without JAK2 kinase protein was treated as the 100% inhibition group, and the group with JAK2 kinase protein but not the test

30 compound was treated as the 0% inhibition group. The percentage of inhibition on JAK2 kinase activity by the test compound was calculated using the following formula:

Percentage of inhibition = 100 - 100 * ($ratio_{compound}$ - $ratio_{100\%\ inhibition}$) / ($ratio_{0\%\ inhibition}$ - $ratio_{100\%\ inhibition}$)

The IC_{50} value of the test compound was calculated from 8 concentration points using the XLfit software (ID Business Solutions Ltd., UK) by the following formula:

Y = Bottom + (Top - Bottom) / (1+10^((logIC50 - X) × slope factor))

Where Y was the percentage of inhibition, X was the logarithm of the concentration of the test compound, Bottom was the bottom plateau value of the S-shaped curve, Top was the top plateau value of the S-shaped curve, and slope factor was the slope coefficient of the curve.

TYK2 Inhibition Assay

The effect of the compounds of the present invention on the enzymatic activity of TYK2 was assessed by detecting the substrate phosphorylation level in a kinase reaction using the HTRF kinase assay detection kit (Cisbio, Cat. No. 62TK0PEC).

The experimental method is generally described below:

A reaction buffer contained the following components: an enzyme reaction buffer (1×), 5 mM $MgCl_2$, 1 mM DTT and 0.01% Brij35 from the kit. A TYK2 kinase solution contained human recombinant TYK2 protein (Carna Biosciences, 08-147) diluted in the reaction buffer to 0.25 ng/μL. A substrate reaction solution contained 11.25 μM ATP and 0.5 μM of a biotinylated tyrosine kinase substrate from the kit in the reaction buffer. A detection solution contained 0.1 ng/μL Eu^{3+}-labeled cage antibody (Cisbio, 61T66KLB) and 25 nM streptavidin-labeled XL665 (Cisbio, 610SAXLB) in the reaction buffer.

The test compound was dissolved in DMSO to 10 μM, followed by a serial 4-fold dilution with DMSO to a minimum concentration of 0.061 nM. Each concentration was further diluted 40-fold with the reaction buffer.

To a 384-well assay plate (Corning, 3674) were added 4 μL of compound solution and 2 μL of TYK2 kinase solution. The mixture was mixed and incubated at room temperature for 15 minutes, and then added with 4 μL of the substrate reaction solution. After further incubation at room temperature for 40 minutes, the reaction mixture was added with an equal volume of 10 μL detection solution and allowed to stand at room temperature for 30 minutes. An Envision plate reader (Perkin Elmer) was then used to measure the progress of the reaction at 620 nm and 665 nm. The ratio of absorbances at 665 nm and 620 nm was positively correlated with the degree of substrate phosphorylation, therefore the activity of TYK2 kinase was detected. In the experiment, the group without TYK2 kinase protein was treated as the 100% inhibition group, and the group with TYK2 kinase protein but not the test

compound was treated as the 0% inhibition group. The percentage of inhibition on TYK2 kinase activity by the test compound was calculated using the following formula:

Percentage of inhibition = 100 - 100 * ($ratio_{compound}$ - $ratio_{100\% inhibition}$) / ($ratio_{0\% inhibition}$ - $ratio_{100\% inhibition}$)

The IC50 value of the test compound was calculated from 8 concentration points using the XLfit software (ID Business Solutions Ltd., UK) by the following formula:

Y = Bottom + (Top - Bottom) / (1+10^((logIC50 - X) × slope factor))

Where Y was the percentage of inhibition, X was the logarithm of the concentration of the test compound, Bottom was the bottom plateau value of the S-shaped curve, Top was the top plateau value of the S-shaped curve, and slope factor was the slope coefficient of the curve.

Compound No.	IC_{50} (nM)	
	JAK2	TYK2
1.	319	125
2.	478	62
3.	113	23
4.	126	49
5.	82	75
6.	113	127
7.	138	186
8.	25	66
9.	38	13
10.	15	2.4
11.	137	21
12.	4.2	1.1
13.	170	8.5
14.	68	14
15.	551	186
16.	0.9	1.2
17.	3.2	1.6
18.	3.5	1.6
19.	8.8	14
20.	1.2	0.5
21.	10	2.0
22.	1.4	0.8
23.	3.0	1.0
24.	20	4.1

25.	0.9	0.3
26.	10	6.1
27.	15	16
28.	0.4	0.2
29.	0.5	0.4
30.	4.6	1.4
31.	0.4	0.5
32.	1.0	0.5
33.	6.2	2.9
34.	1.8	0.6
35.	3.3	0.6
36.	4.1	1.8
37.	15	12
38.	50	43
39.	11	4.4
40.	1.2	0.4
41.	1.7	1.3
42.	20	5.7
43.	18	4.5
44.	20	8.6
45.	19	12
46.	3.9	0.9
47.	51	13
48.	2.5	0.7
49.	71	52
50.	0.1	0.3
51.	7.3	2.7
52.	1.8	0.9
53.	3.8	3.2
54.	0.9	0.2
55.	3.7	1.7
56.	2.5	1.7
57.	3.2	2.3
58.	6.5	5.6
59.	5.1	5.0
60.	5.9	2.2
61.	8.9	1.6
62.	2.6	0.6
63.	1.2	0.3

64.	3.3	0.5
65.	1.3	0.5
66.	0.3	0.2
67.	2.2	6.0
68.	31	1.4
69.	156	98
70.	17	5.3
71.	3.3	1.2
72.	4.5	3.4
73.	6.0	3.3
74.	2.4	1.6
75.	325	98
76.	475	149
77.	136	30
78.	7.6	4.2
79.	40	51
80.	16	19
81.	16	50
82.	14	16
83.	13	7.4
84.	477	186
85.	1.7	2.4
86.	1.7	0.3
87.	9.0	6.0
88.	0.5	0.2
89.	4.5	2.6
90.	0.6	0.1
91.	2.6	3.2
92.	4.1	1.1
93.	91	158
94.	34	224
95.	19	42
96.	3.0	3.4
97.	8.1	56
98.	0.7	0.1
99.	0.5	0.1
100.	5.0	2.2

The compounds of the present invention have a significant inhibitory effect on the activity of TYK2, preferably with an IC_{50} of 10 to 100 nM, and more preferably with an IC_{50}

of less than 10 nM.

Inhibition of IL-12-induced IFN-γ Secretion in NK92 Cells

The effect of the compounds of the present invention on IFN-γ secretion induced by IL-12 in NK92 cells was evaluated by an enzyme-linked immunosorbent assay (ELISA).

IL-12 receptor is mainly expressed in activated T-cells, NK cells (NK92 is a NK cell line), DC cells, and B-cells. When binding to IL-12, it activates JAK2/TYK2 signal transduction pathway within NK cells and T lymphocytes, thereby inducing secretion of IFN-γ.

The experimental method is generally described below:

The test compound was dissolved in DMSO to 2.5 mM, followed by a serial 4-fold dilution with DMSO to a minimum concentration of 0.31 μM. Each concentration was further diluted 50-fold with an FBS-free MEMα medium (Gibco, 12561-056).

NK92 cells (Nanjing Cobioer, CBP60980) were cultured in a complete MEMα medium containing 12.5% FBS (Ausbian, VS500T), 12.5% horse serum (Gibco, 16050-122), 0.02 mM folic acid (Sigma, F8758), 0.2 mM inositol (Sigma, 17850), 0.55 mM β-mercaptoethanol (Gibco, 21985-023), 200 U/mL IL-2 (R&D Systems, 202-1L), and 100 U/mL penicillin (Thermofisher, 15140122). When covering 80-90% of the culture container surface, the cells were dispersed and plated on a 96-well plate (Thermofisher, 167425) with 100,000 cells per well (80 μL of the complete MEMα medium without IL-2). The 96-well plate was then incubated overnight in a 37°C/5% CO2 incubator.

After overnight incubation, 10 μL of the test compound and 10 μL of 50 ng/mL IL-12 (R & D Systems, 219-1L) were added to each well and mix gently, and the 96-well plate was incubated in the 37°C/5% CO2 incubator for additional 24 hours. The plate as centrifuged at 800 rpm for 10 minutes at room temperature and 50 μL of the supernatant from each well was transferred to another 96-well plate (Sigma, CLS3695) coated with anti-IFN-γ antibody. The amount of IFN-γ secretion was detected following the instruction from the Human IFN-γ DuoSet ELISA kit (R & D Systems, DY285B). In the experiment, the group with IL-12 and the test compound being replaced with the MEMα medium was the non-stimulated control group (100% inhibition), and the group with IL-12 and 0.2% DMSO was the stimulated group (0% inhibition). The percentage of inhibition on IL-12 induced IFN-γ secretion in NK-92 cells by the test compound was calculated using the following formula:

Percentage of inhibition = 100 - 100 * ($signal_{compound}$ - $signal_{non\text{-}stimulated\ control}$) /

($signal_{stimulated\ control}$ - $signal_{non\text{-}stimulated\ control}$)

The IC_{50} value of the test compound was calculated from 8 concentration points using the XLfit software (ID Business Solutions Ltd., UK) by the following formula:

Y = Bottom + (Top - Bottom) / (1+10^((logIC50 - X) × slope factor))

Where Y was the percentage of inhibition, X was the logarithm of the concentration of the test compound, Bottom was the bottom plateau value of the S-shaped curve, Top was the top plateau value of the S-shaped curve, and slope factor was the slope coefficient of the curve.

Compound No.	IC_{50} (NK92_IL12/IFNγ) (nM)
10	3795
11	6773
12	419
13	4144
14	1317
16	1007
17	1046
18	617
19	713
20	233
21	490
22	305
23	551
24	1069
25	399
26	652
27	847
28	2210
29	380
30	1211
31	2783
32	668
33	215
34	287
35	453
36	592
37	2098
39	919

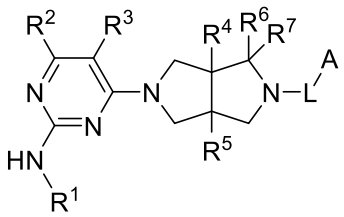
40	422
41	635
42	3468
43	3387
44	3615
45	5393
46	591
47	7919
48	709
50	43
51	597
52	289
53	918
54	934
55	413
56	505
57	5242
58	564
59	2392
60	1384
61	578
62	269
63	267
64	162
65	136
66	66
67	291
68	330
69	7063
70	1199
71	3540
72	824
73	278
74	209
78	2756
79	3967
80	4090
81	3971
82	2870

83	4552
84	8747
85	5349
86	99
87	959
88	67
89	729
90	96
91	388
92	398
95	5852
96	646
98	516
99	158
100	763

The compounds of the present invention have a significant inhibitory effect on IFN-γ secretion induced by IL-12 in NK92 cells, and the IC50 is preferably less than 1000 nM.

Claims:

1. A compound of Formula (I), or a pharmaceutical acceptable salt, stable isotope, stereoisomer thereof:



(I)

wherein:

R^1 is pyrazolyl, where one or more hydrogens of the pyrazolyl are optionally substituted by D, halogen, cyano, $-OR^b$, $-NR^bR^c$, $-COOR^b$, $-C(O)R^b$, $-NR^bC(O)R^c$, $-C(O)NR^bR^c$, $-S(O)_2R^b$, $-S(O)_2NR^bR^c$, $-S(O)(NR^b)R^c$, $-P(O)(CH_3)_2$, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl or 5- to 6-membered heteroaryl;

R^2 is H, D or $-NHR^a$;

R^3 is H, D, halogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl or OC_{1-6} alkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D or F;

R^4 and R^5 are independently selected from H, D, halogen, C_{1-6} alkyl or OC_{1-6} alkyl, where one or more hydrogens of the alkyl are optionally substituted by D or F;

R^6 and R^7 are independently selected from H, D, cyano or C_{1-6} alkyl, where one or more hydrogens of the alkyl is optionally substituted by D or F, or R^6 and R^7 combine as oxo;

L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, $-C(O)N(R^a)-$, $-S(O)_2-$ or $-S(O)_2N(R^a)-$;

A is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, aryl or heteroaryl, where one or more hydrogens of the alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted by D, halogen, cyano, $-OR^d$, $-NR^dR^e$, C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 8-membered heterocyclyl;

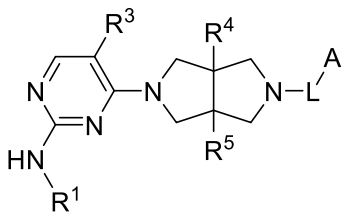
R^a is H, C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D or F;

R^b and R^c are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 8-membered heterocyclyl containing N and/or O, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by D, halogen, CN, -OH, $-NH_2$, C_{1-6} alkyl and $-OC_{1-6}$ alkyl, and

R^d and R^e are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 8-membered heterocyclyl, where one or more hydrogens of the alkyl, cycloalkyl and

heterocyclyl are optionally further substituted by D or F.

2. A compound of Formula (II), or a pharmaceutical acceptable salt, stable isotope, stereoisomer thereof:



(II)

wherein:

R^1 is phenyl, pyridyl or pyrazolyl, where one or more hydrogens of the phenyl, pyridyl and pyrazolyl are optionally substituted by halogen, C_{1-6} alkyl, 4- to 6-membered heterocyclyl containing N and/or O, -C(O)R^b or -C(O)N$R^b$$R^c$, and one or more hydrogens of the alkyl and heterocyclyl are optionally further substituted by D, F, CN, -OH or C_{1-6} alkyl;

R^b and R^c are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl or 4- to 6-membered heterocyclyl containing N and/or O, where one or more hydrogens of the alkyl, cycloalkyl and heterocyclyl are optionally further substituted by C_{1-2} alkyl;

R^3 is H, halogen, cyano, C_{1-6} alkyl or OC_{1-6} alkyl;

R^4 and R^5 are independently H or C_{1-6} alkyl;

L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, -C(O)NH- or -S(O)$_2$-, and

A is C_{1-6} alkyl, C_{3-6} cycloalkyl, 4- to 6-membered heterocyclyl containing N and/or O, pyridyl, pyrimidyl or 5-membered heteroaryl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D, halogen, cyano, -OH, -OC_{1-2} alkyl or C_{1-2} alkyl, and those of the heterocyclyl and heteroaryl are optionally substituted by C_{1-2} alkyl.

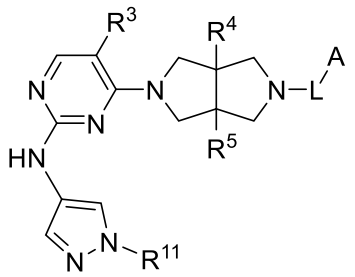
3. The compound of Claim 2, wherein R^1 is pyrazolyl.

4. The compound of Claim 1 or 2, wherein L is -C(O)-.

5. The compound of Claim 1 or 2, wherein A is C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by halogen, cyano, -OH

or -OC_{1-2} alkyl.

6. The compound of Claim 2, which is a compound of Formula (III), or a pharmaceutical acceptable salt, stable isotope, stereoisomer thereof:



(III)

where:

R^3 is H, halogen, cyano, C_{1-6} alkyl, or OC_{1-6} alkyl;

R^4 and R^5 are independently H or C_{1-6} alkyl;

L is a bond, C_{1-6} alkylene, -C(O)-, -C(O)O-, -C(O)NH-, or -$S(O)_2$-;

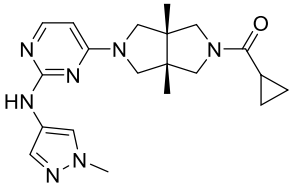
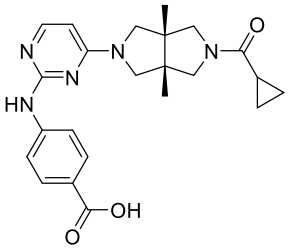
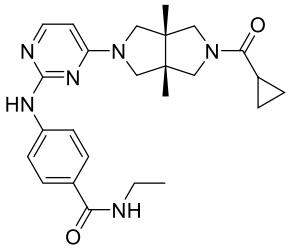
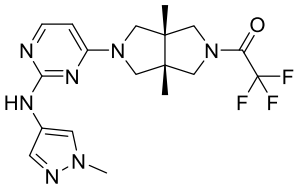
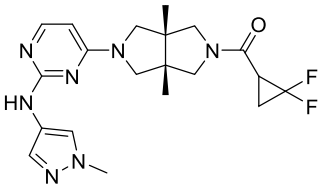
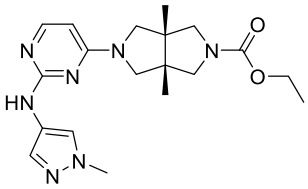
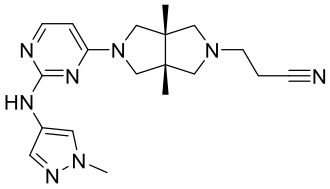
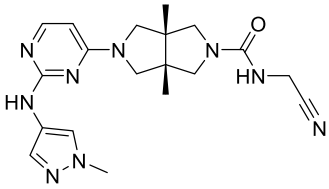
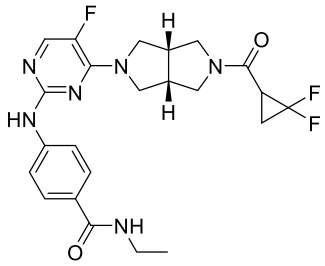
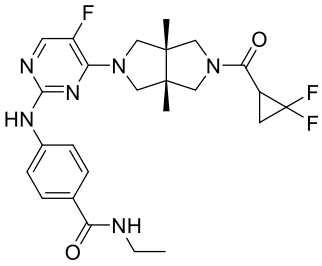
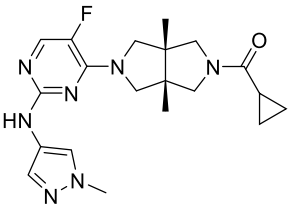
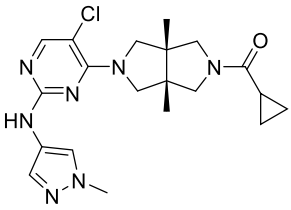
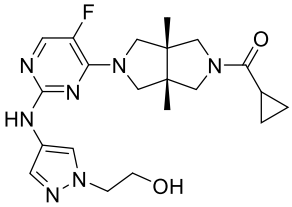
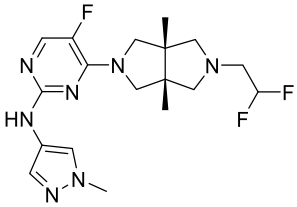
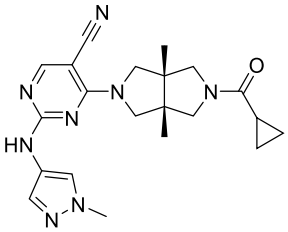
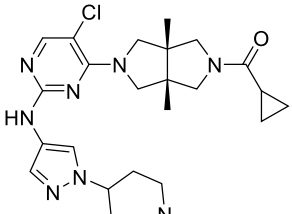
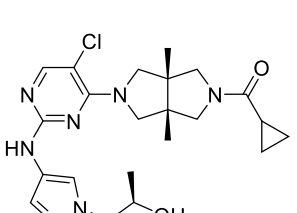
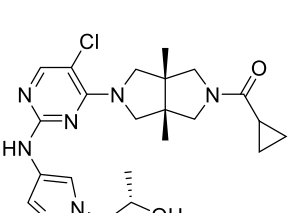
A is C_{1-6} alkyl, C_{3-6} cycloalkyl, 4- to 6-membered heterocyclyl containing N and/or O pyridyl, pyrimidyl, or 5-membered heteroaryl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by D, halogen, cyano, -OH, -OC_{1-2} alkyl or C_{1-2} alkyl, and one or more hydrogens of the heterocyclyl and heteroaryl are optionally substituted by C_{1-2} alkyl, and

R^{11} is H, C_{1-6} alkyl or 4- to 6-membered heterocyclyl containing N and/or O, where one or more hydrogens of the alkyl and heterocyclyl are optionally substituted by D, F, CN, -OH or C_{1-6} alkyl.

7. The compound of Claim 6, wherein A is C_{1-6} alkyl or C_{3-6} cycloalkyl, where one or more hydrogens of the alkyl and cycloalkyl are optionally substituted by halogen, cyano, -OH or -OC_{1-2} alkyl.

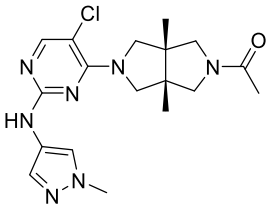
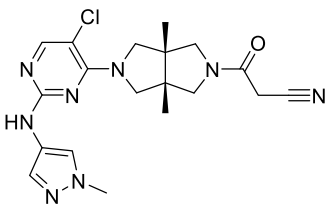
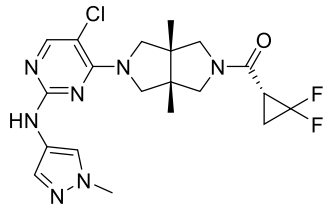
8. The compound of Claim 6, wherein R^{11} is C_{1-6} alkyl, wherein one or more hydrogens of the alkyl are optionally substituted by D, F, CN, -OH, or C_{1-6} alkyl.

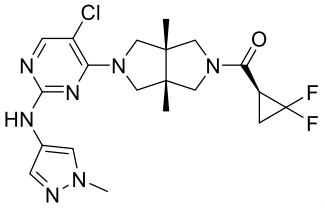
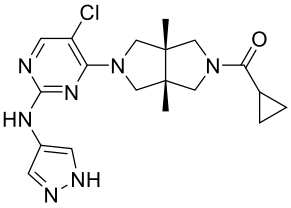
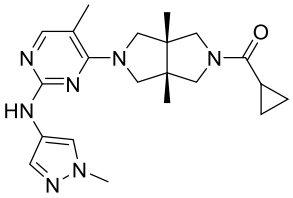
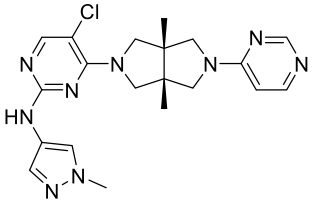
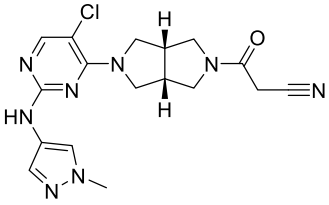
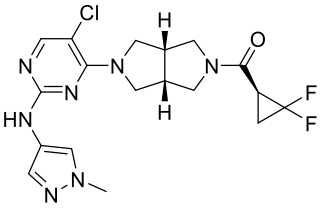
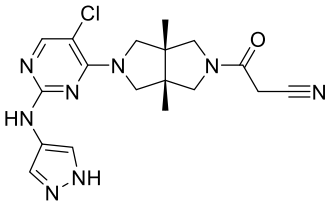
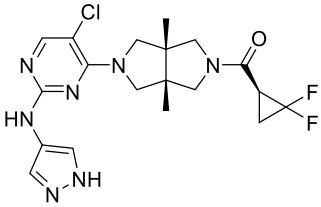
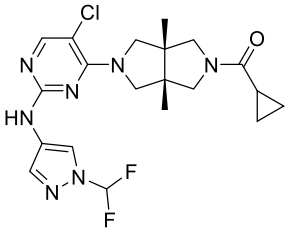
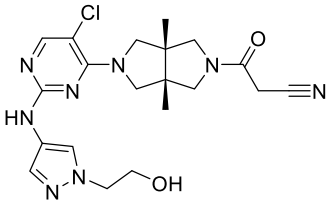
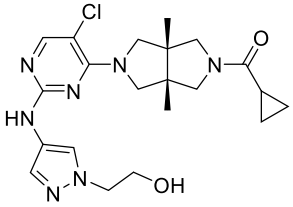
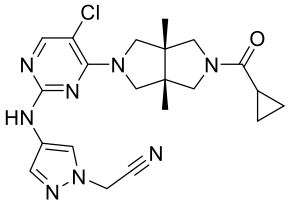
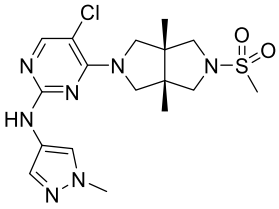
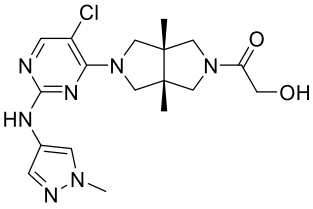
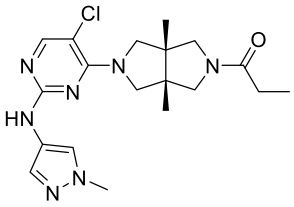
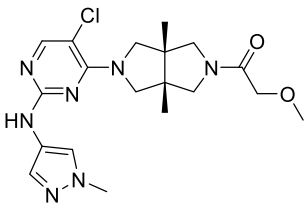
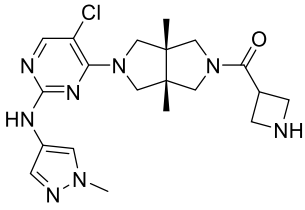
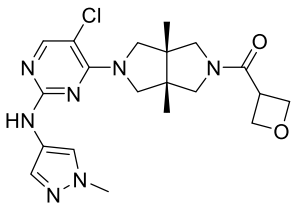
9. The compound according to Claim 1, or a pharmaceutical acceptable salt, stable isotope, stereoisomer thereof, the compound structure is shown below:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

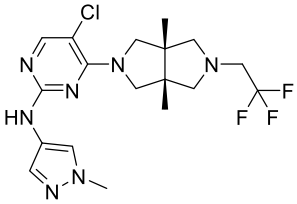
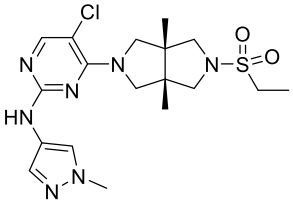
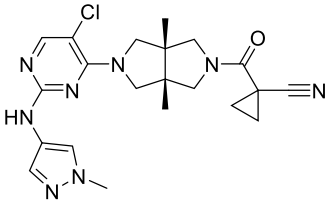
,

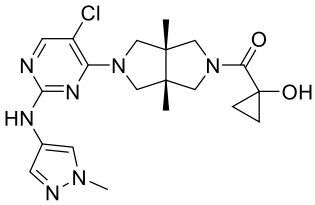
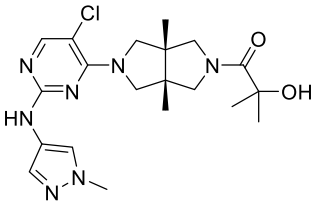
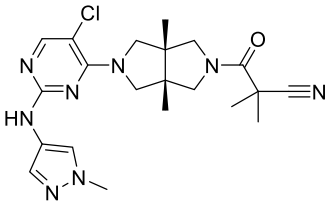
,

,

,

,

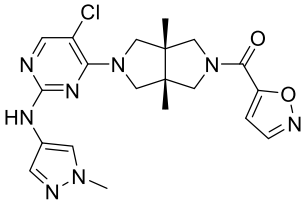
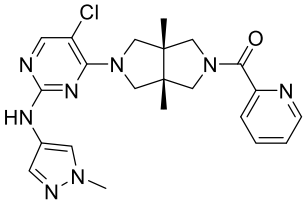
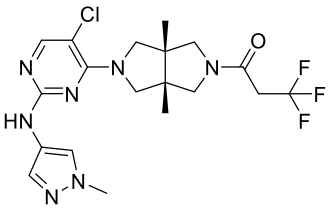

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

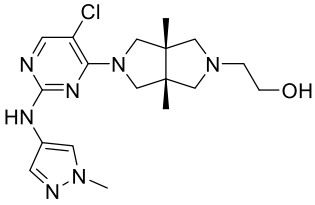
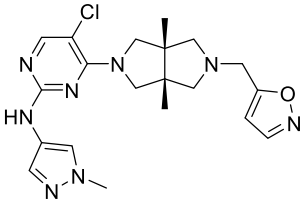
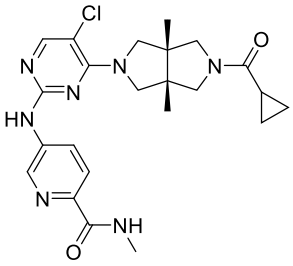
,

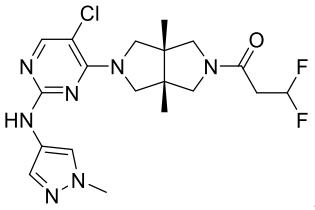
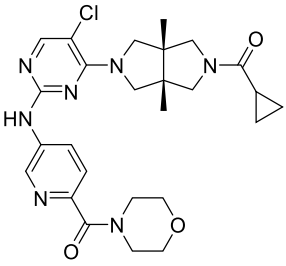
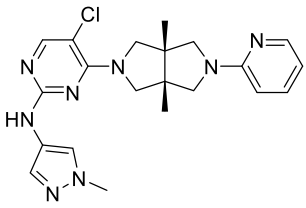
,

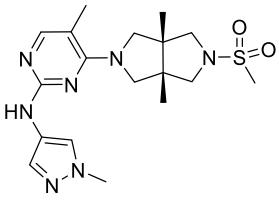
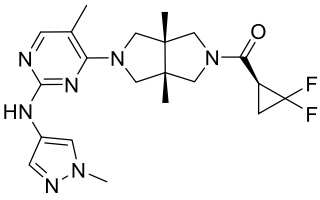
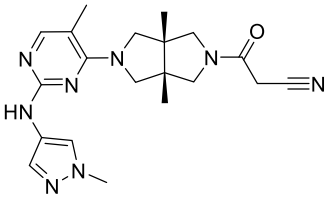
,

,

,

,

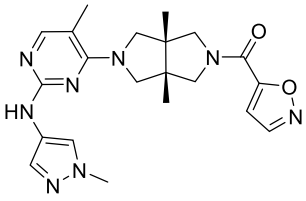
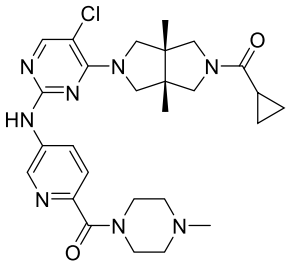
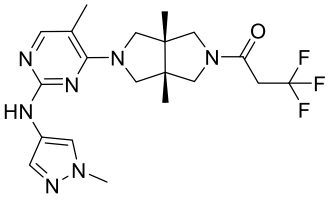

,

,

,

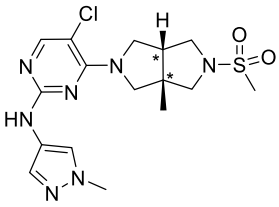
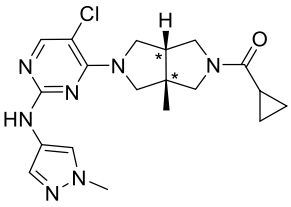
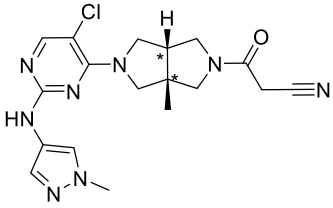

,

,

,

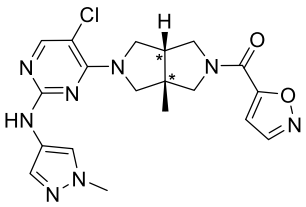
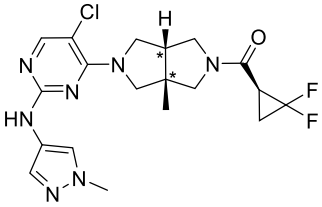
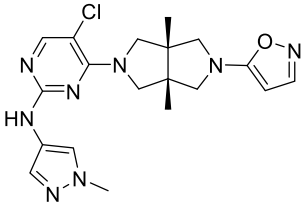
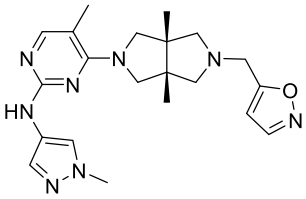
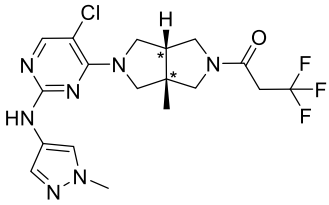
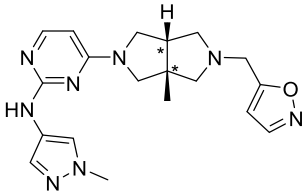
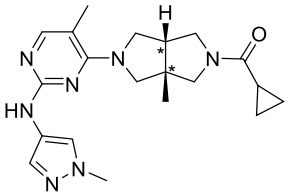
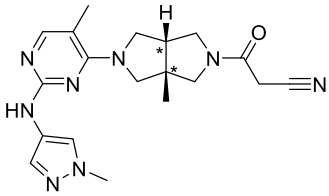
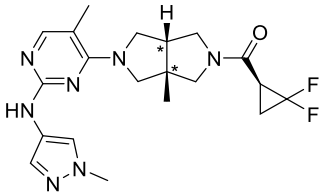
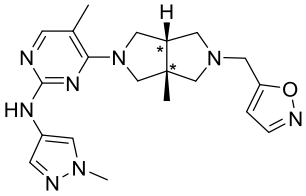
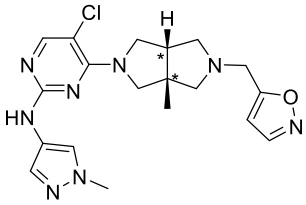
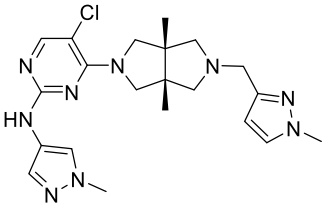
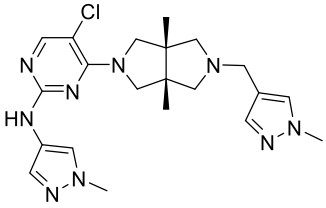
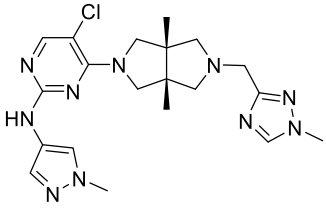
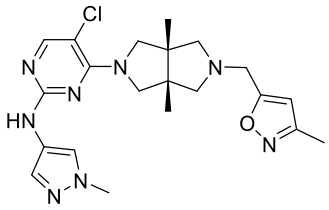
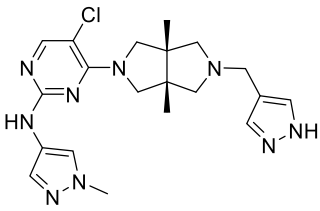
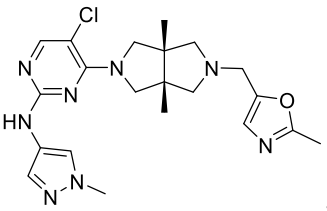
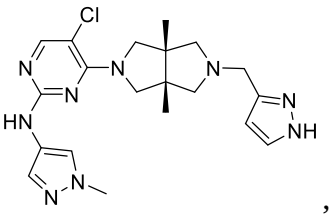

,

,

,


,

,

,


,

,

,

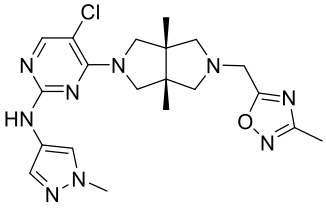
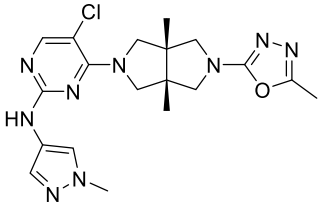
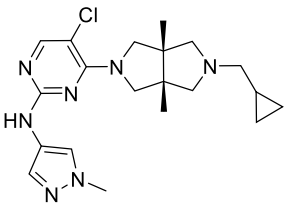
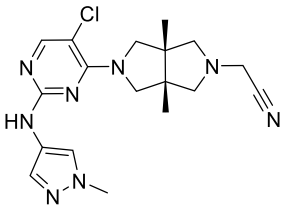
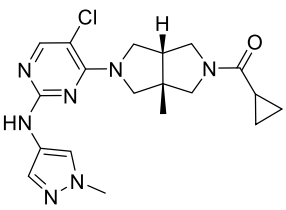
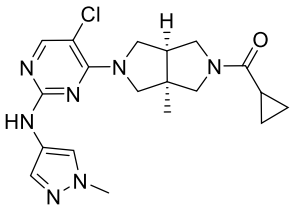

,

,

,

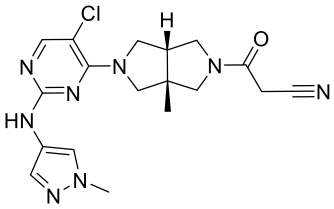
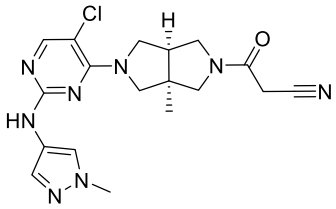
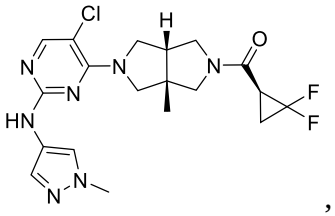
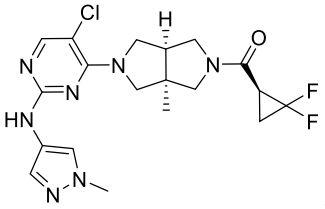
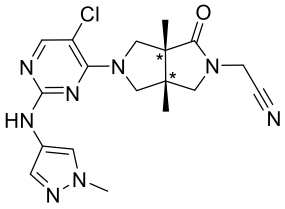
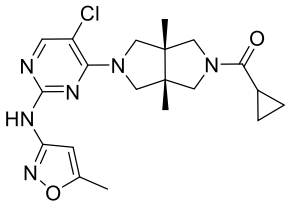
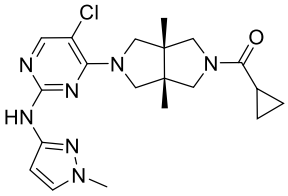
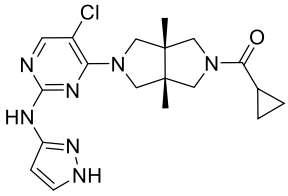
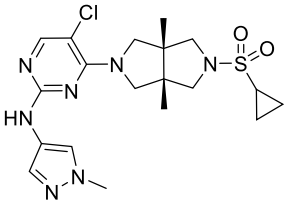
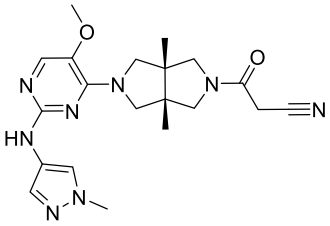
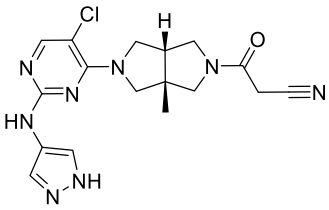
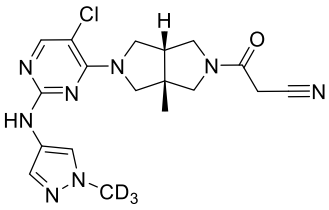

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

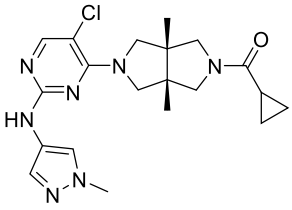
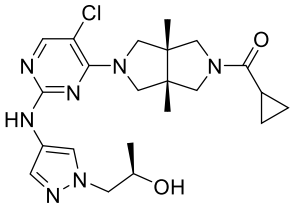
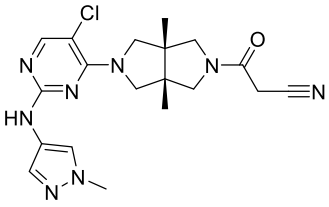
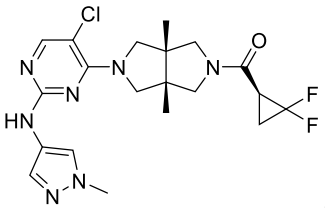
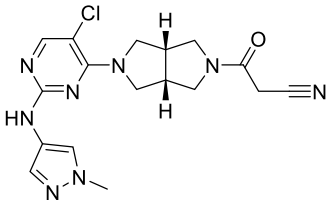
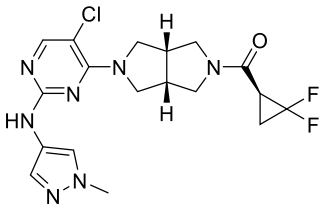
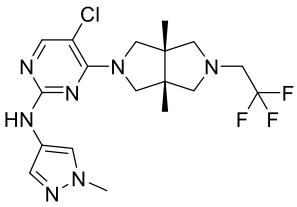
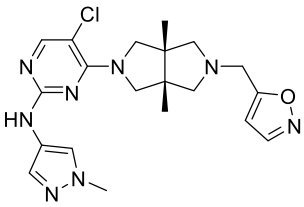
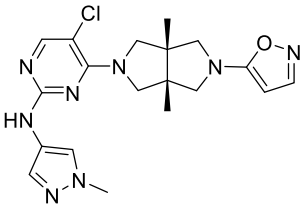
,

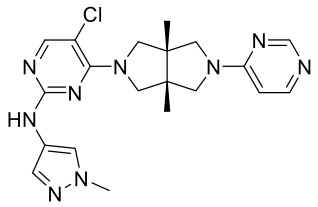
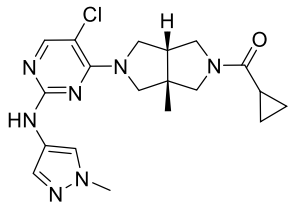
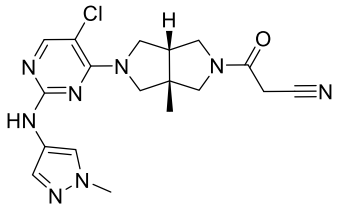
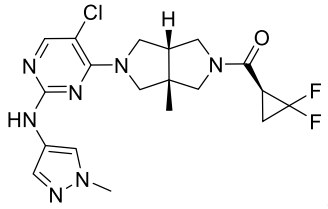
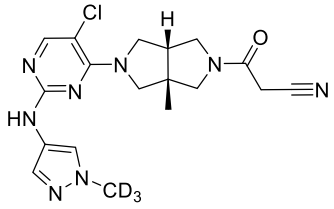
,

,

,

,

,

,

,

,

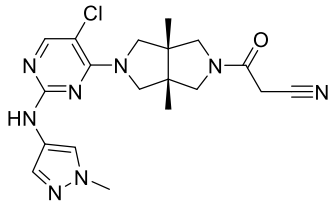
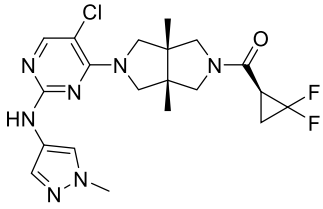
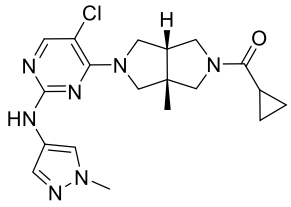
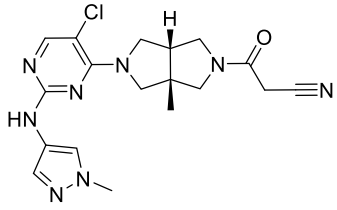
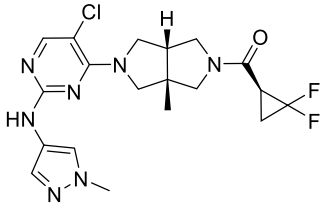
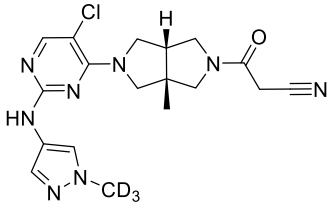

,

,

,

,

,

,

,

,

,

,

, or

(the stereochemistry of the carbon atoms labeled with * is not determined).

10. The compound of Claim 9, which is:


,

,

,

,

,

,

,

,

,


,

,

,

, or

.

11. The compound of Claim 9, which is:


,

,

,

,

, or

.

12. A pharmaceutical composition comprising the compound of any one of Claims 1-11 and a pharmaceutically acceptable carrier or excipient thereof.

13. Use of a therapeutically effective amount of the compounds of any one of Claims 1-11, or pharmaceutically acceptable salts, stable isotope derivatives, stereoisomers thereof, in the manufacture of a medicament for preventing or treating a disease mediated by tyrosine kinase 2 (TYK2), wherein the disease mediated by TYK2 is autoimmune diseases, inflammatory diseases including intestinal diseases, cancers, skin diseases, diabetes, eye diseases, neurodegenerative diseases, anaphylaxis, asthma and other obstructive airway diseases, or transplant rejection.

14. The use of Claim 13, wherein the disease is psoriasis, psoriatic arthritis, ulcerative colitis, Crohn’s disease, systemic lupus erythematosus, lupus nephritis, vitiligo, areata alopecia, dermatitis, or atopic eczema.