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(71) Applicants: SAVIRA PHARMACEUTICALS GMBH [AT/AT]; Veterinaerplatz 1, Building IA, 1210 Vienna (AT). EUROPEAN MOLECULAR BIOLOGY LABORATORY [DE/DE]; Meyerhofstrasse 1, 69117 Heidelberg (DE).

(72) Inventor; and

(71) Applicant (for US only): TAN, Xuefei [US/CN]; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN).

(72) Inventors: SHEN, Hong; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN). WU, Jun; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN). LIU, Yongfu; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN). LI, Dongbo; Sperletweg 59, CH8052, Zurich (CH). WANG, Lisha; Klingnaustrasse 19, 4058 Basel (CH). NEIDHART, Werner; Hirzbodenweg 15,

4052 Basel (CH). SHI, Tianlai; Riehenstrasse 43, 4058 Basel (CH). WU, Guolong; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN).

(74) Agent: ZHONGZI LAW OFFICE; 7F, New Era Building, 26 Pinganli Xidajie, Xicheng District, Beijing 100034 (CN).

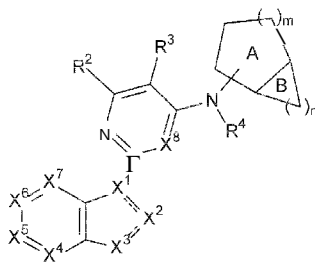
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(54) Title: PYRIMIDINE AND PYRIDINE DERIVATIVES AND USE IN TREATMENT, AMELIORATION OR PREVENTION OF INFLUENZA THEREOF



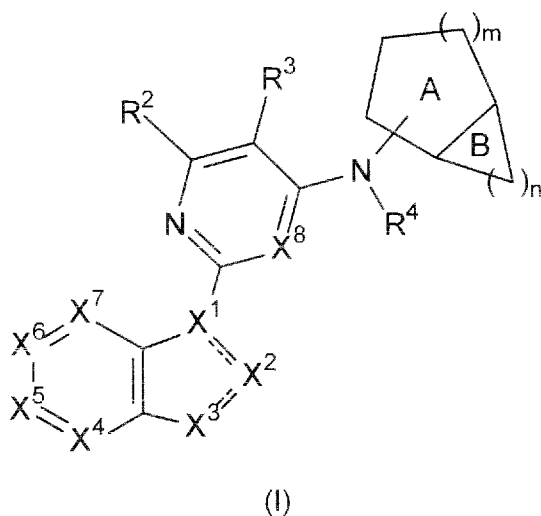
(I)

(57) Abstract: Provided herein is a compound of formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, which is useful in treating, ameliorating or preventing influenza.

**PYRIMIDINE AND PYRIDINE DERIVATIVES AND USE IN TREATMENT, AMELIORATION
OR PREVENTION OF INFLUENZA THEREOF**

Field of the invention

The present invention relates to a compound having the formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



which is useful in treating, ameliorating or preventing influenza.

Background of the invention

Influenza viruses belong to the Orthomyxoviridae family of RNA viruses. Based on antigenic differences of viral nucleocapsid and matrix proteins, influenza viruses are further divided into three types named influenza A, B, and C viruses. All influenza viruses have an

envelope, and their genomes are composed of eight or seven single-stranded, negative-sensed RNA segments. These viruses cause respiratory diseases in humans and animals with a significant morbidity and mortality. The influenza pandemic of 1918, Spanish flu, is thought to have killed up to 100 million people. The reassortment of avian flu RNA fragments with circulating human viruses caused the other two pandemics in 1957 H2N2 "Asian influenza" and 1968 H3N2 "Hong Kong influenza". Now, people around the world face the challenges of influenza from various angles: seasonal influenza epidemics affect about 5-15% of the world's population with an annual mortality ranging from 250,000 to 500,000. Infections of avian flu strains, mostly H5N1, have been reported in many Asian countries. Although no frequent human-to-human spreading has been observed, avian flu infection is serious and associated with a high mortality of up to 60% of infected persons. In 2009, an H1N1 swine flu infection appeared initially in North America and evolved into a new pandemic. Currently, seasonal trivalent influenza vaccines and vaccines specific for H5N1 or swine flu are either available or in the phase of clinical trials. The prophylaxis is an effective method, at least in some populations, for preventing influenza virus infection and its potentially severe complications. However, continuous viral antigenicity shifting and drifting makes future circulating flu strains unpredictable. Furthermore, due to the limitations of mass production of vaccines within a relatively short period of time during a pandemic, other anti-flu approaches such as anti-flu drugs are highly desirable. On the market, there are two types of anti-flu drugs available: neuraminidase inhibitors such as oseltamivir phosphate (Tamiflu) and zanamivir (Relenza); and M2 ion channel blockers such as amantadine and rimantadine. To increase the effectiveness of current anti-flu drugs and prevent or attenuate appearance of drug-resistant viruses, it is invaluable to discover compounds with new mechanisms of anti-influenza action that can be used as a therapeutic or prophylactic agent alone or combined with current anti-flu drugs.

It appears realistic that H5N1 and related highly pathogenic avian influenza viruses could acquire mutations rendering them more easily transmissible between humans. In addition, the new A/H1N1 could become more virulent and only a single point mutation would be enough to confer resistance to oseltamivir (Neumann et al., *Nature* 2009, 18, 459(7249), 931-939). This has already happened in the case of some seasonal H1N1 strains which have recently been identified (Dharan et al., *The Journal of the American Medical Association*, 2009, 301(10), 1034-1041; Moscona et al., *The New England Journal of Medicine* 2009, 360(10), 953-956). The unavoidable delay in generating and deploying a

vaccine could in such cases be catastrophically costly in human lives and societal disruption.

In view of the currently elevated risk of infections of pandemic H1N1 swine flu, highly pathogenic H5N1 avian flu, and drug-resistant seasonal flu, the development of new anti-influenza drugs have again become high priority.

In many cases, the development of anti-viral medicament may be facilitated by the availability of structural data of viral proteins. The availability of structural data of influenza virus surface antigen neuraminidase has, e.g. led to the design of improved neuraminidase inhibitors (Von Itzstein et al., Nature 1993, 363, 418-423). Examples of active compounds which have been developed based on such structural data include zanamivir (Glaxo) and oseltamivir (Roche). However, although these medicaments may lead to a reduction of the duration of the disease, there remains an urgent need for improved medicaments which may also be used for curing these diseases.

Adamantane-containing compounds such as amantadine and rimantadine are another example of active compounds which have been used in order to treat influenza. However, they often lead to side effects and have been found to be ineffective in a growing number of cases (Magden et al., Appl. Microbiol. Biotechnol. 2005, 66, 612-621).

More unspecific viral drugs have been used for the treatment of influenza and other virus infections (Eriksson et al., Antimicrob. Agents Chemother. 1977, 11, 946-951), but their use is limited due to side effects (Furuta et al., Antimicrobial Agents and Chemotherapy 2005, 981-986).

Influenza viruses being Orthomyxoviridae, as described above, are negative-sense ssRNA viruses. Other examples of viruses of this group include Arenaviridae, Bunyaviridae, Ophioviridae, Deltavirus, Bomaviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae and Nyamiviridae. These viruses use negative-sense RNA as their genetic material. Single-stranded RNA viruses are classified as positive or negative depending on the sense or polarity of the RNA. Before transcription, the action of an RNA polymerase is necessary to produce positive RNA from the negative viral RNA. The RNA of a negative-sense virus (vRNA) alone is therefore considered non-infectious.

The trimeric viral RNA-dependent RNA polymerase, consisting of polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2) and polymerase acidic protein (PA) subunits, is responsible for the transcription and replication of the viral RNA genome segments. Structural data of the two key domains of the polymerase, the mRNA cap-binding domain in the PB2 subunit (Guilligay et al., Nature Structural & Molecular Biology 2008, 15(5), 500-506) and the endonuclease-active site in the PA subunit (Dias et al., Nature 2009, 458, 914-918) has become available.

The ribonucleoprotein (RNP) complex represents the minimal transcriptional and replicative machinery of an influenza virus. The polymerase, when comprised in the RNP complex, is also referred to as vRNP enzyme. During replication, the viral RNA polymerase generates a complementary RNA (cRNA) replication intermediate, a full-length complement of the vRNA that serves as a template for the synthesis of new copies of vRNA.

During transcription, the viral RNA polymerase comprised in the RNP complex synthesizes capped and polyadenylated mRNA using 5' capped RNA primers. This process involves a mechanism called cap snatching. The influenza polymerase uses host cell transcripts (capped pre-mRNAs) as primers for the synthesis of viral transcripts. The nucleoprotein is an essential component of the viral transcriptional machinery. The polymerase complex which is responsible for transcribing the single-stranded negative-sense viral RNA into viral mRNAs and for replicating the viral mRNAs, is thus a promising starting points for developing new classes of compounds which may be used in order to treat influenza (Fodor, Acta virologica 2013, 57, 113-122). This finding is augmented by the fact that the polymerase complex contains a number of functional active sites which are expected to differ to a considerable degree from functional sites present in proteins of cells functioning as hosts for the virus (Magden et al., Appl. Microbiol. Biotechnol. 2005, 66, 612-621). As one example, a substituted 2,6-diketopiperazine has been identified which selectively inhibits the cap-dependent transcriptase of influenza A and B viruses without having an effect on the activities of other polymerases (Tomassmi et al., Antimicrob. Agents Chemother. 1996, 40, 1189-1193). In addition, it has been reported that phosphorylated 2'-deoxy-2'-fluoroguanosine reversibly inhibits influenza virus replication in chick embryo cells. While primary and secondary transcription of influenza virus RNA were blocked even at low concentrations of the compound, no inhibition of cell protein synthesis was observed even at high compound concentrations (Tisdale et al., Antimicrob. Agents Chemother. 1995, 39, 2454-2458).

WO 2010/148197, WO 2012/083121, WO 2012/083117, WO 2012/083122 and WO 2013/184985 refer to specific compounds which are stated to be useful in inhibiting the replication of influenza viruses.

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WO 2008/068171 discloses substituted pyrimidines and their use as modulators of c-Jun N-terminal kinases (JNK).

It is an object of the present invention to identify compounds which specifically target the influenza virus cap-binding domain and hence are effective against influenza and which have improved pharmacological properties.

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Summary of the invention

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Accordingly, in a first embodiment, the present invention provides a compound having the formula (I).

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It is understood that throughout the present specification the term "a compound having the formula (I)" encompasses pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof unless mentioned otherwise.

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A further embodiment of the present invention relates to a pharmaceutical composition comprising a compound having the formula (I) and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

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The compounds having the formula (I) are useful for treating, ameliorating or preventing influenza.

Detailed description of the invention

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Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described

herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kolbl, H. eds. (1995). Helvetica Chimica Acta. CH-4010 Basel, Switzerland).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. In the following passages different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Definitions

The term "alkyl" refers to a saturated straight or branched carbon chain, which preferably has 1 to 6 carbon atoms.

The term "aryl" preferably refers to an aromatic monocyclic ring containing 5 or 6 carbon atoms, an aromatic bicyclic ring system containing 10 carbon atoms or an aromatic tricyclic

ring system containing 14 carbon atoms. Examples are phenyl, naphthyl or anthracenyl, preferably phenyl.

"Halogen" represents F, Cl, Br and I, more preferably F or Cl, even more preferably F.

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The term "heteroaryl" preferably refers to a five or six-membered aromatic ring wherein one or more of the carbon atoms in the ring have been replaced by 1, 2, 3, or 4 (for the five membered ring) or 1, 2, 3, 4, or 5 (for the six membered ring) of the same or different heteroatoms, whereby the heteroatoms are selected from O, N and S. Examples of the heteroaryl group are given below.

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The term "heterocyclyl" covers any mono-, bi- or polycyclic ring system which includes one or more heteroatoms in the ring system, whereby the heteroatoms are the same or different and are selected from O, N and S. Preferably the ring system includes 3 to 15 ring atoms.

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More preferably the ring system is mono- or bicyclic and has 5 to 10 ring atoms, even more preferably the ring system is monocyclic and has 5 or 6 ring atoms. Typically the ring system can include 1 to 4, more typically 1 or 2 heteroatoms at available positions. The term "heterocyclyl" also covers heteroaryl rings. Examples include azetidine, pyrrole, pyrrolidine, oxolane, furan, imidazolidine, imidazole, pyrazole, oxazolidine, oxazole, thiazole, piperidine, pyridine, morpholine, piperazine, and dioxolane.

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The term "carbocyclyl" covers any mono-, bi- or polycyclic ring system which does not include heteroatoms in the ring. Preferably the ring system includes 3 to 15 ring atoms. More preferably the ring system is mono- or bicyclic and has 5 to 10 ring atoms, even more preferably the ring system is monocyclic and has 5 or 6 ring atoms. The term "carbocyclic ring" also covers aryl rings. A further example of a "carbocyclic ring" is a C₃₋₆ cycloalkyl ring.

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The term "saturated monocyclic carbocyclic ring" refers to any saturated monocyclic ring which does not include heteroatoms in the ring.

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The term "saturated bridged carbocyclic ring having 5 to 8 ring carbon atoms and 1 to 3 carbon atoms in the bridge" refers to any saturated monocyclic ring having 5 to 8 ring carbon atoms which does not include heteroatoms in the ring, wherein two carbon atoms of the ring are connected to each other by an alkylene bridge having 1 to 3 carbon atoms (i.e., -(CH₂)_q-, with q = 1 to 3).

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If a compound or moiety is referred to as being "optionally substituted" it can in each instance include one or more of the indicated substituents, whereby the substituents can be the same or different.

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The term "saturated bridged heterocyclic ring having 5 to 8 ring carbon atoms and 0 to 2 heteroatoms in the ring, and 0 to 2 carbon atoms and 0 to 2 heteroatoms in the bridge" refers to any saturated monocyclic ring having 5 to 8 ring carbon atoms which may or may not include heteroatoms in the ring, and which may or may not contain carbon atoms and/or heteroatoms in the bridge, provided that there is at least one carbon atom or at least one heteroatom in the bridge. The bridge may be formed by connecting two atoms of the ring via the bridge. The saturated bridged heterocyclic ring has at least one heteroatom, either in the ring or in the bridge and may contain up to two heteroatoms in the ring and/or the bridge.

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The term "pharmaceutically acceptable salt" refers to a salt of a compound of the present invention. Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by mixing a solution of compounds of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, gluccheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate,

mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, 5 stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, S. M. Berge et al., "Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977)).

When the compounds of the present invention are provided in crystalline form, the structure 10 can contain solvent molecules. The solvents are typically pharmaceutically acceptable solvents and include, among others, water (hydrates) or organic solvents. Examples of possible solvates include ethanolates and iso-propanoates.

The term "codrug" refers to two or more therapeutic compounds bonded via a covalent 15 chemical bond. A detailed definition can be found, e.g., in N. Das et al., European Journal of Pharmaceutical Sciences, 41, 2010, 571-588.

The term "cocrystal" refers to a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a 20 stoichiometric or non-stoichiometric ratio of a target molecule or ion (i.e., compound of the present invention) and one or more neutral molecular cocrystal formers. A detailed discussion can be found, for example, in Ning Shan et al., Drug Discovery Today, 13(9/10), 2008, 440-446 and in D. J. Good et al., Cryst. Growth Des., 9(5), 2009, 2252-2264.

25 The compounds of the present invention can also be provided in the form of a prodrug, namely a compound which is metabolized *in vivo* to the active metabolite. Common groups which can be attached to the compounds of the present invention are disclosed in Nature Reviews - Drug Discovery 2008, vol. 7, pages 255 to 270, the entire content of which is included herein by reference, in particular the examples of groups suitable for prodrugs.

30 In the following, specific examples of groups are exemplified which may be used in prodrugs. This list is, however, not to be regarded as limiting on the scope of the present invention as many more groups are known to the skilled person which can be used to convert a drug into a prodrug.

Carboxyl groups, in general, can be converted into esters, thioesters, carbonates, amides or carbamates. This applies in particular to carboxyl groups in and on Rings A and B.

Hydroxyl functionalities can be converted into esters, carbonates, ethers or phosphates. Such esters include esters formed by reaction with one or more amino acids. Furthermore, prodrugs of compounds having hydroxyl functionalities may be formed by oxidation of the hydroxyl functionalities to carboxyl functionalities.

Thiol functionalities can be converted into thioesters or thioethers.

Amino functionalities can be converted into amides, carbamates, N-mannich bases, oximes, imines or phosphates. The phosphates may also be attached via C¹-alkylene glycol linkers, e.g. resulting in phosphonoxyalkyl amides. The amides include amides formed by reaction with one or more amino acids.

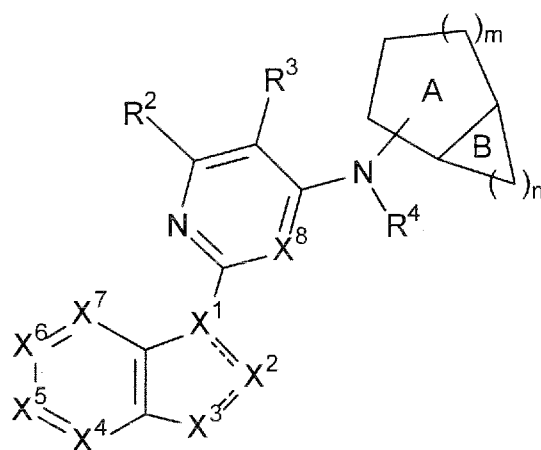
Substituted thiol functionalities can be converted into sulfoxides or sulfones.

Carbonyl groups can be converted into oximes or imines. This applies in particular to ketones, amidines and guanidines.

Phosphonates can be converted into phosphonate esters or phosphonate phosphates.

Compounds having the formula (I)

The present invention provides a compound having the formula (I):



(I)

The present invention provides a compound having the formula (I) in which the following definitions apply.

wherein

==== is a single or double bond;

R¹ is selected from the group consisting of -H, -halogen, -CN, -C(0)R^{**}, -COOR^{**}, -C(0)NR^{**}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(0)R^{**}, -N(R^{**})-C(0)-OR^{**}, -N(R^{**})-C(0)-NR^{**}R^{**}, -N(R^{**})-S(0)₂R^{**}, -(optionally substituted C₁₋₆ alkyl), -OR^{**}, -(optionally substituted heterocyclyl), -(optionally substituted C₁₋₄ alkyiene)-(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl), and -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H, -(optionally substituted C_{1-e} alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(0)R^{***}, -COOR^{***}, -C(0)NR^{***}R^{***}, -NR^{***}R^{***}, -NR^{***}-C(0)R^{***}, -N(R^{***})-C(0)-OR^{***}, -N(R^{***})-C(0)-NR^{***}R^{***}, -N(R^{***})-S(0)₂R^{***}, -OR^{***}, -O-C(0)R^{***}, -O-C(0)-NR^{***}R^{***}, -SR^{***}, -S(0)R^{***}, -S(0)₂R^{***}, -S(0);-NR^{***}R^{***}, -N(R^{***})-S(0)₂-NR^{***}R^{***}, -P(0)(OR^{***})₂, or -O-P(0)(OR^{***})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C₁₋₆ alkyl. R^{***} is H, C₁₋₆ alkyl, heterocyclyl or carbocyclyl. Preferably R¹ is selected from the group consisting of -H, -halogen, -CN, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted C₃₋₆ cycloalkyl), and -OR^{**}, wherein R^{**} is H, -(optionally substituted C_{1-e} alkyl), -(optionally substituted

- heterocyclyl), -(optionally substituted carbocyclyl). The -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{***}, -NR^{***}R^{***}, -NR^{***}-C(O)R^{***}, -N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, ~N(R^{***})-S(O)₂R^{***}, -OR^{***}, ~O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***}, -S(O)₂-NR^{***}R^{***}, -N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C₁₋₆ alkyl. R^{***} is H, C₁₋₆ alkyl, heterocyclyl or carbocyclyl. More preferably R¹ is selected from the group consisting of -H, -halogen, -CN, -(optionally substituted C₁₋₆ alkyl), and -(optionally substituted C₃₋₆ cycloalkyl). The -(optionally substituted) is preferred to be halogen. Even more preferably R¹ is selected from -H, -halogen, -CN, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -cyclopropyl, -CF₃, -CHF₂, and -CH₂F. Most preferably R¹ is selected from -H, -F, -Cl, -CN, -CH₃, and -cyclopropyl.
- R² is selected from the group consisting of -H, -halogen, -CN, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(O)R^{**}, -N(R^{**})-C(O)-OR^{**}, -N(R^{**})-C(O)-NR^{**}R^{**}, -N(R^{**})-S(O)₂R^{**}, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted C₃₋₆ cycloalkyl), -OR^{**}, -SR^{**}, -S(O)R^{**}, -S(O)₂R^{**}, -(optionally substituted heterocyclyl), -(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl), and -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{***}, -NR^{***}R^{***}, -NR^{***}-C(O)R^{***}, -N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, -N(R^{***})-S(O)₂R^{***}, -OR^{***}, -O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***}, -S(O)₂-NR^{***}R^{***}, -N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C₁₋₆ alkyl. R^{***} is H, C₁₋₆ alkyl, benzyl, heterocyclyl or carbocyclyl. Preferably R² is selected from the group consisting of -H, -halogen, -CN, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(O)R^{**}, -N(R^{**})-C(O)-OR^{**}, -N(R^{**})-C(O)-NR^{**}R^{**}, -N(R^{**})-S(O)₂R^{**}, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted C₃₋₆ cycloalkyl), -OR^{**}, -(optionally substituted heterocyclyl), -(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl), and -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H,

-(optionally substituted C_{1-6} alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(0)R^{***}, -COOR^{***}, -C(0)NR^{***}R^{**}, -NR^{***}R^{**}, -NR^{***}-C(0)R^{***},
 5 -N(R^{***})-C(0)-OR^{**}, -N(R^{***})-C(0)-NR^{***}R^{**}, -N(R^{***})-S(0)₂R^{***}, -OR^{***},
 -O-C(0)R^{***}, -O-C(0)-NR^{***}R^{**}, -SR^{**}, -S(0)R^{***}, -S(0)₂R^{***}, -S(0)₂-NR^{***}R^{**},
 -N(R^{***})-S(0)₂-NR^{***}R^{**}, -P(0)(OR^{***})₂, or -O-P(0)(OR^{***})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C_{1-6} alkyl. R^{***} is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. More preferably, R² is selected from the group consisting of -H,
 10 -halogen, -CN, -NR^{**}R^{**}, -NR^{**}-C(0)R^{**}, -N(R^{**})-C(G)-GR^{**}, -N(R^{**})-C(0)-NR^{**}R^{**},
 -N(R^{**})-S(0)₂R^{**}, -OR^{**}, -(optionally substituted C_{1-6} alkyl), -(optionally substituted C_{3-6} cycloalkyl), -(optionally substituted C_{1-4} alkylene)-(optionally substituted heterocyclyl),
 -(optionally substituted C_{1-4} alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H,
 -(optionally substituted C_{1-6} alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally substituted) can be independently -halogen, -CN,
 15 -NO₂, oxo, -C(0)R^{**}, -COOR^{**}, -C(0)NR^{**}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(0)R^{**},
 -N(R^{**})-C(0)-OR^{**}, -N(R^{**})-C(0)-NR^{**}R^{**}, -N(R^{**})-S(0)₂R^{**}, -OR^{**},
 -O-C(0)R^{**}, -O-C(0)-NR^{**}R^{**}, -SR^{**}, -S(0)R^{**}, -S(0)₂R^{**}, -S(0)₂-NR^{**}R^{**},
 -N(R^{**})-S(0)₂-NR^{**}R^{**}, -P(0)(OR^{**})₂, or -O-P(0)(OR^{**})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C_{1-6} alkyl. R^{***} is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. Even more preferably R² is -H.

R³ is selected from the group consisting of -H, -halogen, -CN, -NO₂, -C(0)R^{**}, -COOR^{**},
 25 -C(0)NR^{**}R^{**}, -OR^{**}, -SR^{**}, -S(0)R^{**}, -S(0)₂R^{**}, -(optionally substituted C_{1-6} alkyl),
 -(optionally substituted C_{3-6} cycloalkyl), -(optionally substituted C_{1-4} alkylene)-(optionally substituted heterocyclyl), -(optionally substituted C_{1-4} alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H, -(optionally substituted C_{1-6} alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally substituted) can be
 30 independently -halogen, -CN, -NO₂, oxo, -C(0)R^{***}, -COOR^{***}, -C(0)NR^{***}R^{***},
 -NR^{***}R^{***}, -NR^{***}-C(0)R^{***}, -N(R^{***})-C(0)-OR^{**}, -N(R^{***})-C(0)-NR^{***}R^{***},
 -N(R^{***})-S(0)₂R^{***}, -OR^{***}, -O-C(0)R^{***}, -O-C(0)-NR^{***}R^{***}, -SR^{***}, -S(0)R^{***},
 -S(0)₂R^{***}, -S(0)₂-NR^{***}R^{***}, -N(R^{***})-S(0)₂-NR^{***}R^{***}, -P(0)(OR^{***})₂, or
 -O-P(0)(OR^{***})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C_{1-6} alkyl. R^{***} is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. Even more preferably R² is -H.

substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C₁₋₆ alkyl. R^{***} is H, C₁₋₆ alkyl, benzyl, heterocyclyl or carbocyclyl.

Preferably, R³ is selected from the group consisting of -H, -halogen, -CN, -NO₂, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{*}, -OR^{*}, -(optionally substituted C₁₋₆ alkyl), -(optionally

substituted C₃₋₆ cycloalkyl), -(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl), - (optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl),

wherein R^{**} is H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally substituted) can be independently

-halogen, -CN, -NO₂, oxo, -C(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{***}, -NR^{***}R^{***},

-NR^{***}-C(O)R^{***}, -N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, -N(R^{***})-S(O)₂R^{***},

-OR^{***}, -O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***},

-S(O)₂-NR^{***}R^{***}, -N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂. in the

case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the

-(optionally substituted) can be any of the aforementioned substituents or can be C₁₋₆ alkyl.

R^{***} is H, C₁₋₆ alkyl, heterocyclyl or carbocyclyl. More preferably, R³ is selected from the group consisting of -H, -halogen, -CN, -OR^{*}, -(optionally substituted C₁₋₆ alkyl),

-(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl). -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl). wherein R^{*} is H, -(optionally

substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl). or -(optionally substituted

carbocyclyl). The -(optionally substituted) can be independently -halogen, -CN, oxo,

-C(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{***}, -NR^{***}R^{***}, -NR^{***}-C(O)R^{***},

-N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, -N(R^{***})-S(O)₂R^{***}, -OR^{***},

-O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***}, -S(O)₂-NR^{***}R^{***},

-N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂. In the case of -(optionally

substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted)

can be any of the aforementioned substituents or can be C₁₋₆ alkyl. R^{***} is H, C₁₋₆ alkyl,

heterocyclyl or carbocyclyl. Even more preferably R³ is -halogen.

Alternatively, R² and R³ are linked together to form, with the carbon atoms to which they are

attached, a carbocyclic or heterocyclic 5 to 7-membered ring which optionally comprises 0

to 3 heteroatoms (e.g., selected from N, O and S, particularly N or O, more particularly N) in

the ring and which may be substituted with one or more substituents independently selected

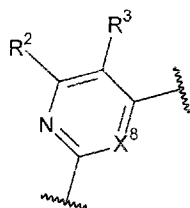
from R⁶. Preferably R² and R³ are linked together to form, with the carbon atoms to which

they are attached, a 5 or 6-membered carbocyclic or heterocyclic ring which comprises 0, 1

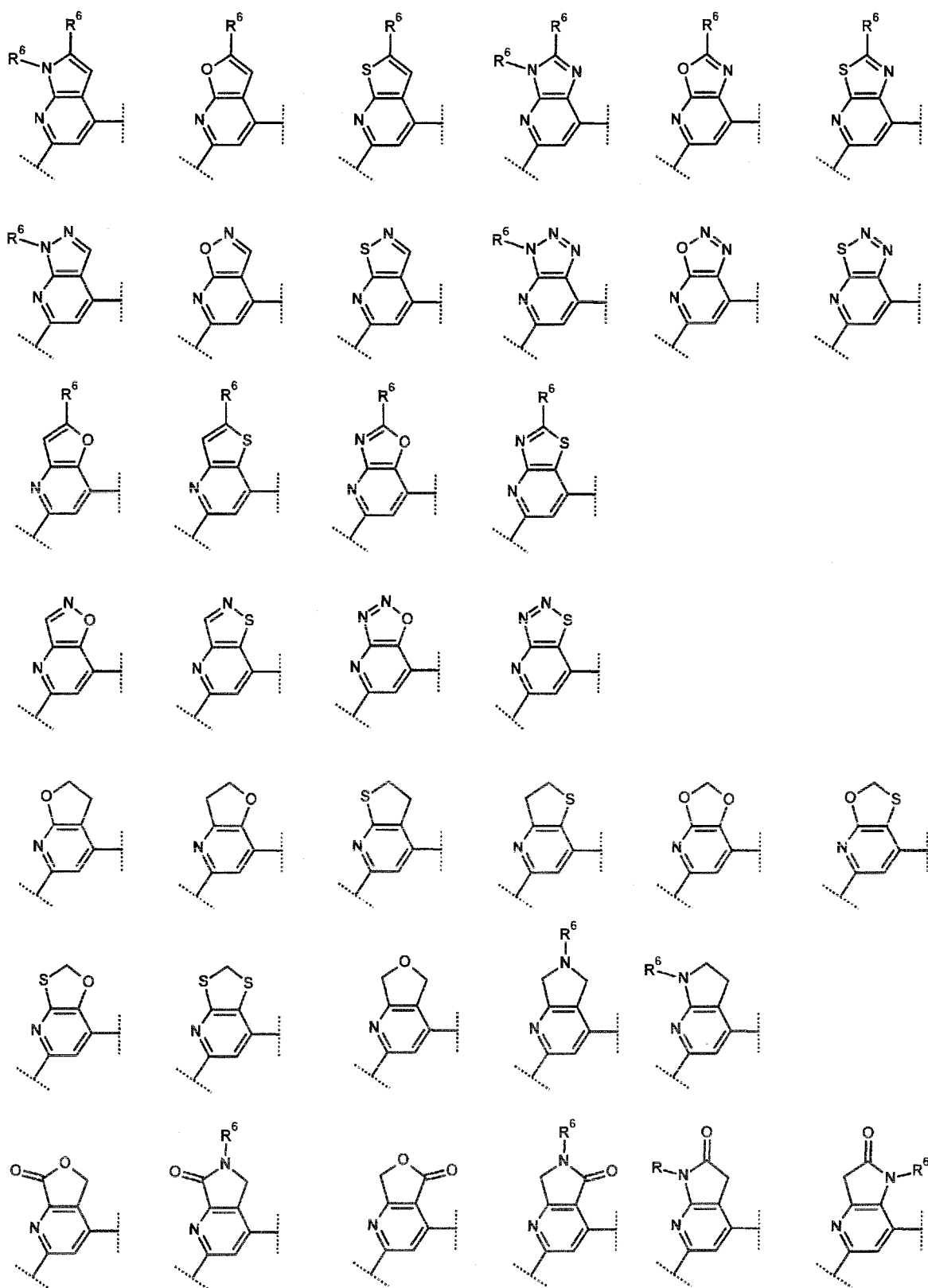
or 2 heteroatoms (e.g., selected from N, O and S, particularly N or O, more particularly N) in

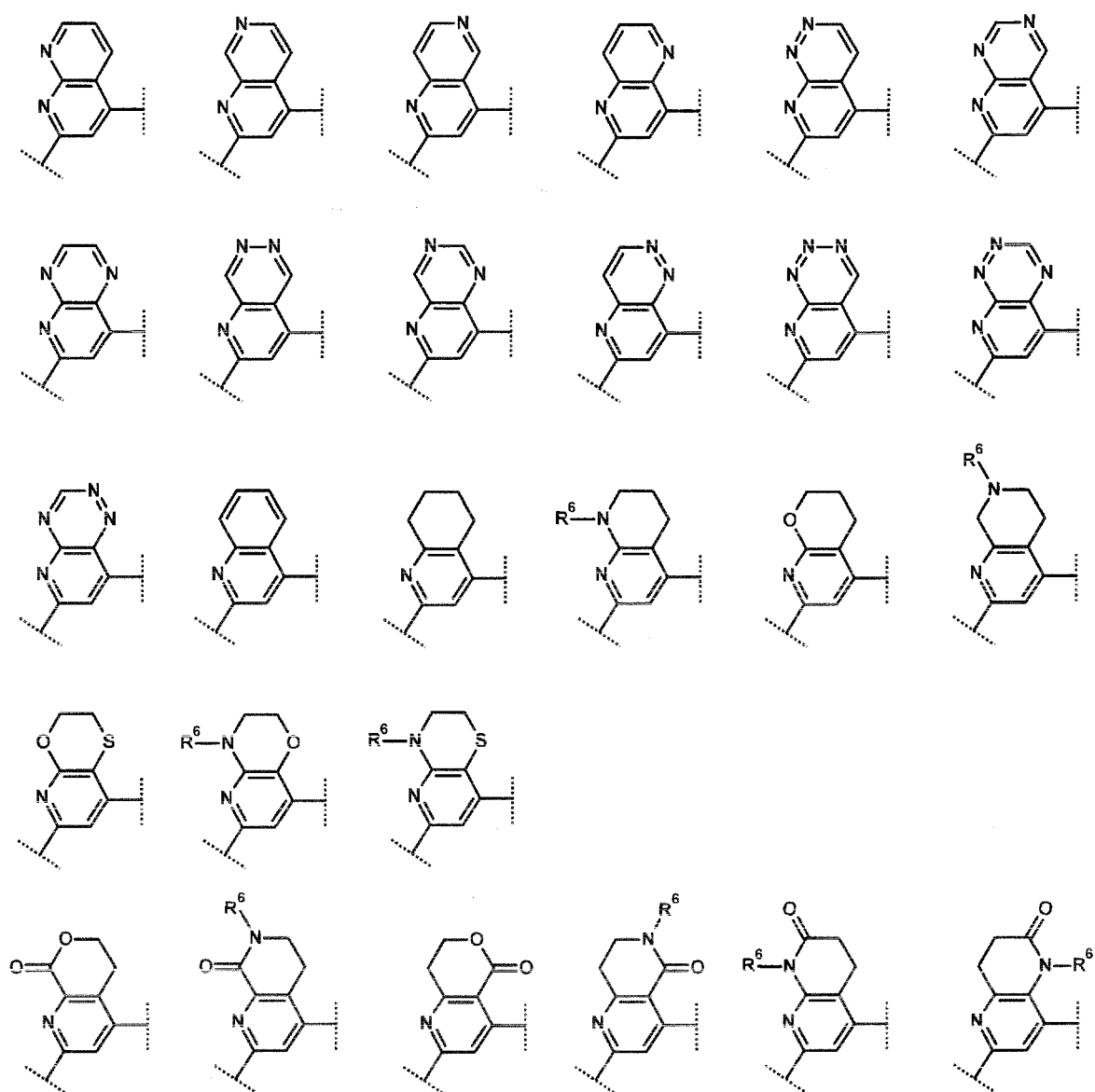
the ring and which may be substituted with one or more substituents independently selected from **R**⁶.

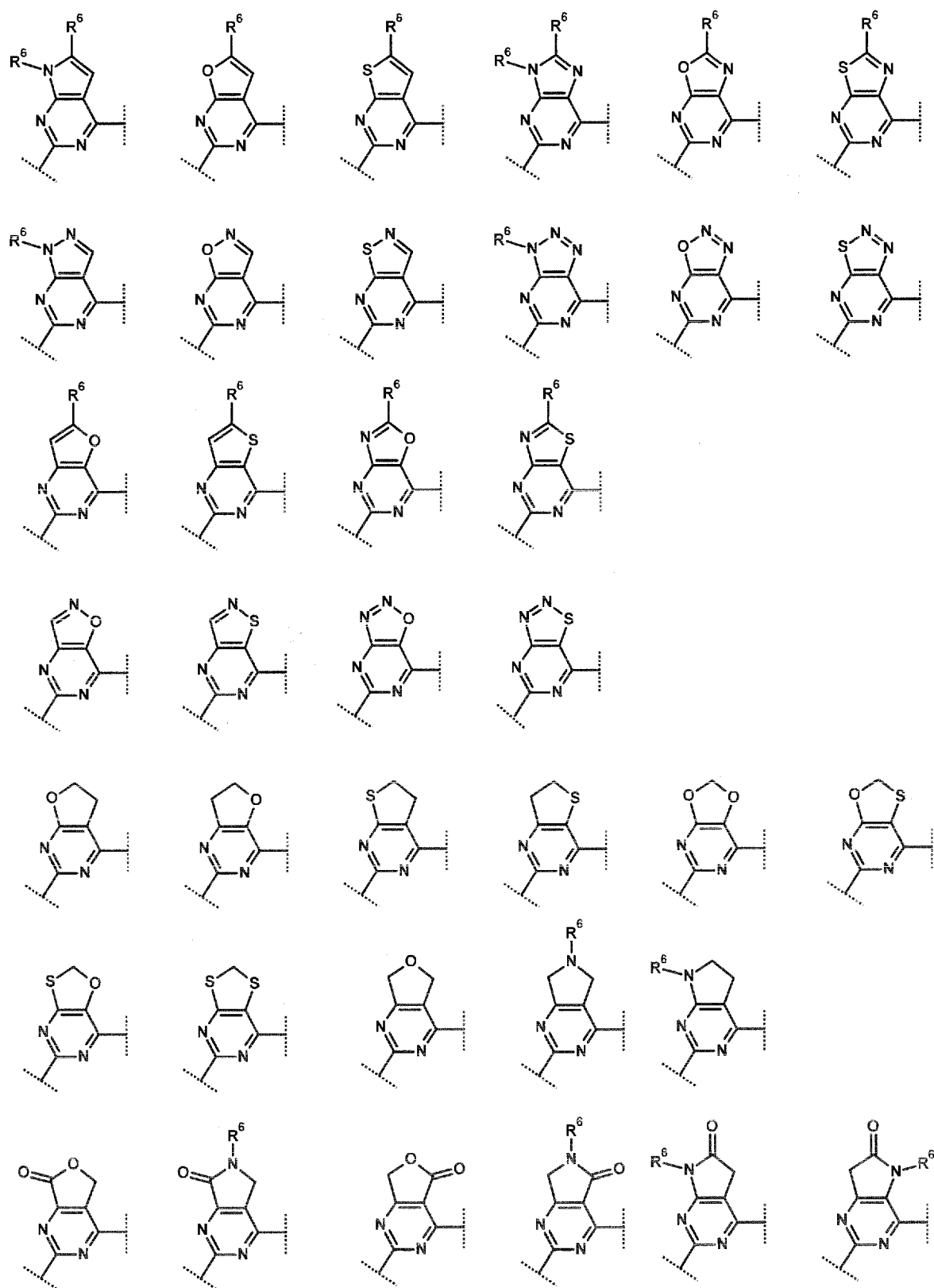
5 In the present invention, when **R**² and **R**³ are linked together to form, with the carbon atoms to which they are attached, a carbocyclic or heterocyclic 5 to 7-membered ring which optionally comprises 0 to 3 heteroatoms in the ring, the substructure

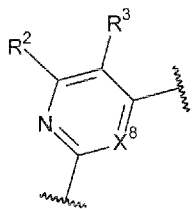
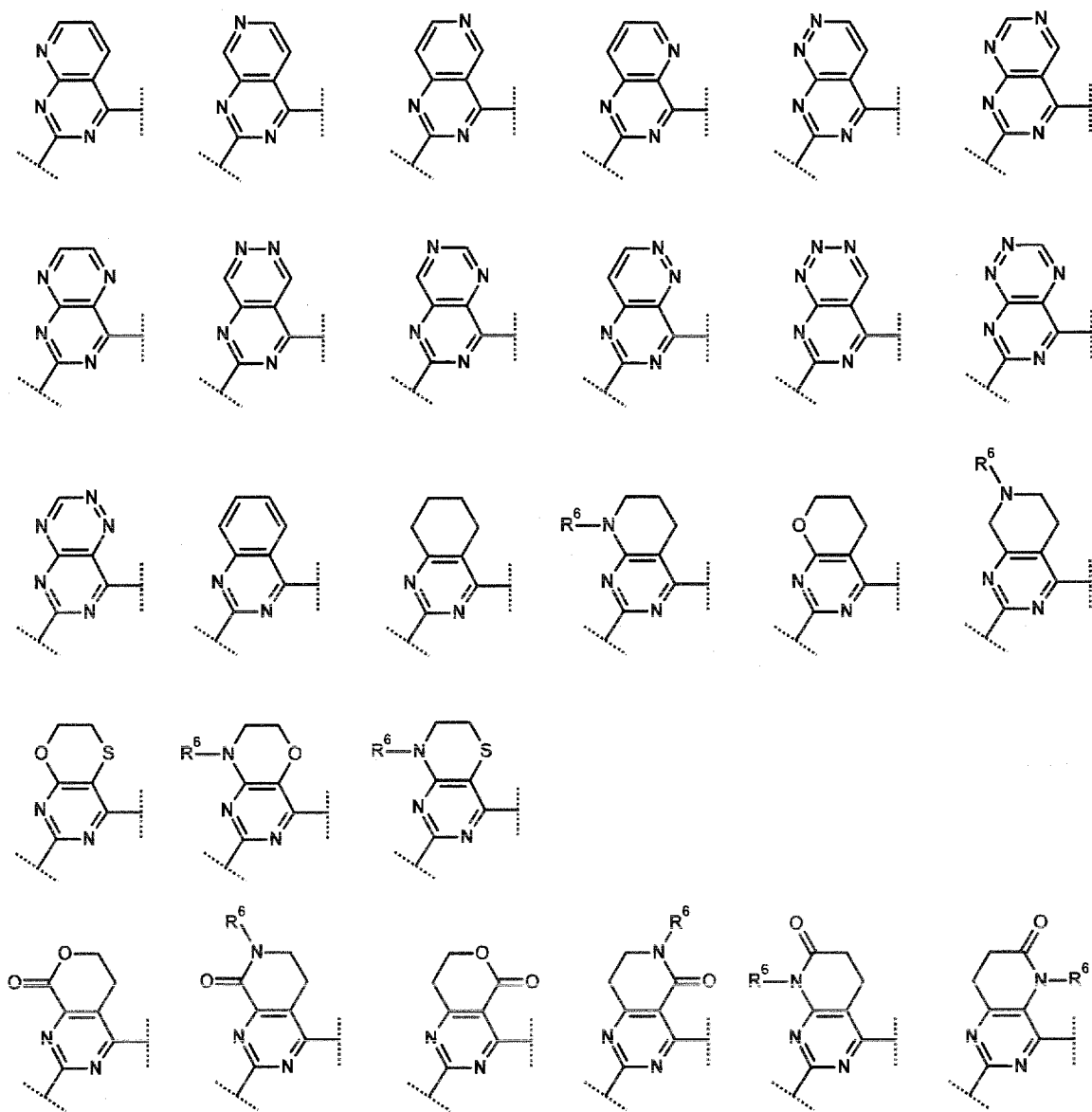


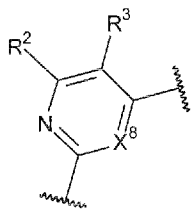
can be chosen from the following non-limiting examples:

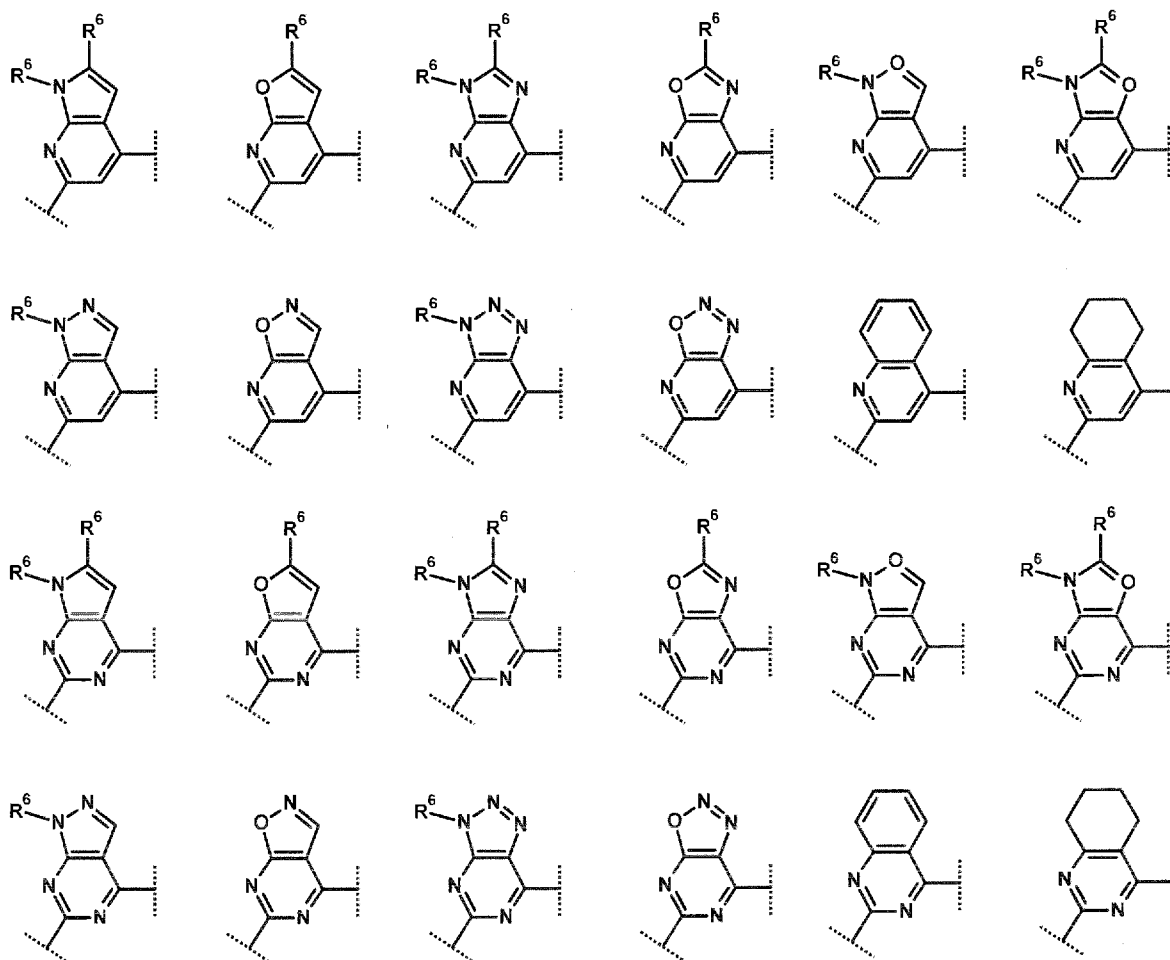




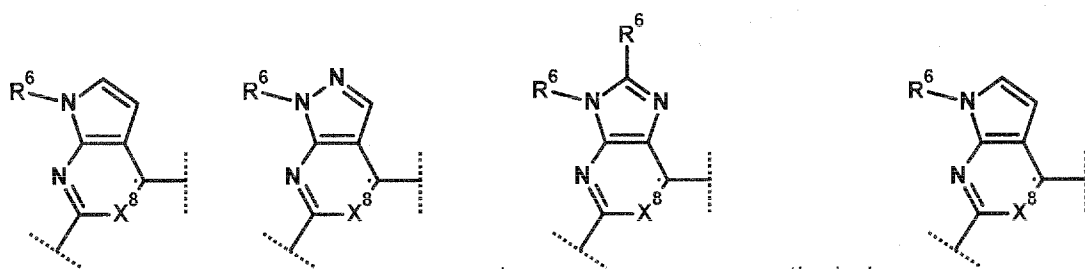




Preferred examples of  are the following



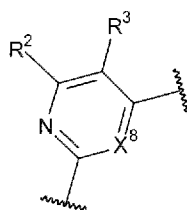
More preferred is



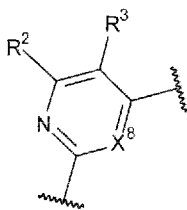
5

, and

, particularly



It is to be understood that in any examples of  in which one or more C-H groups are indicated, these may each optionally be replaced by C-R⁶. Furthermore, any



CH₂ groups in the examples of  may be replaced by CR⁶R⁶.

- 5 **R⁴** is selected from the group consisting of -H and -(optionally substituted C₁₋₆ alkyl), -(optionally substituted carbocyclyl), and -(optionally substituted heterocyclyl), wherein the -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{*}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(O)R^{**}, -N(R^{**})-C(O)-OR^{**}, -N(R^{**})-C(O)-NR^{*}R^{**}, -N(R^{**})-S(O)₂R^{**}, -OR^{**}, -O-C(O)R^{**}, -O-C(O)-NR^{**}R^{**},
 10 -SR^{**}, -S(O)R^{**}, -S(O)₂R^{**}, -S(O)₂-NR^{**}R^{**}, -N(R^{**})-S(G)₂-NR^{**}R^{**}, -P(O)(OR^{**})₂, or -O-P(O)(OR^{**})₂. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be C₁₋₆ alkyl. R^{**} is H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl which can optionally be substituted with halogen. Preferably **R⁴** is -C₁₋₆ alkyl or -H, more preferably -H.

15

R^{5a} is selected from the group consisting of -halogen, -OR^{*}, and -CN, wherein R^{*} is -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl). Preferably **R^{5a}** is selected from the group consisting of -halogen, -CN, and -O-(optionally substituted C₁₋₆ alkyl).

20

R^{5b} is selected from the group consisting of -H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl), -(optionally substituted d₁₋₄ alkylene)-(optionally substituted heterocyclyl) and -(optionally substituted d₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{*} is -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl).
 25 Preferably **R⁵** is selected from the group consisting of -H, -(optionally substituted d₁₋₄ alkylene), -(optionally substituted heterocyclyl), and -(optionally substituted carbocyclyl).

Preferably R^{5b} is selected from the group consisting of -H, -(optionally substituted C_{1-6} alkyl), -(optionally substituted heterocyclyl), and -(optionally substituted carbocyclyl).

The -(optionally substituted heterocyclyl) and -(optionally substituted carbocyclyl) may furthermore be bridged and the bridge may contain 0 to 2 carbon atoms and 0 to 2 heteroatoms.

The -(optionally substituted) can be independently -halogen, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-NR^*R^*$, $-NR^*COR^*$, $-NR^*C(O)NR^*R^*$, $-NR^*S(O_2)NR^*R^*$, $-C(O)OR^*$, $-C(O)NR^*R^*$, $-OR^*$, or $-O-C_{1-6}$ alkyl, wherein each R^* is H, C_{1-6} alkyl or C_{3-6} cycloalkyl. In the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl) the -(optionally substituted) can be any of the aforementioned substituents or can be Cl_{1-6} alkyl.

R^6 is independently selected from the group consisting of -H, -Hal, $-OR^{**}$, OxO , -CN, $-NO_2$, $-C(O)R^{**}$, $-COOR^{**}$, $-C(O)NR^{**}R^{**}$, $-NR^{**}R^{**}$, $-NR^{**}C(O)R^{**}$, $-NR^{**}C(O)NR^{**}R^{**}$, $-NR^{**}S(O_2)NR^{**}R^{**}$, $-(CH_2)_pSR^{**}$, $-(CH_2)_pS(O)R^{**}$, $-(CH_2)_pSO_2R^{**}$, $-(CH_2)_pSO_2NR^{**}$, -(optionally substituted C_{1-5} alkyl), $-C(O)NR^{**}R^{**}$, $-NR^{**}R^{**}$, $-NR^{**}C(O)R^{**}$, $-NR^{**}C(O)NR^{**}R^{**}$, $-NR^{**}S(O_2)NR^{**}R^{**}$, $-(CH_2)_pSR^{**}$, $-(CH_2)_pS(O)R^{**}$, $-(CH_2)_pSO_2R^{**}$, $-(CH_2)_pSO_2NR^{**}$, -(optionally substituted C_{1-6} alkyl), -O-(optionally substituted C_{1-6} alkyl), -(optionally substituted C_{1-4} alkylene)-O-(optionally substituted C_{1-6} alkyl). The —(optionally substituted) can be independently -H, —halogen, -OH, and -CN. Preferably, R^6 is independently selected from the group consisting of -H, -Hal, $-OR^{**}$, -CN, $-NO_2$, $-C(O)R^{**}$, $-COOR^{**}$, $-C(O)NR^{**}R^{**}$, $-NR^{**}R^{**}$, $-NR^{**}C(O)R^{**}$, $-NR^{**}C(O)NR^{**}R^{**}$, $-NR^{**}S(O_2)NR^{**}R^{**}$, $-(CH_2)_pSR^{**}$, $-(CH_2)_pS(O)R^{**}$, $-(CH_2)_pSO_2R^{**}$, $-(CH_2)_pSO_2NR^{**}$, -(optionally substituted C_{1-6} alkyl), -O-(optionally substituted C_{1-6} alkyl), -(optionally substituted carbocyclyl) and -(optionally substituted heterocyclyl), wherein R^{**} is H, -(optionally substituted C_{1-6} alkyl), -(optionally substituted C_{1-4} alkylene)-O-(optionally substituted C_{1-6} alkyl). The -(optionally substituted) can be independently -H, -halogen, -OH, and -CN. More preferably, R^6 is selected from the group consisting of -H, -Hal, and -(optionally substituted C_{1-6} alkyl). The optionally substituted is preferred to be -halogen.

R^7 is selected from the group consisting of -H and $-Cl_{1-6}$ alkyl. Preferably R^7 is -H or $-CH_3$, more preferably R^7 is -H.

R^8 is independently selected from the group consisting of -H, -Hal, -CN, -NR^{**}R^{**},
 -(optionally substituted C₁₋₆alkyl), -OR^{**}, -(optionally substituted heterocyclyl), -(optionally
 substituted carbocyclyl), wherein R^{**} is H, -(optionally substituted C₁₋₆ alkyl), -(optionally
 substituted heterocyclyl), or -(optionally substituted carbocyclyl). The -(optionally
 5 substituted) is preferably halogen. Preferably R^8 is -H.

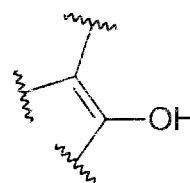
R^9 is independently selected from the group consisting of -H, -C₁₋₆ alkyl, -Hal, -OR^{*},
 -NR^{*}R^{*}, -CN, and CF₃, wherein R^{*} is -H or -C₁₋₆ alkyl. Preferably R^9 is -H or -Hal.

10 R^{10} is independently selected from the group consisting of -H, -Hal, -CN, -NO₂,
 -(optionally substituted C₁₋₆ alkyl), -NR^{*}R^{*}, and -OR^{*}, wherein R^{*} is -H, or -(optionally
 substituted C₁₋₆ alkyl). The -(optionally substituted) is preferably halogen. Preferably R^{10} is
 -H.

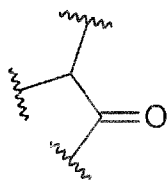
15 X^1 is selected from the group consisting of N and C. In one embodiment, X^1 is N. In another
 embodiment X^1 is C.

X^2 is selected from the group consisting of N and CR⁹. In one embodiment, X^2 is N. In
 another embodiment, X^2 is CR⁹.

20



When X^2 is C-R⁹ and R⁹ is -OH, e.g., resulting in the partial structure , any
 compound containing the tautomer thereof having the following partial structure



is also comprised.

25 X^3 is selected from the group consisting of N, NR⁹, CR⁹ and CR⁹₂, as valency permits. In
 one embodiment, if " X^2 ----- X^3 " is " X^2 - X^3 ", then X^3 is NR⁹. In another embodiment, X^2 -----
 X^3 is " X^2 = X^3 " then X^3 is CR⁹.

X^4 is selected from the group consisting of N and CR^9 . In one embodiment, X^4 is N. In further embodiment, X^4 is CR^9 . In a further embodiment, X^4 is C-Hal (e.g., C-F), wherein Hal may be any halogen isotope.

- 5 X^5 is selected from the group consisting of N and CR^8 . In one embodiment, X^5 is N. In another embodiment, X^5 is CR^8 .

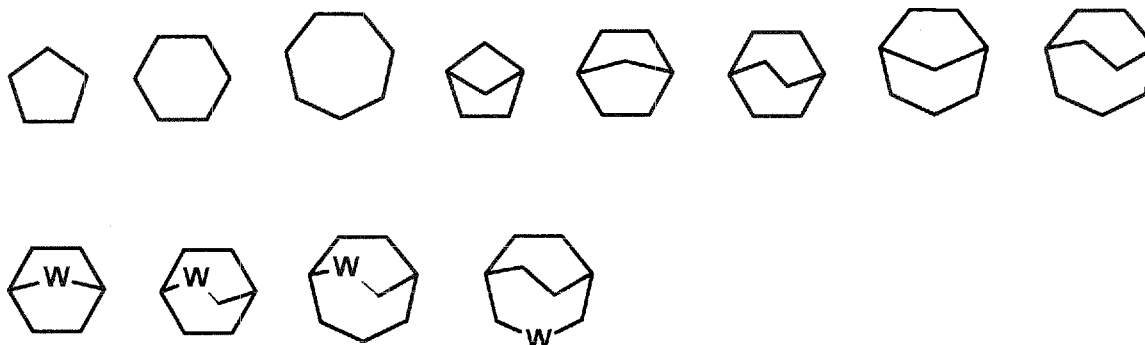
X^6 is selected from the group consisting of N and CR^1 . In one embodiment, X^6 is N. In another embodiment, X^6 is CR^1 , wherein R^1 is preferably -H, -halogen, -CN, -CH₃,
10 -CH₂CH₃, -CH(CH₃)₂, -cyclopropyl, -CF₃, -CHF₂, or -CH₂F.

X^7 is selected from the group consisting of N and CR^8 . In one embodiment, X^7 is N. In another embodiment, X^7 is CR^8 .

- 15 The above definitions apply with the proviso that $X^1 \text{-----} X^2 \text{-----} X^3$ is $X^1 \text{---} X^2 \text{---} X^3$ if X^1 is N and $X^1 \text{-----} X^2 = \text{---} X^3$ is $X^1 \text{---} X^2 \text{---} X^3$ if X^1 is C; and with the further proviso that at least one of X^1 , X^2 , and X^3 is N or NR^9 .

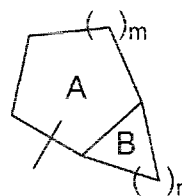
- 20 X^8 is selected from the group consisting of N and CR^{10} . In one embodiment, X^8 is N. In another embodiment, X^8 is CR^{10} .

The ring A is a saturated monocyclic carbocyclic ring having 5 to 8 ring carbon atoms or a saturated bridged carbocyclic ring having 5 to 8 ring carbon atoms and 1 to 3 carbon atoms in the bridge or a saturated bridged heterocyclic ring having 5 to 8 ring carbon atoms and 0
25 to 2 heteroatoms (e.g., selected from N, O and S) in the ring, and 0 to 2 carbon atoms and 0 to 2 heteroatoms (e.g., selected from N, O and S) in the bridge, provided that there is at least one heteroatom in the saturated bridged heterocyclic ring, which may be either in the main ring or in the bridge. Preferably the ring A is a saturated monocyclic carbocyclic ring having 5 or 6 ring carbon atoms or a saturated bridged carbocyclic ring having 6 or 7 ring
30 carbon atoms and 1 or 2 carbon atoms in the bridge or a saturated bridged heterocyclic ring having 6 or 7 ring carbon atoms, and 1 or 2 carbon atoms and 1 to 2 heteroatoms in the bridge (e.g., selected from N, O and S). Preferred examples of the ring A include



wherein each W is independently selected from C, N, O and S, wherein ring A can be substituted in any available position by one or two substituents which are selected from the group consisting of -L-R⁵.

5



It is to be understood that the corners of the ring A in are not limited to represent substituted or unsubstituted carbon atoms but one or more of these corners may also represent substituted or unsubstituted heteroatoms (e.g., selected from N, O and S).

- 10 The ring A can be optionally substituted in any available position by one or more substituents which are selected from the group consisting of -L-R⁵ in a preferred embodiment the ring A is substituted, for example by one or two substituents.

The ring A can be attached to the -N(R⁴)- moiety at any available position.

15

The ring B is fused to the ring A. The ring B is a saturated monocyclic carbocyclic ring having 3 to 6 ring carbon atoms. Preferably the ring B is a saturated monocyclic carbocyclic ring having 3 ring carbon atoms. A preferred example of the ring B is

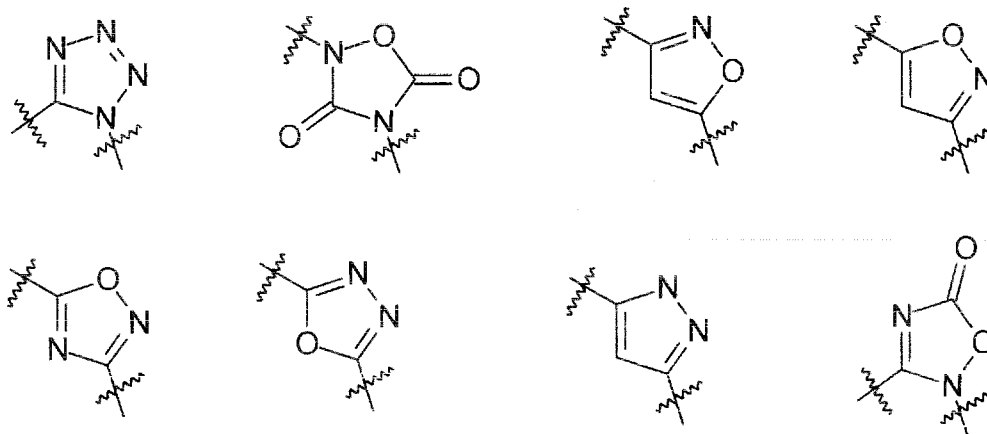


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The ring B can be optionally substituted in any available position by one or more substituents which are selected from the group consisting of -L-R⁵. Preferably the ring is unsubstituted.

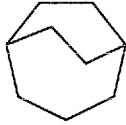
- L-R⁵ is selected from -L^a-R^{5a} and -L^b-R^{5b}, preferably -L-R⁵ is -L^b-R^{5b}.

L^a is selected from the group consisting of -(CH₂)_p-C(=O)-, -(CH₂)_p-CR⁷(OR⁷)-, -(CH₂)_p-C(=O)-N(R⁷)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-C(=O)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-S(=O)₂-, -(CR⁷R⁷)_p-S(=O)-, -(CR⁷R⁷)_p-S(=O)₂-, -(CR⁷R⁷)_p-S(=O)-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(=O)₂-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-(optionally substituted heterocyclylene)- and a bond. The optionally substituent of the heterocyclylene is independently selected from one or more groups selected from -Hal, -CN, -NO₂, -OH and -NH₂. The substituted heterocyclylene is preferably selected from 5- or 6-membered heterocyclene containing 1 to 4 heteroatoms independently selected from N, O and S. Specific examples of substituted heterocyclylenes are the following:



L^b is selected from the group consisting of -(CH₂)_p-C(=O)-O-, -(CH₂)_p-C(=O)-, -(CH₂)_p-CR⁷(OR⁷)-, -(CH₂)_p-C(=O)-N(R⁷)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-, -(CH₂)_p-N(R⁷)-C(=O)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-C(=O)-C(=O)-, -(CH₂)_p-N(R⁷)-C(Q)-O-, -(CH₂)_p-N(R⁷)-C(=O)-N(R⁷)-, -(CH₂)_p-N(R⁷)-S(=O)₂-, -N(R⁷)-S(=O)₂-N(R⁷)-, -(CH₂)_p-O-C(=O)-, -(CH₂)_p-O-C(=O)-N(R⁷)-, -(CR⁷R⁷)_p-O-, -(CR⁷R⁷)_p-S(=O)-, -(CR⁷R⁷)_p-S(=O)₂-, -(CR⁷R⁷)_p-S-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(=O)-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(=O)₂-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(=O)₂-N(R⁷)-, -(CR⁷R⁷)_p-S(=O)₂-N(R⁷)-C(=O)-, -(CR⁷R⁷)_p-P(=O)(OR⁷)O-, -O-P(=O)(OR⁷)O-, -P(=O)₂O-, -(CR⁷R⁷)_p-(optionally substituted heterocyclylene)- and a bond. The optionally substituent of the heterocyclylene is independently selected from one or more groups selected from -Hal, -CN, -NO₂, -OH and -NH₂. The substituted heterocyclylene is preferably selected from 5- or 6-membered heterocyclene containing 1 to 4 heteroatoms independently selected from N, O and S. Specific examples of substituted heterocyclylenes are shown above.

Preferably L^b is selected from the group consisting of $-C(O)-O-$, $-C(O)-N(R^7)-$, $-N(R^7)-C(O)-$, $-N(R^7)-C(O)-N(R^7)-$, and $-(CR^7R^7)_p-O-$. In more preferred examples, L^b is $-C(O)-O-$, $-N(R^7)-C(O)-$ or $-N(R^7)-C(O)-N(R^7)-$.

- 5 In one preferred embodiment, ring A is selected from  and , and L^b is $-C(O)O-$.

In another preferred embodiment, ring A is  or  and L^b is selected from $-N(R^7)-C(O)-$ and $-N(R^7)-C(O)-N(R^7)-$.

- 10 In one embodiment, L^b is $-(CR^7R^7)_p-O-$. In this embodiment R^{5b} is preferably $-H$ or $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, more preferably $-H$ or $-C_{1-6} \text{ alkyl}$.

- In another embodiment, L^b is selected from the group consisting of $-C(O)-O-$, $-O-C(O)-$, $-C(O)-N(R^7)-$, $-N(R^7)-C(O)-$, $-N(R^7)-C(O)-N(R^7)-$ and R^{5b} is selected from the group
 15 consisting of $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, $-(\text{optionally substituted heterocyclyl})$, and $-(\text{optionally substituted carbocyclyl})$, more preferably R^{5b} is selected from the group consisting of $-H$, $-C_{1-6} \text{ alkyl}$, $-(\text{optionally substituted heterocyclyl})$, and $-(\text{optionally substituted carbocyclyl})$.

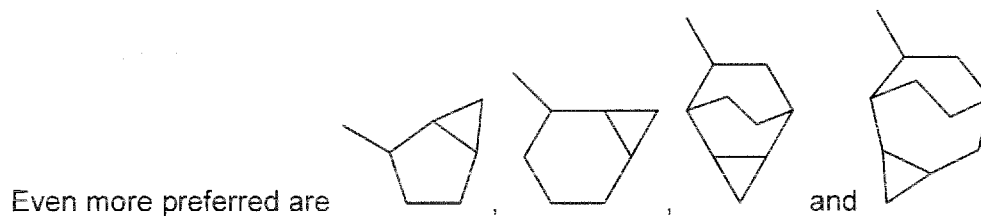
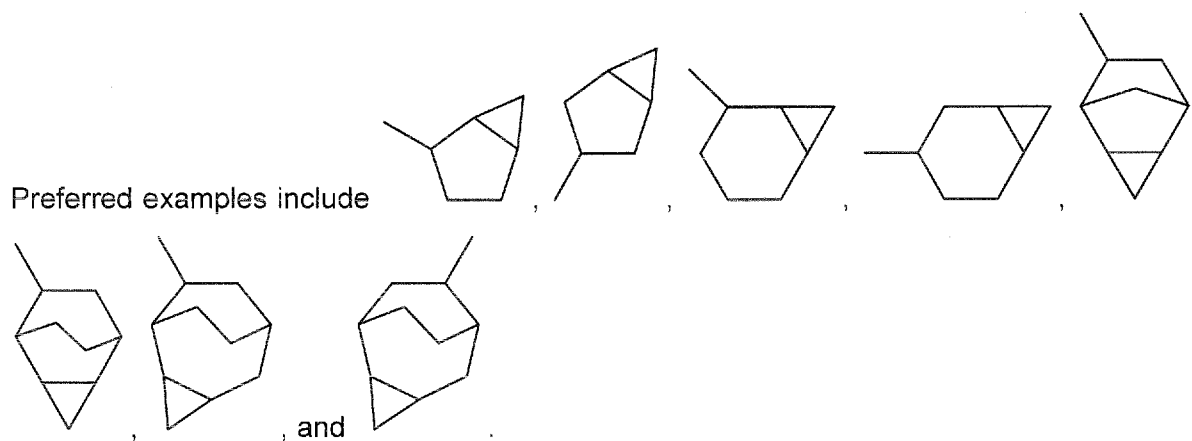
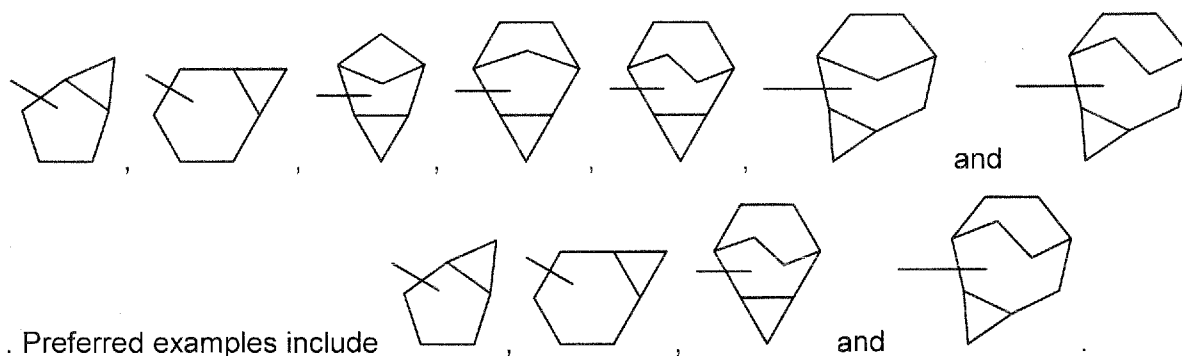
- 20 m is 1 to 3. Preferably m is 2 or 3.

n is 1 to 4. Preferably n is 1.

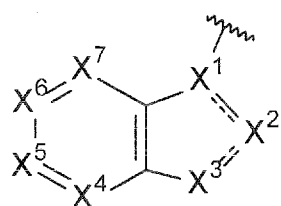
p is 0 to 6. Preferably p is 0 to 4, more preferably p is 0 or 1

25

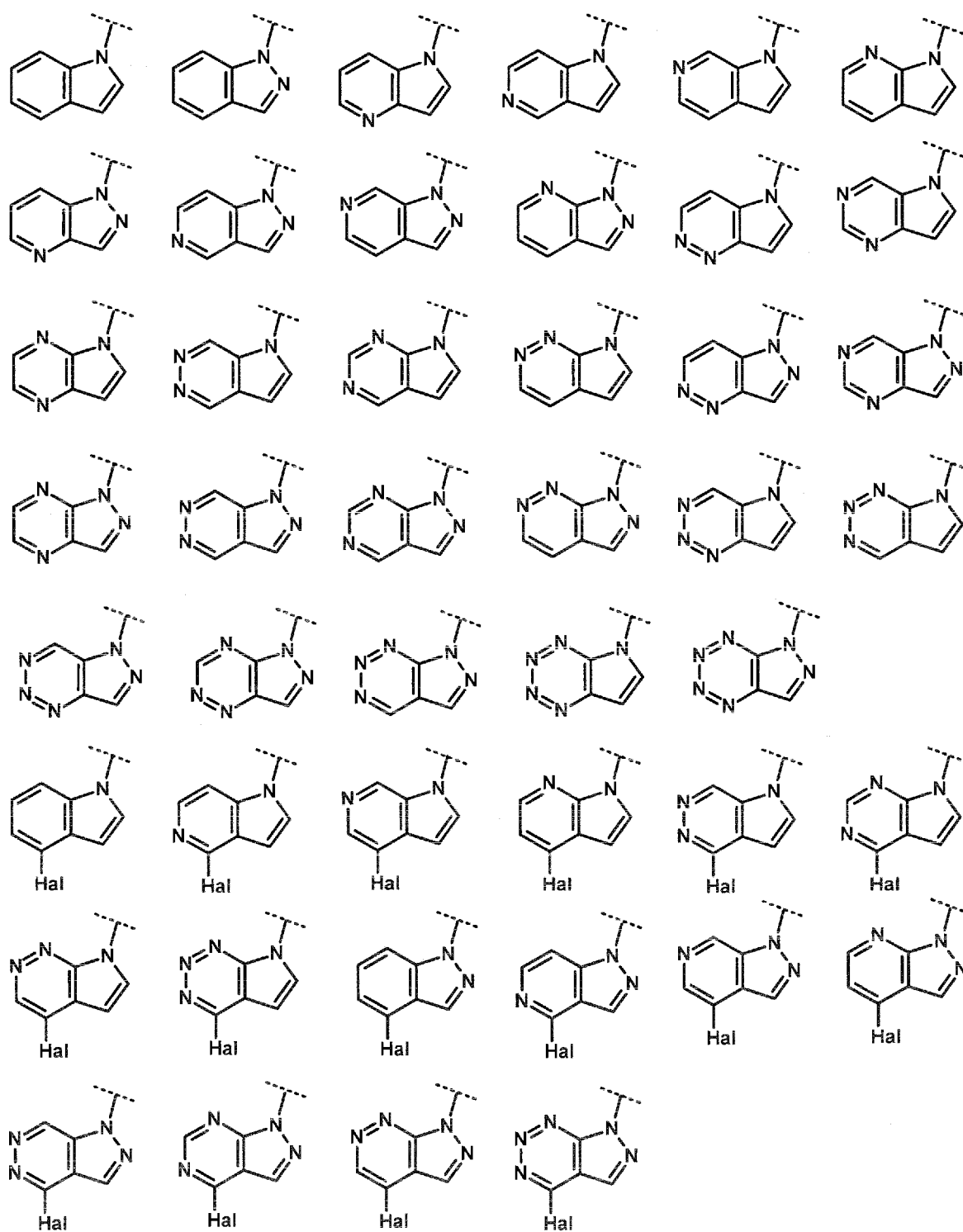
Examples of the fused ring system provided by rings A and B include:

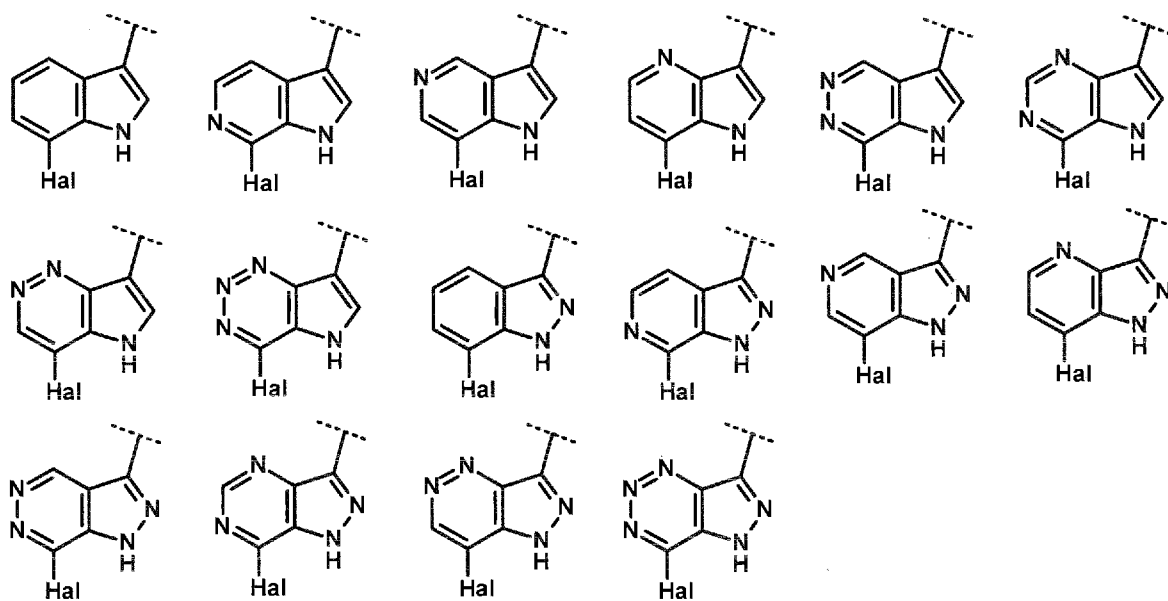


in the present invention,

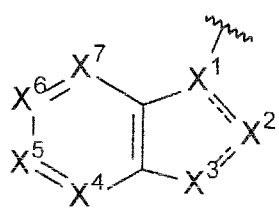
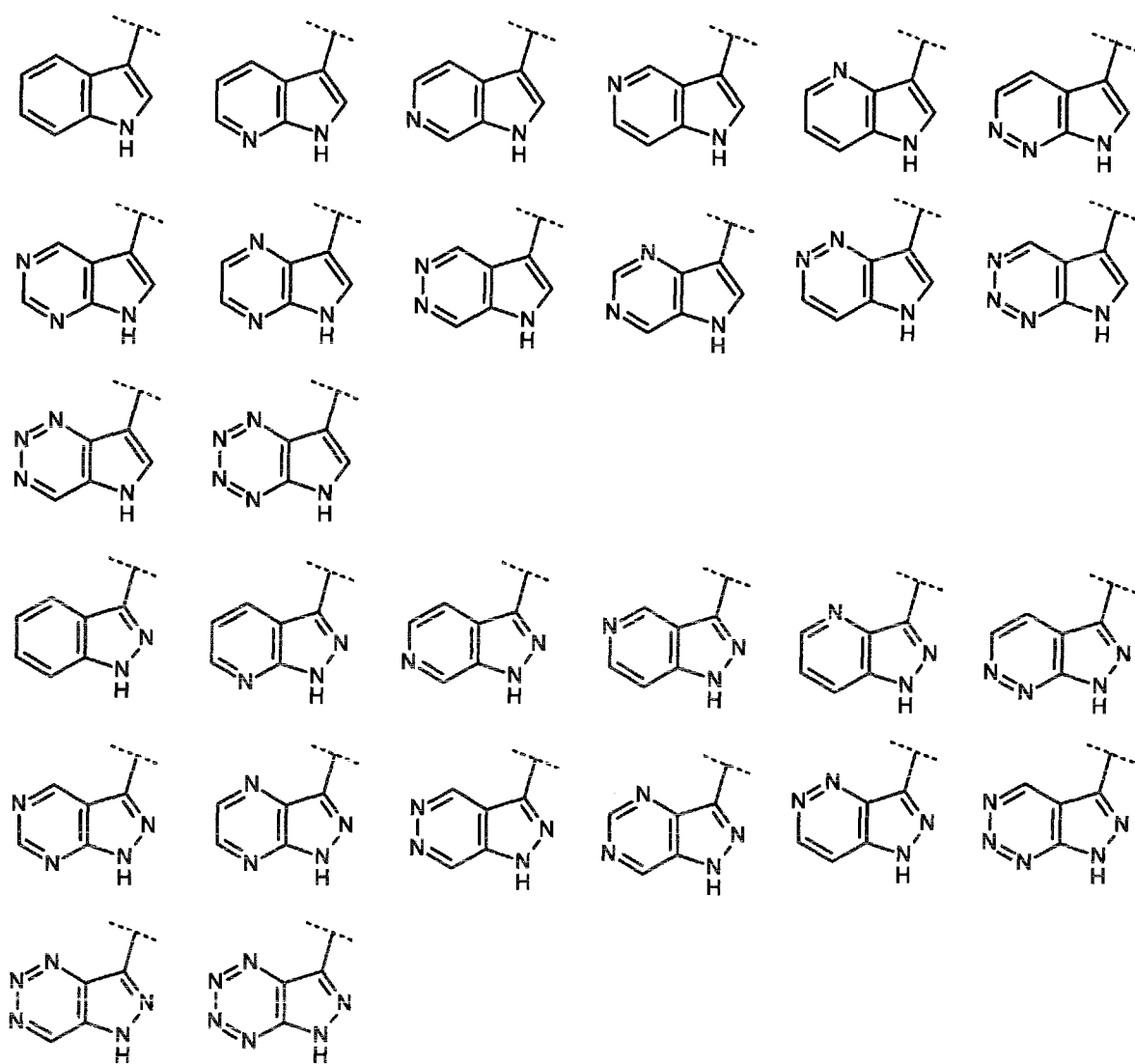


can be chosen from the following non-limiting examples:



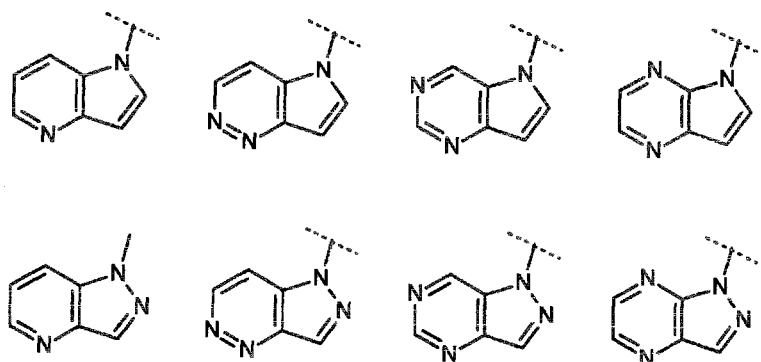


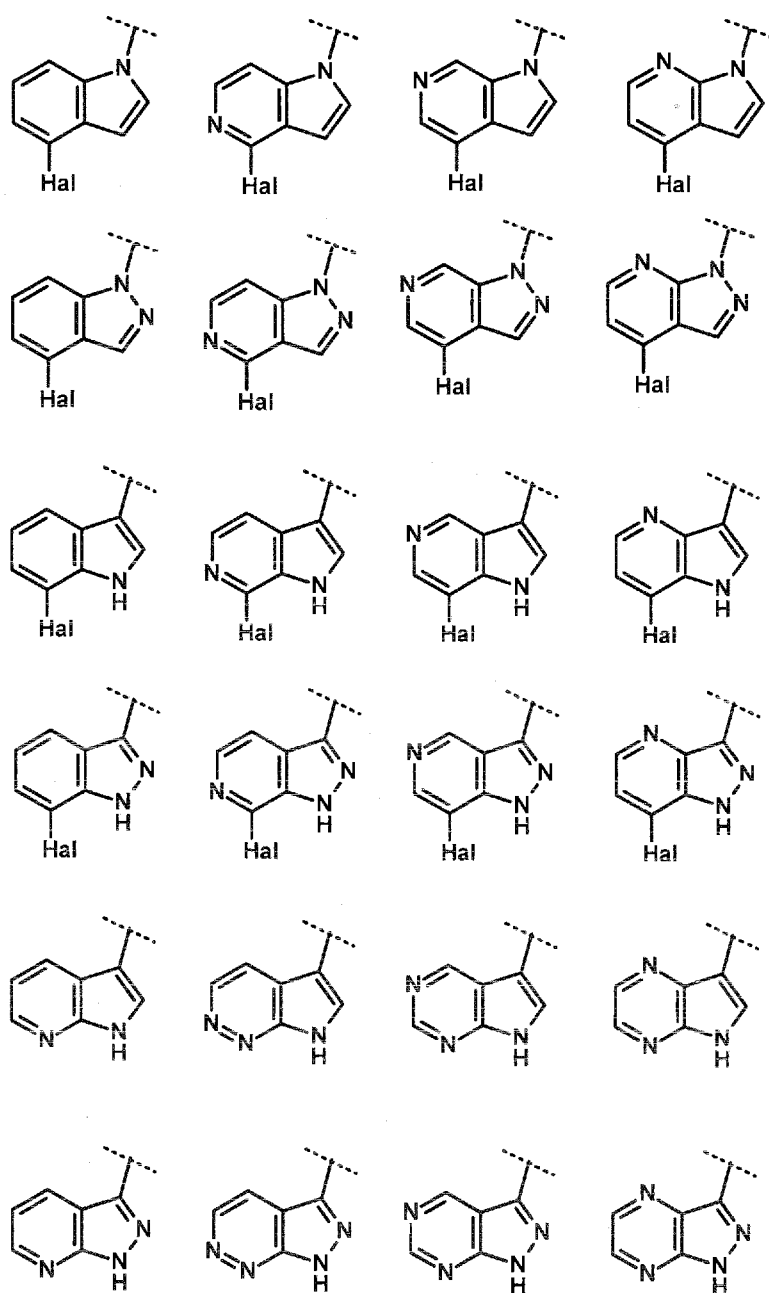
wherein Hal is selected from F, Cl, Br and I, preferably F,



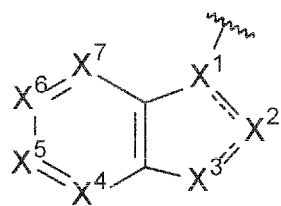
Preferably,

is selected from the group consisting of



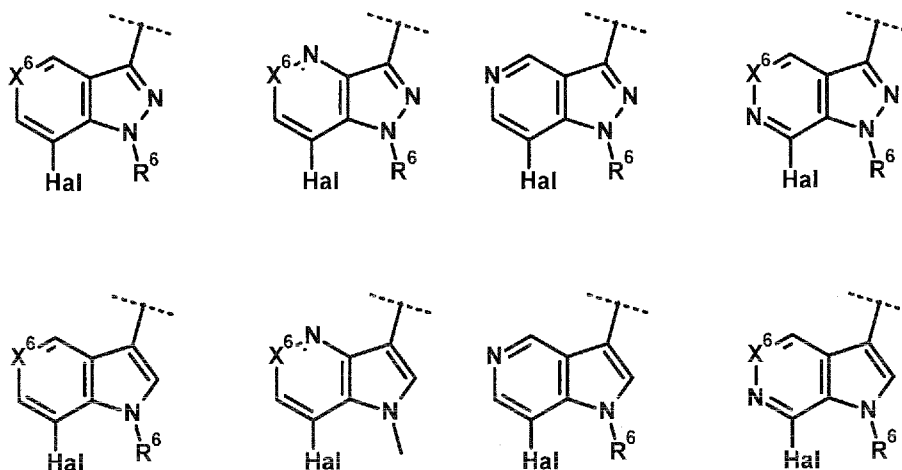


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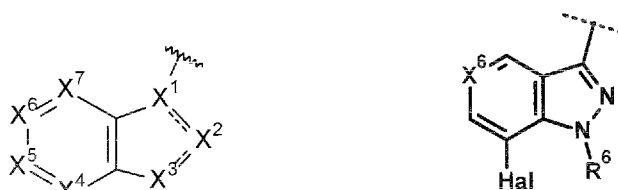
More preferably,

is selected from the group consisting of

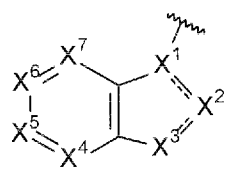


wherein X^6 is CR^1 . Preferably, R^1 is selected from H, F, Cl, Me, CF_3 , CHF_2 , CH_2F , OMe, OCF_3 , $OCHF_2$, OCH_2F , and cyclopropyl.

5

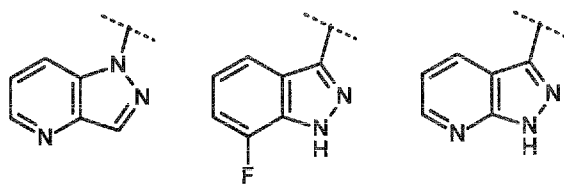


Even more preferably, is selected from wherein each X^6 is CR^1 . Preferably, R^1 is selected from H, F, Cl, Me, CF_3 , CHF_2 , CH_2F , OMe, OCF_3 , $OCHF_2$, OCH_2F and cyclopropyl, and R^6 is preferably H.

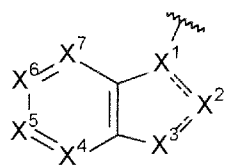


10 In the above examples of , the residue R_6 can be the same as R_9 .

Most preferred are:

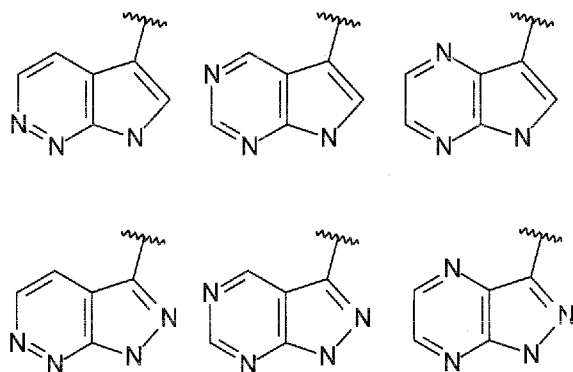


15

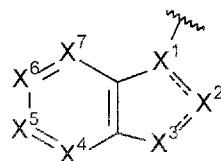


In one proviso,

does not represent any one of the following:



5

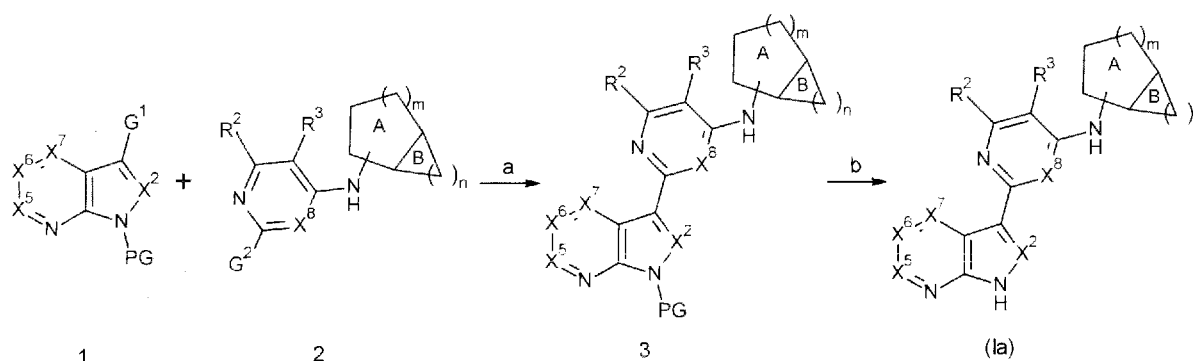


It is to be understood that in any examples of in which one or more of X¹, X², X³, X⁴, X⁵ and X⁷ is/are shown as CH, the CH may also be replaced by C-R⁸ and X⁶ may be replaced by C-R¹.

10 GENERIC SYNTHESIS / ASSAY DESCRIPTION

The compounds having the formula (I) can be prepared by any desired route. In one illustrative embodiment which is not limiting, the method comprises a step of reacting compound **1** with compound **2** to form a compound **3**, which after protection group cleavage to gives the compound having the formula (Ia), as shown in Scheme A below.

Scheme A



G¹ is halogen or boronic ester; G² is halogen or trialkylstannane;

Azaindole or azaindazole compounds **1** with G¹ = halogen (preferably iodine) are known.

5 They can be prepared by methods described in the exemplary synthesis of intermediates A, C, D and E or by methods known to a person skilled in the art. If desired, the amine group of the compounds **1** can be protected by an amine protecting group (PG). Any known amine protecting group such as THP, SEM, Ts, or Boc can be employed.

10 Azaindole or azaindazole compounds **1** with G¹ = halogen (preferably iodine) can then be converted to the corresponding azaindole or azaindazole 3-boronated intermediate. Any suitable reaction condition known in the art can be used for the generation of azaindole or azaindazole 3-boronated intermediate. For example, reaction of compound **1** with a boronic ester like 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-

15 dioxaborolane in a solvent like DMSO or dioxane in the presence of a base like potassium acetate and a catalyst like PdCl₂(dppf) at an elevated temperature about 70 °C can be used. If desired, the azaindole or azaindazole 3-boronated intermediate (G¹ = boronic acid/ester) can be purified by silica gel flash chromatography. Alternatively, it can be used without purification in the next reaction step. The azaindole or azaindazole 3-boronated

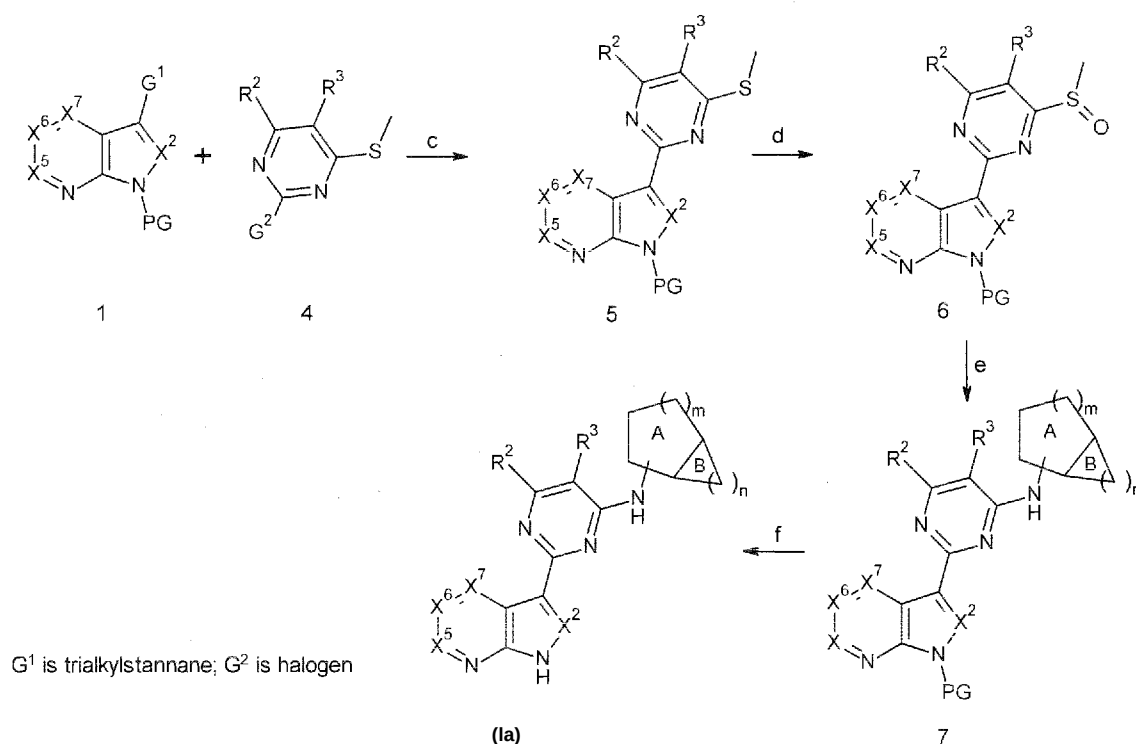
20 intermediate (G¹ = boronic acid/ester) can then be reacted with a suitable heteroaryl halide compound **2** (G² = halogen, bromine and chlorine preferred) in the presence of a catalyst like Pd₂(dba)₃, and in the presence of a base, such as K₃PO₄, and in a solvent, such as dioxane and H₂O, and in an inert atmosphere such as argon or nitrogen at a temperature range preferably from room temperature to about 130 °C to give a Suzuki coupling product,

25 compound **3** (step a). Alternatively, compound **3** can also be synthesized via a Stille coupling reaction known in the art. For example, reaction of compound **2** (G² = halogen, chlorine preferred) with a trialkyl tin reagent such as hexa-n-butyltin in a solvent like dioxane, in the presence of a catalyst like Pd(PPh₃)₄ at an elevated temperature about 125

°C can be used. The organo tin intermediate, obtained either in situ or after silica gel flash chromatography purification, can then be reacted with a suitable azaindole or azaindazole halide, compound 1 (G^1 = halogen, iodine preferred) in a solvent like dioxane, and in the presence of a catalyst like $\text{Pd}(\text{PPh}_3)_4$, and in an inert atmosphere such as argon or nitrogen at an elevated temperature of about 140 °C to give a Stille coupling product, compound 3 (step a). The Suzuki or Stille coupling product, compound 3 is then de-protected using conditions known in the art to give a compound represented by the formula (Ia), where the azaindole or azaindazole N1 substitution is H (step b). Specific conditions are described in the Examples Section below.

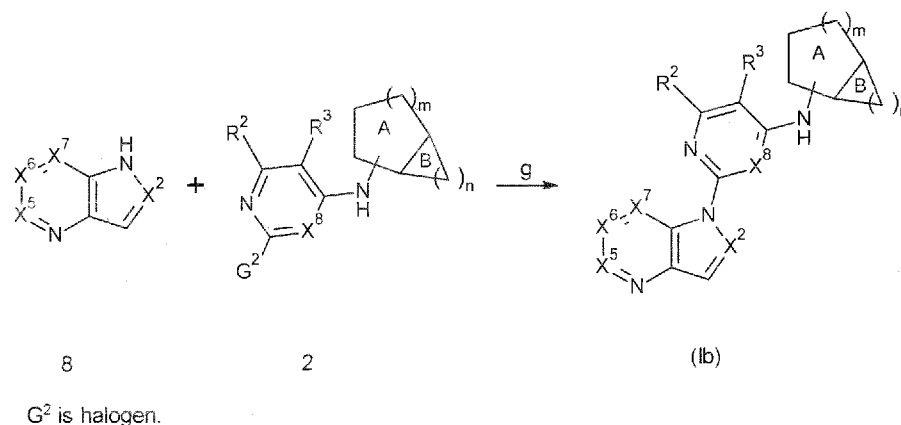
In another embodiment which is illustrated in Scheme B, the compounds of formula (Ia) can be prepared by a method which comprises the steps of reacting 2-chloro-6-methyl sulfide pyrimidine compound 4 with an organo tin Intermediate compound 1 (G^1 = trialkylstannane), which was generated in situ or by silica gel flash chromatography purification from reaction of azaindole or azaindazole compound 1 (G^1 = halogen, iodine preferred) with a trialkyl tin reagent like R_3Sn_2 in solvent like dioxane, and in the presence of a catalyst like $\text{Pd}(\text{PPh}_3)_4$ at an elevated temperature of about 100 °C (step c). The Stille coupling product, compound 5, then underwent oxidation using an oxidant such as mCPBA in a solvent like DCM to give a compound 6 (step d). Subsequent displacement of the sulfinyl compound 6 with an amine in the presence of a base, such as DSPEA, in a solvent like i-PrOH at an elevated temperature then affords compound 7 (step e). The definitions of structural formula (Ia), compounds 1, 2, 3, 4, 5, 6, and 7 are independently as defined in any of the embodiments described above. PG is a protecting group and can be for example THP, SEM, Ts, or Boc. The de-protecting reaction using conditions known in the art then generates the compounds of formula (Ia), where azaindole or azaindazole N1 substitution is H (step f). Specific conditions are described in the Examples Section below.

Scheme B



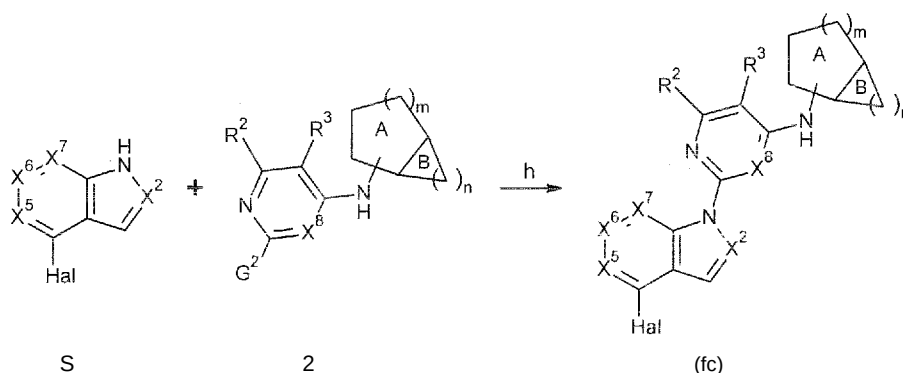
In another embodiment which illustrated in Scheme C, the compounds of formula (lb) can be prepared by a method via reaction of azaindole or azaindole compound 8 (such as intermediate F) with a suitable heteroaryl halide, compound 2 (G² = halogen, bromine and chlorine preferred) in a solvent like dioxane, in the presence of a catalyst like CuI, a ligand like (1R,2S)-cyclohexane-1,2-dioamine, and a base like potassium phosphate at elevated temperature about 120 °C to give a Ullmann coupling reaction product, compound (lb) (step g). The definitions of structural formula (lb) and compounds 2 and 8 are independently as defined in any of the embodiments described above. Specific conditions are described in the Examples Section below.

Scheme C



In another embodiment which illustrated in Scheme D, the compounds of formula (Ic) can be prepared by a method via reaction of 4-halogen substituted indole/azaindole or indazole/azaindazole compound 9 with a suitable heteroaryl halide, compound 2 (G^2 = halogen, bromine and chlorine preferred) in a solvent like dioxane, in the presence of a catalyst like CuI, a ligand like (1R,2S)-cyclohexane-1,2-dioamine, and a base like potassium phosphate at elevated temperature about 120 °C to give a Ullman coupling reaction product, compound (Ic) (step h). The definitions of structural formula (Ic) and compounds 2 and 9 are independently as defined in any of the embodiments described above. Specific conditions are described in the Examples Section below.

Scheme D



G^2 is halogen.

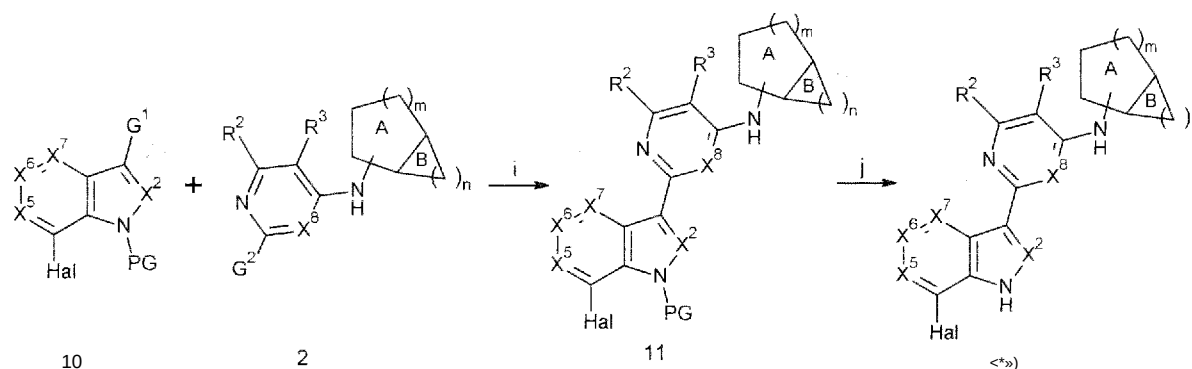
In another embodiment which is not limiting, the compounds of formula (Id) can be prepared by the method comprises a step of reacting compound 10 with compound 2 to form a compound 11, which after protection group cleavage to give the compound having the formula (Id), as shown in Scheme E below.

7-halogen substituted (preferably fluorine) indole/azaindole or indazole/azaindazole compounds 10 with G^1 = halogen (preferably iodine) are known. They are either commercially available or can be prepared by methods described in the exemplary synthesis of intermediates G or by methods known to a person skilled in the art. If desired, the amine group of the compounds 10 can be protected by an amine protecting group, PG. Any known amine protecting group such as THP, SEM, Ts, or Boc can be employed.

7-halogen substituted (preferably fluorine) indole/azaindole or indazole/azaindazole compounds 10 with G^1 = halogen (preferably iodine) can be converted to the corresponding 7-halogen substituted (preferably fluorine) indole/azaindole or indazole/azaindazole 3-

boronated intermediate. Any suitable reaction condition known in the art can be used for the generation of corresponding 3-boronated intermediate. For example, reaction of compound **10** with a boronic ester like 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane in a solvent like DMSO or dioxane in the presence of a base like potassium acetate and a catalyst like $\text{PdCl}_2(\text{dppf})$ at an elevated temperature about 70 °C can be used. If desired, the indole/azaindole or indazole/azaindazole 3-boronated intermediate (G^1 = boronic acid/ester) can be purified by silica gel flash chromatography. Alternatively, it can be used without purification in the next reaction step. The 7-halogen substituted (preferably fluorine) indole/azaindole or indazole/azaindazole 3-boronated intermediate (G^1 = boronic acid/ester) can then be reacted with a suitable heteroaryl halide **2** in the presence of a catalyst like $\text{Pd}_2(\text{dba})_3$, and in the presence of a base, such as K_3PO_4 , and in a solvent, such as dioxane and H_2O , and in an inert atmosphere such as argon or nitrogen at a temperature range preferably from room temperature to about 130 °C to give a Suzuki coupling reaction product, compound **11** (step i). Alternatively, compound **11** can also be synthesized via a Stille coupling reaction known in the art. For example, reaction of compound **2** (G^2 = halogen, bromine or chlorine preferred) with a trialkyl tin reagent such as hexa-n-butylditin in a solvent like dioxane, in the presence of catalyst like $\text{Pd}(\text{PPh}_3)_4$ at an elevated temperature about 125 °C can be used. The organo tin intermediate, obtained either in situ or after silica gel flash chromatography purification, can then be reacted with a suitable 7-halogen substituted (preferably fluorine) indole/azaindole or indazole/azaindazole halide, compound **10** (G^1 = halogen, iodine preferred) in a solvent like dioxane, and in the presence of catalyst like $\text{Pd}(\text{PPh}_3)_4$, and in an inert atmosphere such as argon or nitrogen at an elevated temperature of about 140 °C to give a Stille coupling product, compound **11** (step i). The Suzuki or Stille coupling product, compound **11** is then de-protected using conditions known in the art to give a compound represented by the formula (Id), where the 7-halogen substituted (preferably fluorine) indole/azaindole or indazole/azaindazole N1 substitution is H (step j). The definitions of structural formula (Id), compounds **2**, **10**, and **11** are independently as defined in any of the embodiments described above. PG is a protecting group and can be for example THP, SEM, Ts, or Boc. Specific conditions are described in the Examples Section below.

Scheme E

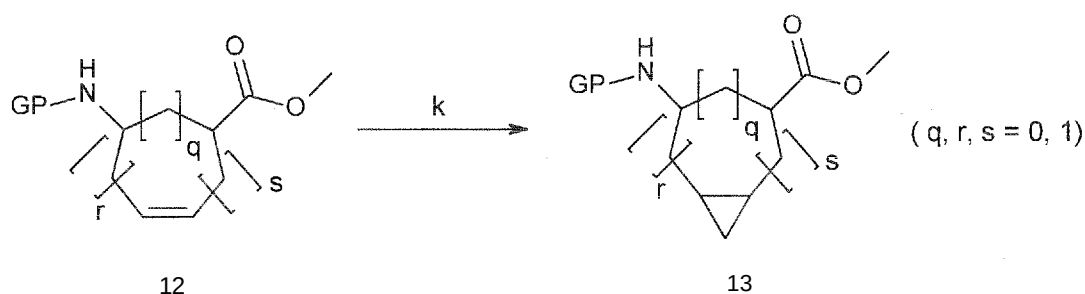


G^1 is halogen or boronic ester; G^2 is halogen or trialkylstannane

In another embodiment, cyclopropanation methodology that is known in the art is used to synthesize compounds 13 and 15. Specific exemplary conditions are described in the exemplary synthesis of intermediates B or known to a person skilled in the art. Using a Simmons Smith reaction as an example (Scheme F), a cyclic alkene compound 12 was reacted with iodomethyl zinc iodide, which was generated by a zinc reagent such as diethyl zinc in the presence of diiodomethane. Alternatively, the in situ generated iodomethyl zinc can be reacted in the presence of TFA, which could give a different stereochemical cyclopropanation product.

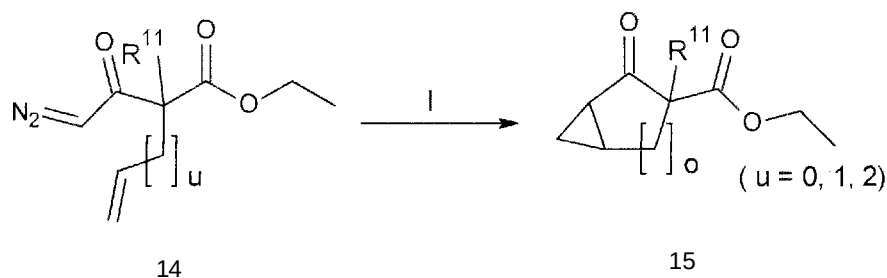
The variables of compounds 12 and 13 are independently as defined in any of the embodiments described above. PG can be Boc or CBz.

15 Scheme F



In another embodiment, the synthesis of the cyclopropylated compound 15 (Scheme G) comprises a reaction of a diazo compound 14, in the presence of a Pd catalyst such as allylpalladium chloride dimer in a solvent such as toluene at low temperatures of about -10 °C to give a cyclopropylated product, compound 15. The variables of compounds 14 and 15 are independently as defined in any of the embodiments described above.

Scheme G



The compounds of the present invention can be administered to a patient in the form of a pharmaceutical composition which can optionally comprise one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

The compounds of the present invention can be administered by various well known routes, including oral, rectal, intragastrical, intracranial and parenteral administration, e.g. intravenous, intramuscular, intranasal, intradermal, subcutaneous, and similar administration routes. Oral, intranasal and parenteral administration are particularly preferred. Depending on the route of administration different pharmaceutical formulations are required and some of those may require that protective coatings are applied to the drug formulation to prevent degradation of a compound of the invention in, for example, the digestive tract.

Thus, preferably, a compound of the invention is formulated as a syrup, an infusion or injection solution, a spray, a tablet, a capsule, a capslet, lozenge, a liposome, a suppository, a plaster, a band-aid, a retard capsule, a powder, or a slow release formulation. Preferably the diluent is water, a buffer, a buffered salt solution or a salt solution and the carrier preferably is selected from the group consisting of cocoa butter and vitebesole.

Particular preferred pharmaceutical forms for the administration of a compound of the invention are forms suitable for injectable use and include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases the final solution or dispersion form must be sterile and fluid. Typically, such a solution or dispersion will include a solvent or dispersion medium, containing, for example, water-buffered aqueous solutions, e.g. biocompatible buffers, ethanol, polyol, such as glycerol, propylene glycol, polyethylene glycol, suitable mixtures thereof, surfactants or vegetable oils. A compound of the invention can also be formulated

into liposomes, in particular for parenteral administration. Liposomes provide the advantage of increased half life in the circulation, if compared to the free drug and a prolonged more even release of the enclosed drug.

- 5 Sterilization of infusion or injection solutions can be accomplished by any number of art recognized techniques including but not limited to addition of preservatives like anti-bacterial or anti-fungal agents, e.g. parabene, chlorobutanol, phenol, sorbic acid or thimersal. Further, isotonic agents, such as sugars or salts, in particular sodium chloride may be incorporated in infusion or injection solutions.

10

Production of sterile injectable solutions containing one or several of the compounds of the invention is accomplished by incorporating the respective compound in the required amount in the appropriate solvent with various ingredients enumerated above as required followed by sterilization. To obtain a sterile powder the above solutions are vacuum-dried or freeze-

15 dried as necessary. Preferred diluents of the present invention are water, physiological acceptable buffers, physiological acceptable buffer salt solutions or salt solutions. Preferred carriers are cocoa butter and vitebesole. Excipients which can be used with the various pharmaceutical forms of a compound of the invention can be chosen from the following non-limiting list:

20

- a) binders such as lactose, mannitol, crystalline sorbitol, dibasic phosphates, calcium phosphates, sugars, microcrystalline cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone and the like;
- b) lubricants such as magnesium stearate, talc, calcium stearate, zinc stearate, stearic
- 25 acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,
- c) disintegrants such as starches, croscarmellose, sodium methyl cellulose, agar, bentomte, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

30

In one embodiment the formulation is for oral administration and the formulation comprises one or more or ail of the following ingredients: pregelatinized starch, talc, povidone K 30, croscarmellose sodium, **sodium** stearyl fumarate, gelatin, titanium dioxide, sorbitol, monosodium citrate, xanthan gum, titanium dioxide, flavoring, sodium benzoate and saccharin sodium.

If a compound of the invention is administered intranasally in a preferred embodiment, it may be administered in the form of a dry powder inhaler or an aerosol spray from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoro-
5 alkane such as 1,1,1,2-tetrafluoroethane (HFA 134A™) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA™), carbon dioxide, or another suitable gas. The pressurized container, pump, spray or nebulizer may contain a solution or suspension of the compound of the invention, e.g., using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g., sorbitan trioleate.

10 Other suitable excipients can be found in the Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association, which is herein incorporated by reference.

15 It is to be understood that depending on the severity of the disorder and the particular type which is treatable with one of the compounds of the invention, as well as on the respective patient to be treated, e.g. the general health status of the patient, etc., different doses of the respective compound are required to elicit a therapeutic or prophylactic effect. The determination of the appropriate dose lies within the discretion of the attending physician. It
20 is contemplated that the dosage of a compound of the invention in the therapeutic or prophylactic use of the invention should be in the range of about 0.1 mg to about 1 g of the active ingredient (i.e. compound of the invention) per kg body weight. However, in a preferred use of the present invention a compound of the invention is administered to a subject in need thereof in an amount ranging from 1.0 to 500 mg/kg body weight, preferably
25 ranging from 1 to 200 mg/kg body weight. The duration of therapy with a compound of the invention will vary, depending on the severity of the disease being treated and the condition and idiosyncratic response of each individual patient. In one preferred embodiment of a prophylactic or therapeutic use, between 100 mg to 200 mg of the compound is orally administered to an adult per day, depending on the severity of the disease and/or the
30 degree of exposure to disease carriers.

As is known in the art, the pharmaceutically effective amount of a given composition will also depend on the administration route. In general the required amount will be higher, if the administration is through the gastrointestinal tract, e.g., by suppository, rectal, or by an
35 intragastric probe, and lower if the route of administration is parenteral, e.g., intravenous.

Typically, a compound of the invention will be administered in ranges of 50 mg to 1 g/kg body weight, preferably 100 mg to 500 mg/kg body weight, if rectal or intragastric administration is used and in ranges of 10 to 100 mg/kg body weight, if parenteral administration is used.

5

If a person is known to be at risk of developing a disease treatable with a compound of the invention, prophylactic administration of the biologically active blood serum or the pharmaceutical composition according to the invention may be possible. In these cases the respective compound of the invention is preferably administered in above outlined preferred and particular preferred doses on a daily basis. Preferably, from 0.1 mg to 1 g/kg body-weight once a day, preferably 10 to 200 mg/kg body weight. This administration can be continued until the risk of developing influenza has lessened. In most instances, however, a compound of the invention will be administered once a disease/disorder has been diagnosed. In these cases it is preferred that a first dose of a compound of the invention is administered one, two, three or four times daily.

15

The compounds of the present invention are particularly useful for treating, ameliorating, or preventing influenza. Preferably the compounds of the present invention are employed to treat influenza. Within the present invention, the term "Influenza" includes influenza A, B, C, isavirus and thogotovirus and also covers bird flu and swine flu. The subject to be treated is not particularly restricted and can be any vertebrate, such as birds and mammals (including humans).

20

The present inventors have found that the compounds of the present invention are not only capable of inhibiting transcription but, surprisingly, also inhibit replication in viruses, in particular, in influenza viruses.

25

Without wishing to be bound by theory it is assumed that the compounds of the present invention are capable of inhibiting binding of host mRNA cap structures to the cap-binding domain (CBD), particularly of the influenza virus. More specifically it is assumed that they directly interfere with the CBD of the influenza PB2 protein. However, delivery of a compound into a cell may represent a problem depending on, e.g., the solubility of the compound or its capabilities to cross the cell membrane. The present invention not only shows that the claimed compounds have *in vitro* polymerase inhibitory activity but also *in vivo* antiviral activity.

30

35

The compounds having the formula (I) can be used in combination with one or more other medicaments. The type of the other medicaments is not particularly limited and will depend on the disorder to be treated. Preferably the other medicament will be a further medicament which is useful in treating, ameliorating or preventing a viral disease, more preferably a further medicament which is useful in treating, ameliorating or preventing influenza.

The further medicament can be selected, for example, from endonuclease inhibitors (particularly targeting influenza), cap binding inhibitors (particularly targeting influenza), (preferably influenza) polymerase inhibitors, neuramidase inhibitors, M2 channel inhibitors, alpha glucosidase inhibitors, ligands of other influenza targets, antibiotics, anti-inflammatory agents like COX inhibitors (e.g., COX-1/COX-2 inhibitors, selective COX-2 inhibitors), lipxygenase inhibitors, EP ligands (particularly EP4 ligands), bradykinin ligands, and/or cannabinoid ligands (e.g., CB2 agonists).

Various modifications and variations of the invention will be apparent to those skilled in the art without departing from the scope of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be covered by the present invention.

The following examples are merely illustrative of the present invention and should not be construed to limit the scope of the invention as indicated by the appended claims in any way.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Abbreviations

	AcOH:	acetic acid	
	MeCN:	acetonitrile	
	CBz:	benzyloxycarbonyl	
	HATU:	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium	3-oxid
5		hexafluorophosphate	
	Boc:	t-butoxycarbonyl	
	mCPBA:	m-chloroperoxybenzoic acid	
	TIPSCl:	chloro(triisopropyl)silane	
	CDCl ₃ :	deuterated chloroform	
10	DCM:	dichloromethane	
	DCE:	dichloroethane	
	DIEPA:	diisopropylethylamine	
	DMF:	dimethyl formamide	
	DCC:	dicyclohexylcarbodiimide	
15	Xphos:	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl	
	Xantphos:	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene	
	DHP:	3,4-dihydro-2H-pyran	
	DIEPA:	diisopropylethylamine	
	DMAP:	4-dimethylaminopyridine	
20	DMSO:	dimethylsulfoxide	
	DPPA:	diphenylphosphoryl azide	
	EtOAc:	ethyl acetate	
	EA:	ethyl acetate	
	Hz:	hertz	
25	NIS:	N-iodosuccinimide	
	LDA:	lithium diisopropylamide	
	MS (ESI):	mass spectroscopy (electron spray ionization)	
	MHz:	megahertz	
	TsOH:	4-methylbenzenesulfonic acid	
30	μg:	microgram	
	μL:	microliter	
	μM:	micromoles per liter	
	mg:	milligram	
	mL:	milliliter	
35	mmol:	millimole	

- EC₅₀: The molar concentration of an agonist, which produces 50% of the maximum possible response for that agonist.
- NMR: nuclear magnetic resonance
- Pre-HPLC: preparation-high performance liquid chromatography
- 5 PG: protective group
- PTS: puridinium p-toluenesulfonate
- THF: tetrahydrofuran
- THP: tetrahydropyran-2-yl
- Pd(PPh₃)₄: tetrakis(triphenylphosphine)palladium
- 10 TLC: thin layer chromatography
- Ts: p-toluenesulfonyl
- TEA: triethylamine
- TFA: 2,2,2-trifluoroacetic acid
- TFAA: trifluoroacetic anhydride
- 15 Tf₂Q: trifluoromethanesulfonic anhydride
- SEM: 2-(trimethylsilyl)ethoxymethyl
- SEMCI: 2-(trimethylsilyl)ethoxymethyl chloride
- SFC: supercritical fluid chromatography
- Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium

20

General Experimental Conditions

- Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii)
- 25 ISCO combi-flash chromatography instrument. Silica gel Brand and pore size: i) KP-SIL 60 A, particle size: 40-60 μm; ii) CAS registry NO. Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd. pore: 200-300 or 300-400.
- 30 Intermediates and final compounds were purified by preparative HPLC on a reversed phase column using X Bridge™ Perp C₁₈ (5 μm, OBD™ 30 × 100 mm) column or SunFire™ Perp C₁₈ (5 μm, OBD™ 30 × 100 mm) column.
- LC/MS spectra were obtained using a Waters UPLC-SQD Mass. Standard LC/MS
- 35 conditions were as follows (running time 3 minutes):

Acidic condition: A: 0.1% formic acid and 1% acetonitrile in H₂O ; B: 0.1 % formic acid in acetonitrile;

Basic condition: A: 0.05% NH₃·H₂O in H₂O ; B: acetonitrile.

- 5 Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion (M+H)⁺.

NMR Spectra were obtained using Bruker Avance 400MHz.

All reactions involving air-sensitive reagents were performed under an argon atmosphere.

- 10 Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

Biological Assays and Data

15

Luciferase Reporter Assay (LRA)

Assay purpose and principle

- This in vitro, cell-based assay, is used to identify small molecule inhibitors of influenza A virus and relies upon a replication competent influenza reporter virus. This virus was generated in a A/WSN background (Szretter KJ, Baltsh AL, Katz JM. Curr Protoc Microbiol. Influenza: propagation, quantification, and storage. 2006 Dec:Chapter 15:Unit 15G.1 . doi: 10.1002/0471729256.mc15g01s3) and contains the extremely bright luciferase variant, NanoLuc (Promega), which has been appended to the C-terminus of the polymerase subunit, PA. The reporter virus replicates with near native properties both in cell culture and in vivo. Thus, NanoLuc luciferase activity can be used as a readout of viral infection.
- 20
- 25

- In order to identify small molecule inhibitors of influenza A virus, A549 (human non-small cell lung cancer) cells are infected with the reporter virus and following infection, the cells are treated with serially diluted compounds. The inhibitory effect of the small molecules tested is a direct measure of viral levels and can be rapidly obtained by measuring a reduction in luciferase activity.
- 30

Determination of viral replication inhibition by Luciferase Reporter Assay (LRA)

A549 cells were plated in 384-well plates at a density of 10,000 cells per well in Dulbecco's modified Eagle's medium with Glutamax (DMEM, Invitrogen) supplemented 10% fetal bovine serum (FBS, Invitrogen) and 1X penicillin/streptomycin (Invitrogen), herein referred to as complete DMEM, and incubated at 37°C, 5% CO₂ overnight. The following day, cells were washed once with 1X PBS and then infected with virus, MOI 0.1 in 10 μ I of infection media for 60 min. 15 μ I of complete media and diluted compounds (1% DMSO final) added to the wells, and the plates were incubated for 24 h at 37°C, 5% CO₂. 15 μ I of Nano-Glo reagent (Promega) was added to each well and luminescence was read using a Paradigm Microplate reader (Molecular Devices). Cell viability was determined similarly, in the absence of virus, by measurement of ATP levels with CellTiter-Glo reagent (Promega). EC₅₀ and CC₅₀ values were calculated by fitting dose-response curves with XLFit 4-parameter model 205 software (IDBS).

Virus and cell culture methods

A/WSN/33 influenza virus containing the NanoLuc reporter construct was obtained from the laboratory of Andrew Mehle (University of Wisconsin). A549 human lung carcinoma cells were purchased (ATCC). All studies were performed with A549 cells cultured in complete DMEM. Influenza virus stocks were propagated in MDBK cells (ATCC) using standard methods (Szretter KJ, Balish AL, Katz JM. Curr Protoc Microbiol. Influenza: propagation, quantification, and storage. 2006 Dec:Chapter 15:Unit 15G.1. doi: 10.1002/0471 729256.mc15g01s3), and stocks frozen at -80°C. Viral infections were carried out using DMEM Glutamax supplemented with 0.3% BSA (Sigma), 25mM Hepes (Sigma), and 1X penicillin/streptomycin (Invitrogen).

Influenza A or B Filter RNP Transcription and Influenza A RNP-based Replication Assay

Preparation of virus lysate containing native influenza vRNP complex

Influenza purified virus (Influenza A/PR/8/34, Influenza B/Lee/40) was obtained from Charles River Laboratories International Inc. as suspension in HEPES buffer. Virions were disrupted by incubation with an equal volume of 2% Triton X-100 for 30 minutes at room temperature in a buffer containing 40 mM Tris-HCl, pH 8. 5 mM MgCl₂, 200 mM KCl, 100 mM NaCl, 10 mM dithiothreitol [DTT], 5% Glycerol, 40 U/ml RNase Inhibitor, 10 mM 2-Mercaptoethanol, and 2 mg/ml Lysolecithin. The virus lysate was aliquot and stored at -80°C in aliquots.

ASSAY PURPOSE & PRINCIPLE of Influenza A or B Filter RNP Transcription Assay

This *in vitro* assay is developed to identify inhibitors of Cap-binding, endonuclease and polymerase activities of the Influenza A or B virus. Influenza ribonucleoprotein complexes (RNPs) are responsible for the transcription and replication of viral genomic negative strain RNA to positive strain mRNA and positive strain cRNA respectively. The transcription is initiated by the "cap-snatching" mechanism which consists of two steps: The cap-binding of cellular mRNA by the PB2 subunit and the cleavage of the capped RNA by the PA subunit. The resulting 9-13 nucleotide long, capped RNA oligo serves as a primer for the subsequent synthesis of viral mRNA by the polymerase subunit PB1. During the mRNA synthesis, radiolabeled nucleotide will be incorporated into the mRNA product, which will be captured on a specific filter plate by TCA precipitation. The efficiency of nucleotide incorporation is then determined by scintillation counting of captured mRNA on the filter plate. A higher rate of mRNA synthesis leads to higher signals. Due to the essential involvement of cap-binding and cleavage reaction prior to polymerization of mRNA, it is possible to inhibit transcription by either blocking the endonuclease active site of PA or the cap-binding site of PB2 and therefore to determine IC₅₀ values of both endonuclease and cap-binding inhibitors.

Material and methods for Filter RNP transcription assay:

Virus lysate (H1N1 Influenza strain A/PR/8/34, Charles River, Cat #10100374; influenza B\Lee\40, Charles River, Cat# 10100379) was pre-incubated with compounds for 30 min at 30°C in the reaction buffer containing 24 mM HEPES (pH 7.5), 118 mM NaOAc, 1 mM Mg(OAc)₂, 0.1 mM Mn(OAc)₂, 0.1 mM EDTA, 2 mM DTT, 0.3 U RNase inhibitor (Riboguard), 70 mM ATP/CTP/UTP, 14 mM GTP and 0.175 µCi ³³P-GTP. Then capped RNA substrate was added to the reaction at 0.07 µM (5'-m⁷G-ppp-GAA UAC UCA AGC UAU GCA UC-3', 5'-triphosphorylated RNA was purchased from Fidelity Systems and the capping reaction was performed using the ScriptCap Capping System from CellScript). The Cap-snatching and subsequent mRNA synthesis reactions were performed for 90 min at 30°C before the reactions were terminated by EDTA addition. Synthesized mRNA products were precipitated on the filter plate (Millipore) using 20% TCA at 4 °C for 35 min and followed by three times wash with 10% TCA and 1 time with 70% ethanol on the vacuum manifold system (Millipore). After complete dry of the filter plate, Microsint 20 solution was added to the wells and scintillation counting was performed on the TopCount equipment for 1 min/well.

ASSAY PURPOSE & PRINCIPLE of Influenza A RNP-based Replication Assay

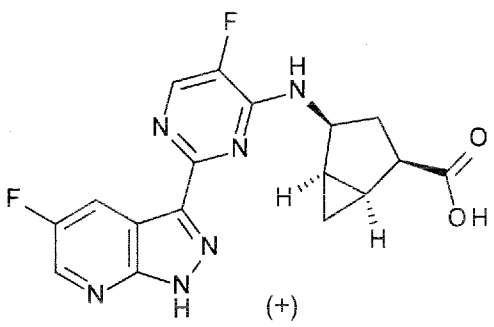
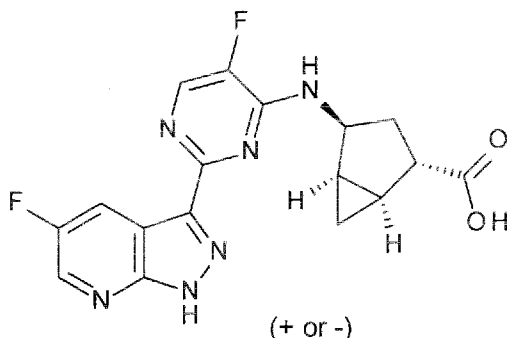
This *in vitro* assay is developed to identify inhibitors targeting polymerase activities of the Influenza A virus. Influenza ribonucleoprotein complexes (RNPs) are responsible not only for the transcription of negative-sense viral genomic RNA (vRNA) to positive-sense mRNA, but also for the replication of full-length complementary genomic RNA (cRNA). A pppApG dinucleotide is provided to the RNPs to initiate the cRNA synthesis and during the elongation process, radiolabeled nucleotide will be incorporated into the cRNA product, which will be captured on a specific filter plate by TCA precipitation. The efficiency of nucleotide incorporation is then determined by scintillation counting of captured cRNA on the filter plate. A higher rate of cRNA synthesis leads to higher signals. Due to the essential involvement of polymerase subunit for the polymerization of cRNA, it is possible to inhibit replication by either directly blocking the polymerase active site of PB1 or by preventing the conformational changes of RNP that is required for the realignment of polymerase complex on the vRNA template. Therefore this assay is able to determine IC₅₀ values of replication inhibitors.

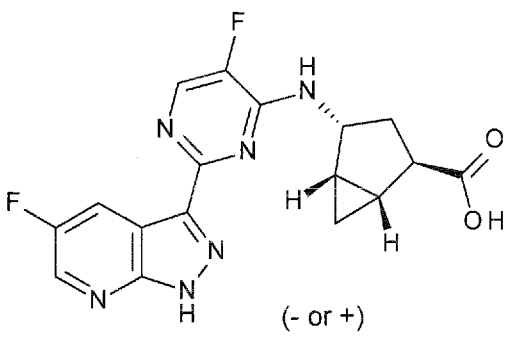
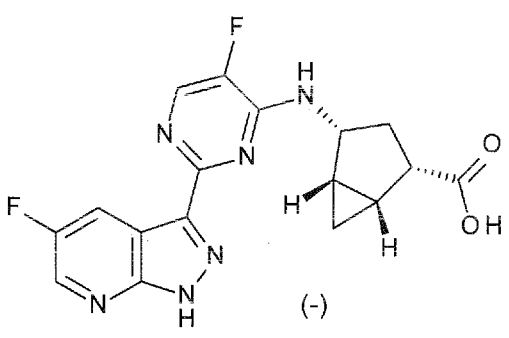
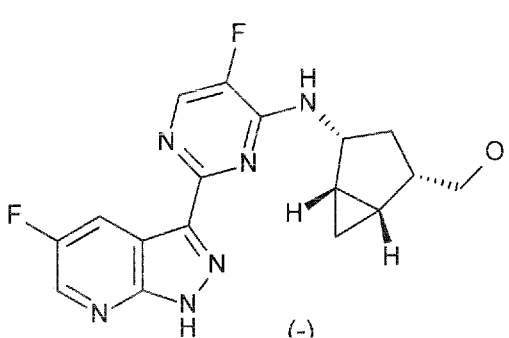
Material and methods for replication assay:

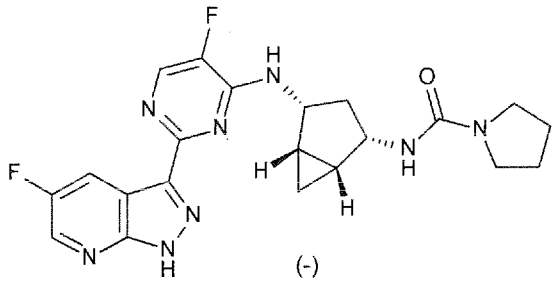
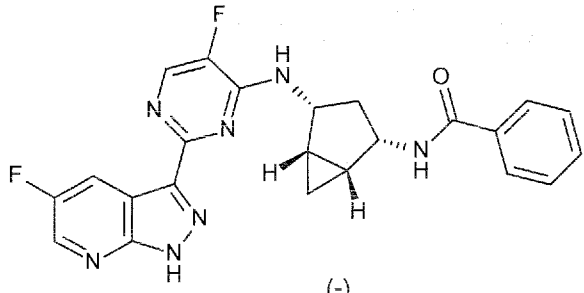
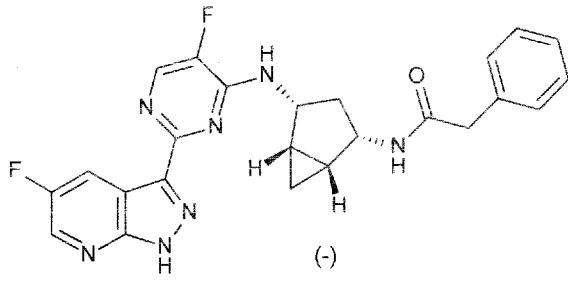
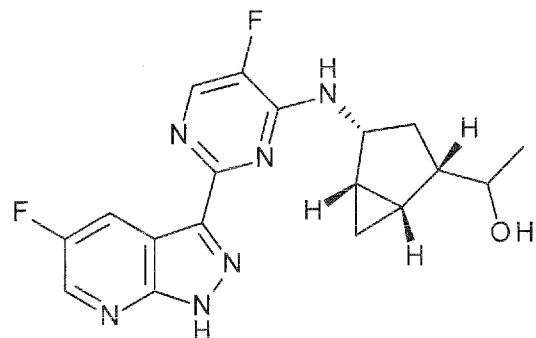
The concentrations refer to final concentrations unless mentioned otherwise. Cap-binding inhibitors were serially diluted 4 fold in 40% DMSO and 2ul of diluted compound was added to 17 ul reaction mix containing 0.35 nM vRNP enzyme, 20 mM HEPES (pH 7.5), 100 mM NaOAc, 1 mM Mg(OAc)₂, 0.1 mM Mn(OAc)₂, 0.1 mM EDTA, 2 mM DTT, 0.25 U RNase inhibitor (Epicentre), 70 uM ATP/CTP/UTP, 14 uM GTP and 0.175 μ CI ³³P-GTP for 30 minutes at 30°C. pppApG dinucleotide was added to the reaction at 75 uM as final concentration. Reactions were performed for 3 hours at 30°C and then stopped by adding EDTA to a final concentration of 56 mM. Synthesized cRNA products from the replication reaction were precipitated on the filter plate (Millipore) using 20% TCA at 4 °C for 35 minutes and followed by three times wash with 10% TCA and 1 time with 70% ethanol on the vacuum manifold system (Millipore). After complete air dry of the filter plate, Microsint 20 solution was added to the wells and scintillation counting was performed on the TopCount equipment for 1 min/well. Dose-response curves were analyzed using 4-parameter curve fitting methods. The concentration of test compound resulting in 50% inhibition to that of the control wells were reported as IC₅₀.

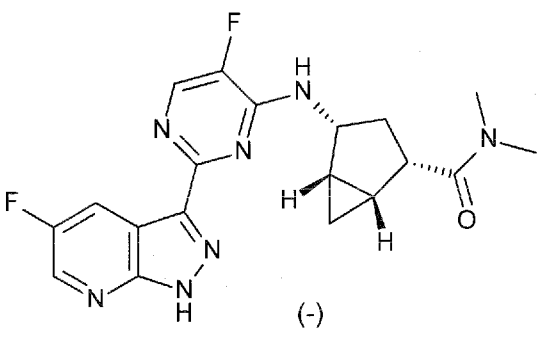
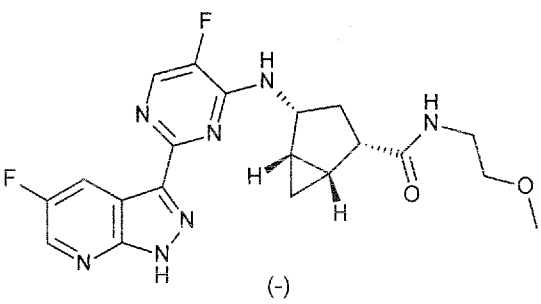
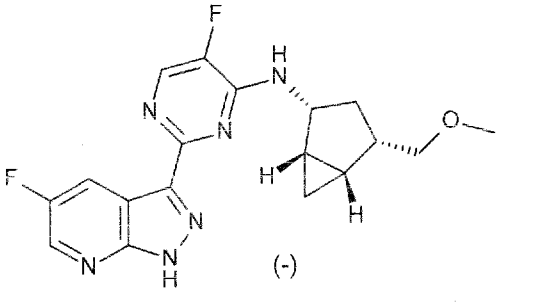
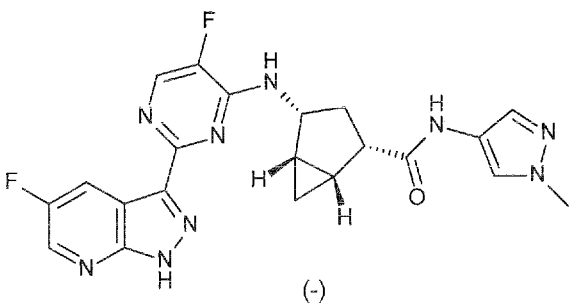
RESULTS OBTAINED FOR THE EXAMPLES USING THE BIO-ASSAYS

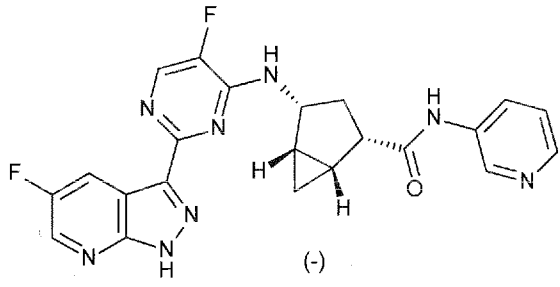
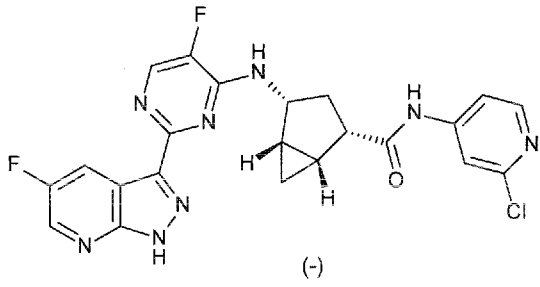
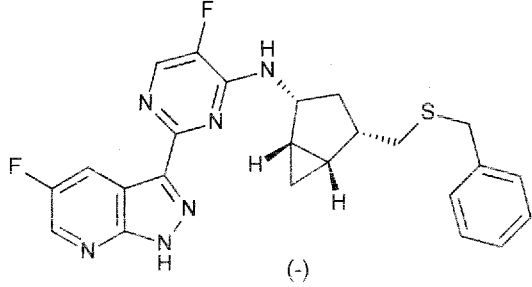
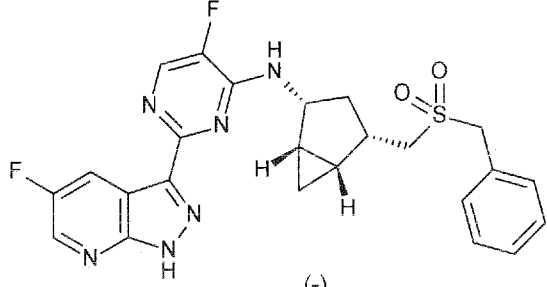
Table 1.

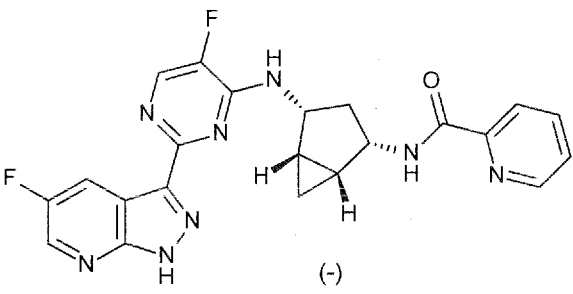
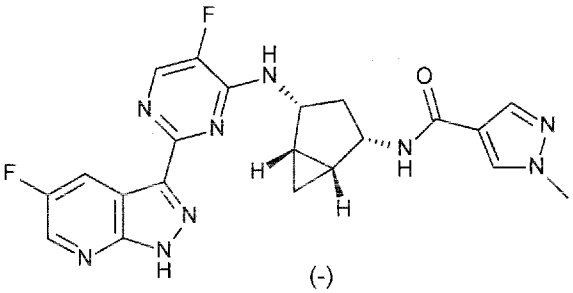
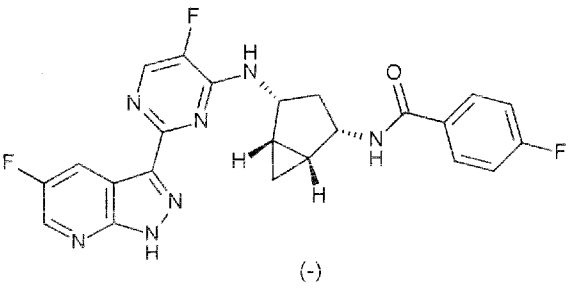
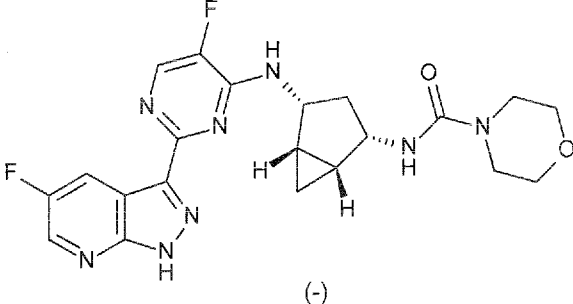
Compound	RNP IC ₅₀ [μM]	LRA IC ₅₀ [μM]
Example 1  (+)	143.8	na
Example 2  (+ or -)	> 200	> 12.5

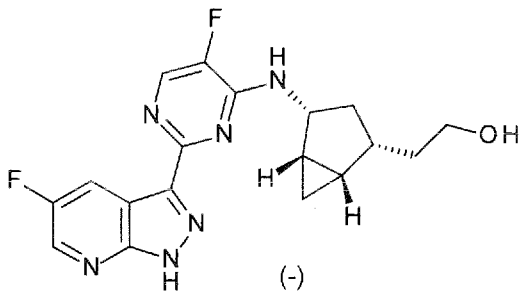
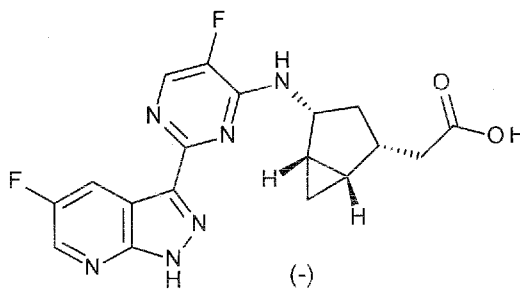
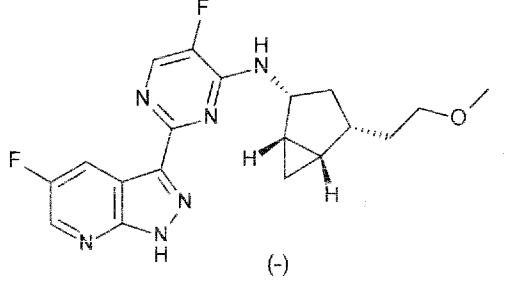
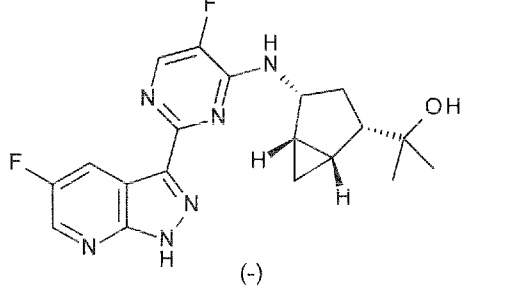
Example 3  (- or +)	11.23	10.24
Example 4  (-)	0.56	10.61
Example 5  (-)	1.44	0.013

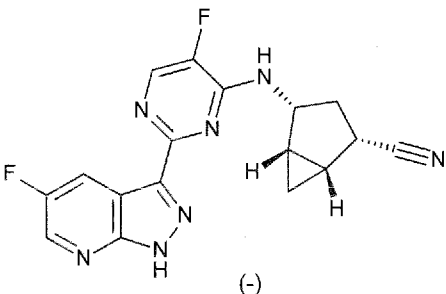
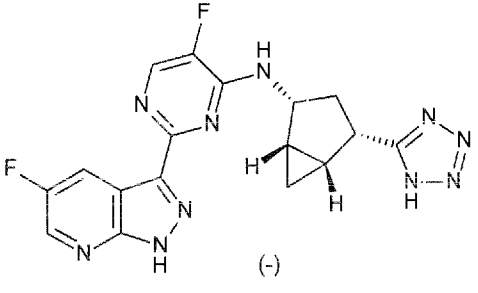
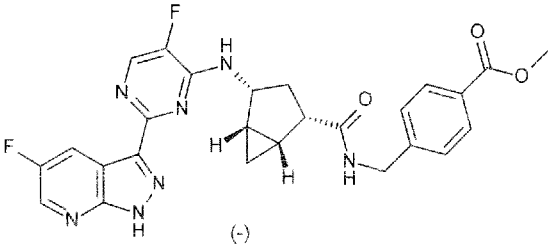
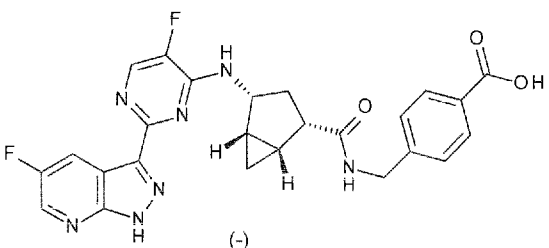
Example 6  (-)	1.34	0.019
Example 7  (-)	0.112	0.003
Example 8  (-)	1.237	0.067
Example 9  (-)	31.2	0.24

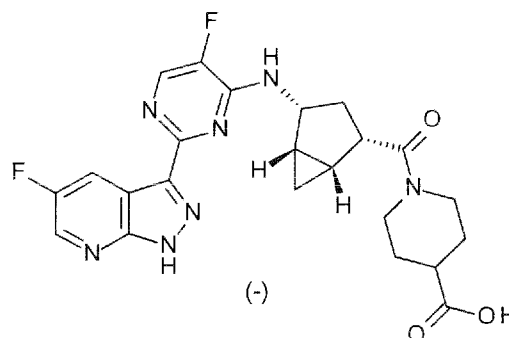
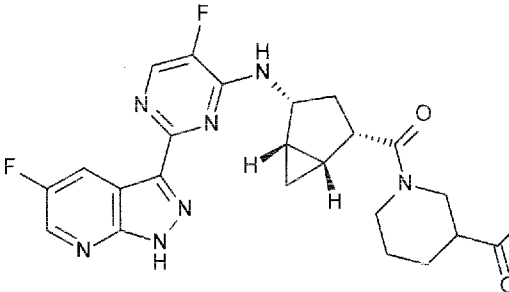
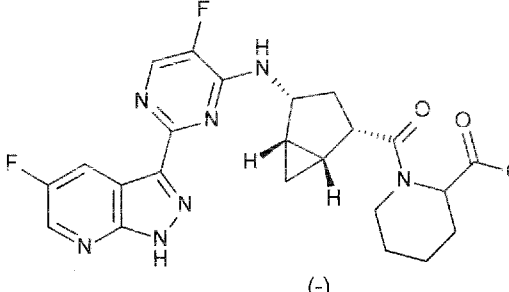
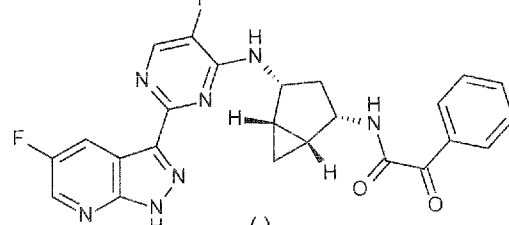
Example 10  (-)	> 200	2.02
Example 11  (-)	> 200	1.69
Example 12  (-)	160	0.683
Example 13  (-)	0.238	0.108

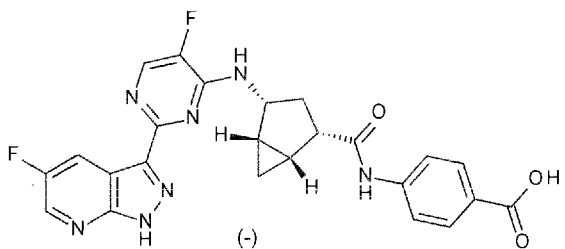
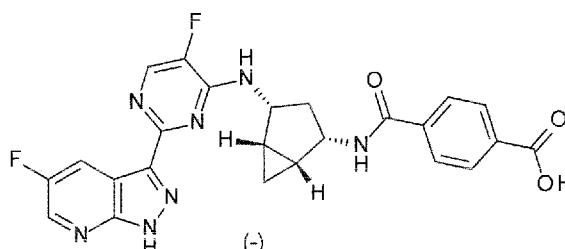
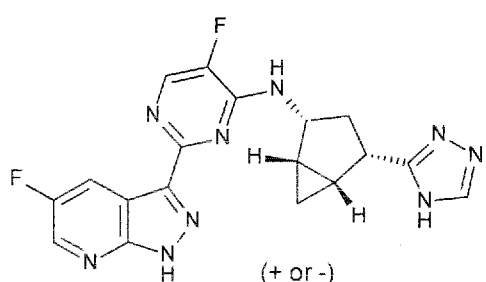
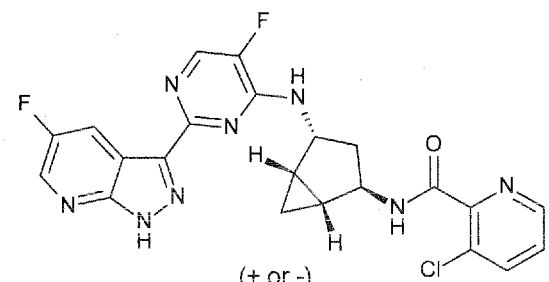
Example 14  (-)	0.222	0.015
Example 15  (-)	0.0008	0.012
Example 16  (-)	19.06	0.177
Example 17  (-)	> 200	0.165

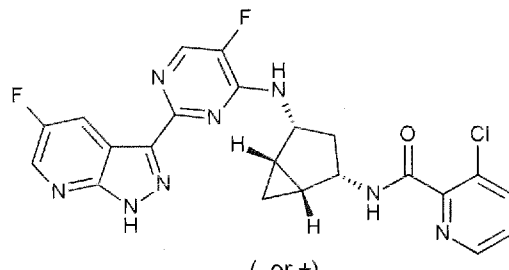
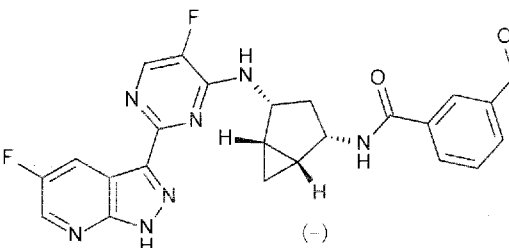
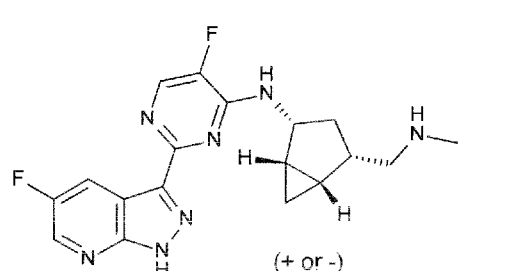
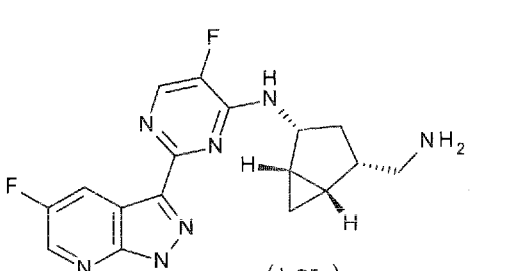
Example 18  (-)	27.64	0.255
Example 19  (-)	2.05	0.753
Example 20  (-)	0.212	0.002
Example 21  (-)	na	0.412

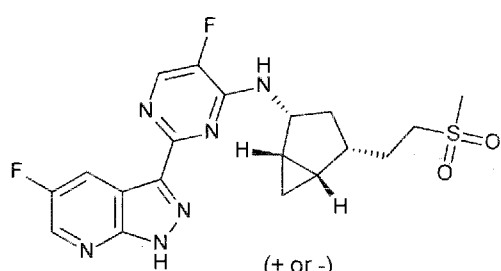
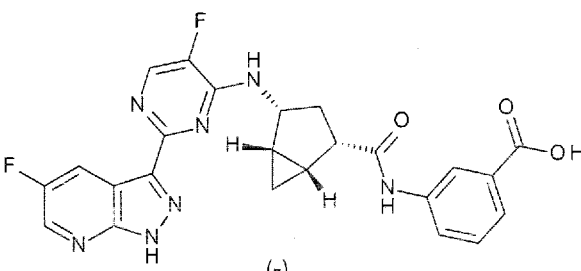
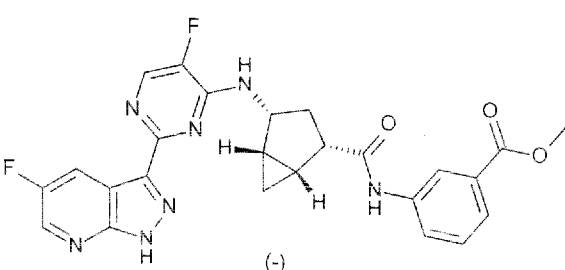
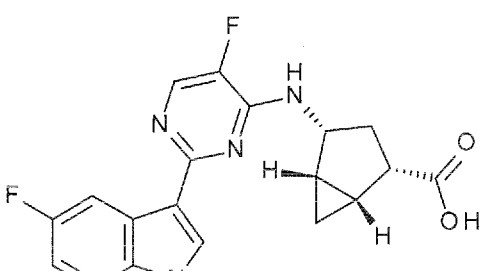
Example 22  (-)	0.107	0.02
Example 23  (-)	0.022	0.678
Example 24  (-)	2.044	0.025
Example 25  (-)	46	0.183

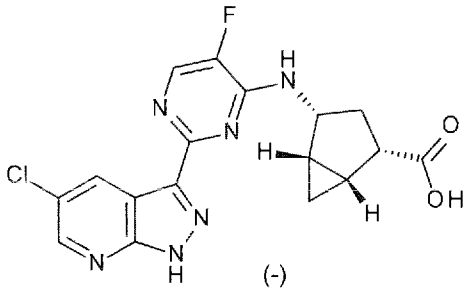
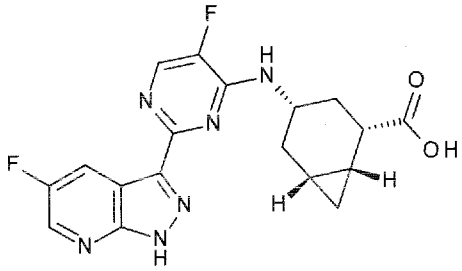
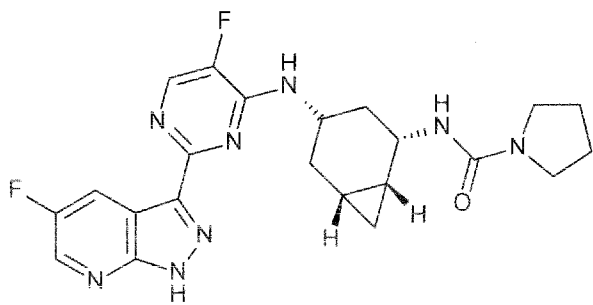
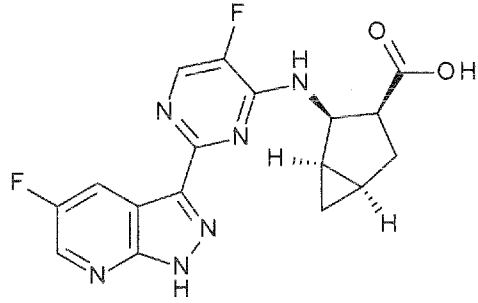
Example 26  (-)	3.586	0.035
Example 27  (-)	120.3	> 100
Example 28  (-)	> 200	0.303
Example 29  (-)	1.92	78.68

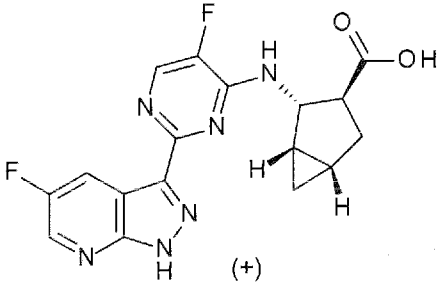
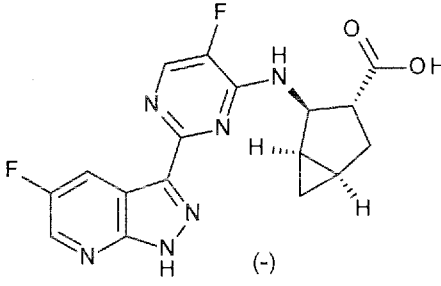
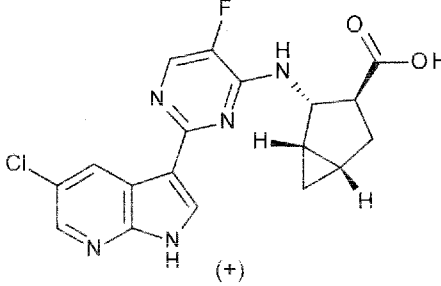
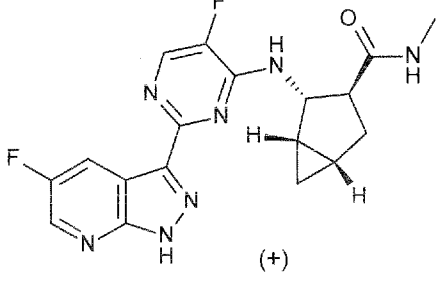
Example 30  (-)	4.41	> 100
Example 31  (-)	3.52	> 100
Example 32  (-)	1.226	26.4
Example 33  (-)	10	4.13

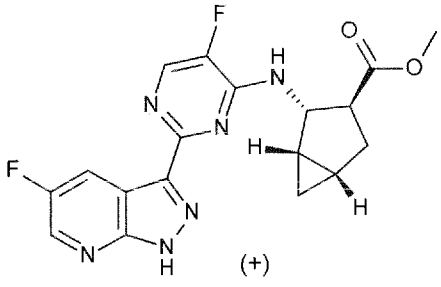
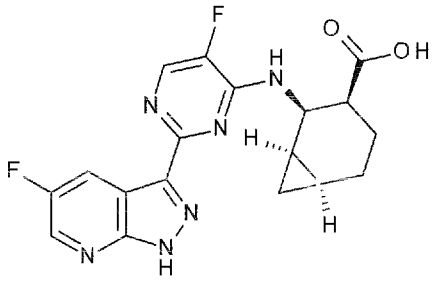
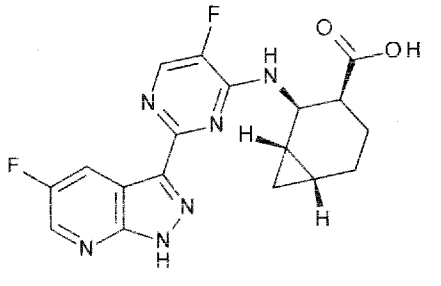
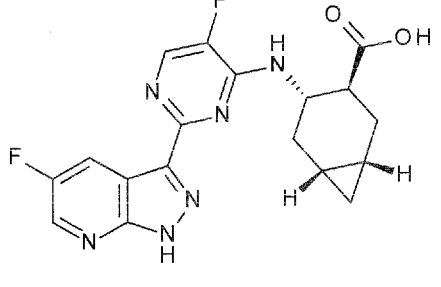
Example 34  (-)	0.001	0.506
Example 35  (-)	0.032	9.2
Example 36  (+ or -)	3.69	0.274
Example 37  (+ or -)	30.9	0.375

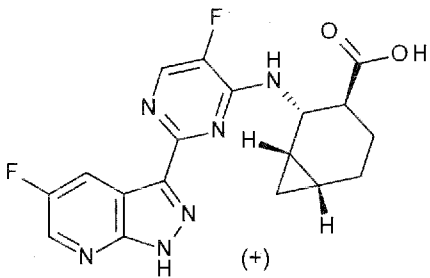
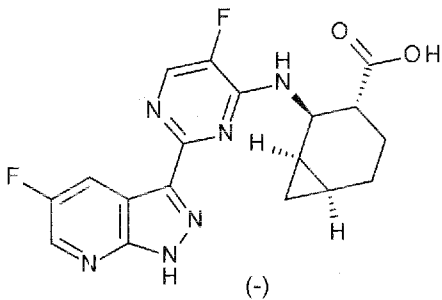
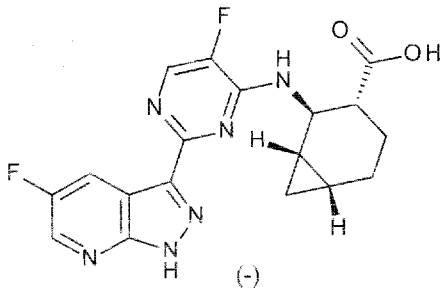
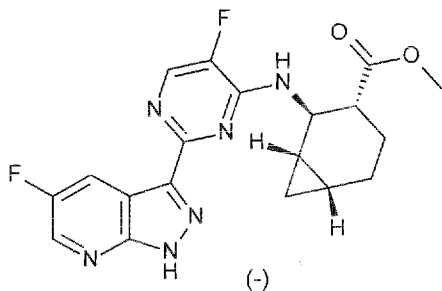
Example 38  (- or +)	2.49	0.024
Example 39  (-)	0.0008	1.84
Example 40  (+ or -)	137.6	6.73
Example 41  (+ or -)	161.8	0.982

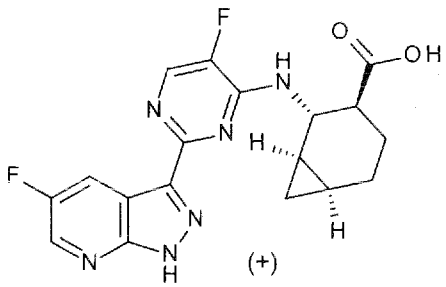
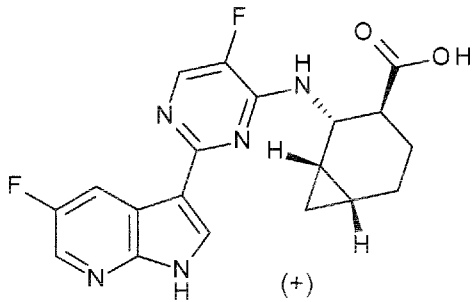
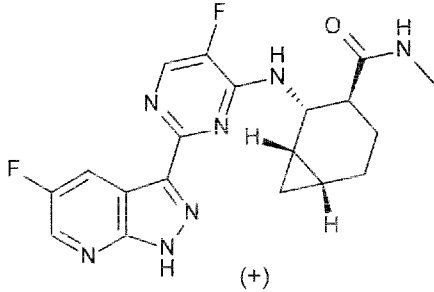
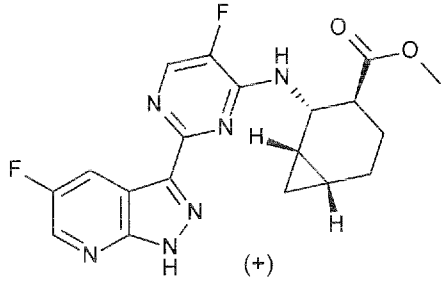
Example 42  (+ or -)	22.4	0.262
Example 43  (-)	0.003	0.522
Example 44  (-)	0.022	0.011
Example 45  (-)	23.3	7.3

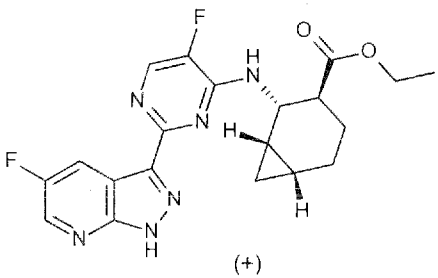
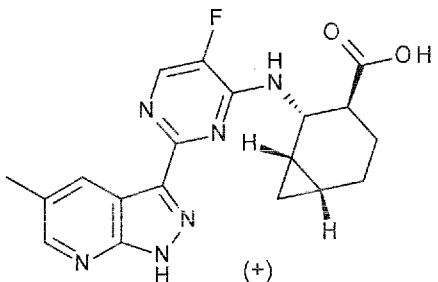
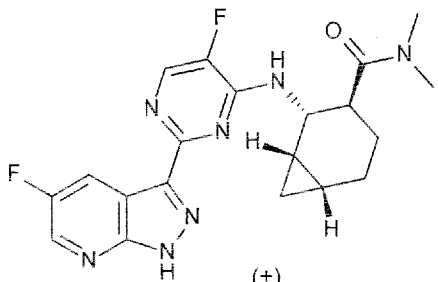
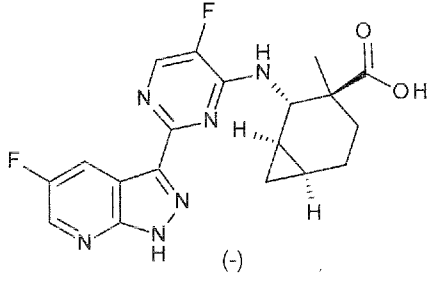
Example 46  (-)	0.108	0.642
Example 47 	0.026	1.186
Example 48 	0.003	0.002
Example 49 	4.04	27.5

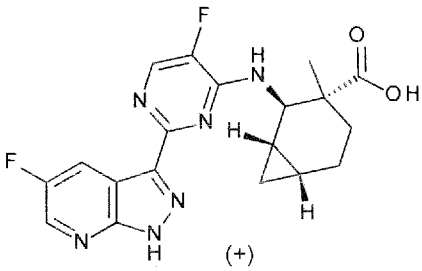
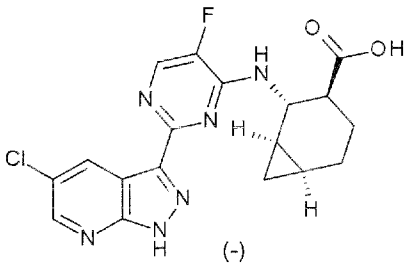
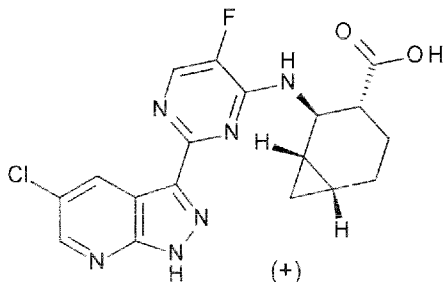
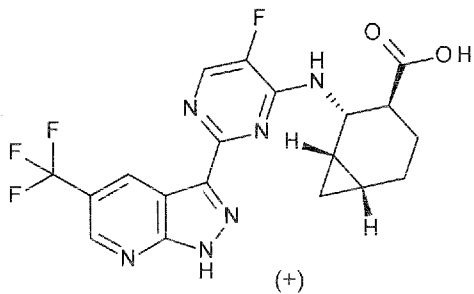
Example 50  (+)	0.542	0.061
Example 51  (-)	37.78	6.97
Example 52  (+)	0.63	0.043
Example 53  (+)	> 200	0.253

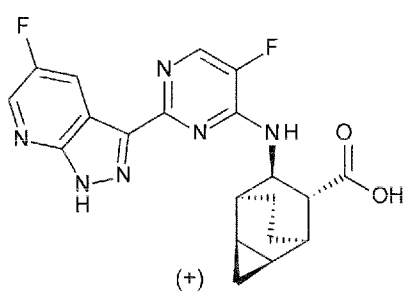
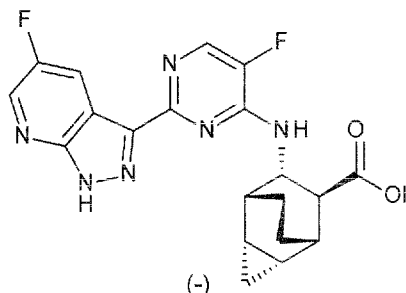
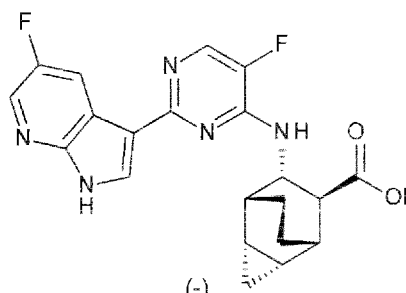
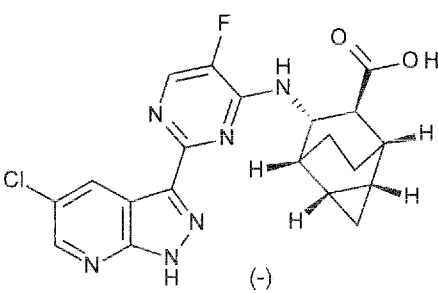
Example 54  (+)	40.38	0.044
Example 55  (+)	4.56	2.22
Example 56  (+)	1.49	0.985
Example 57  (+)	0.205	0.437

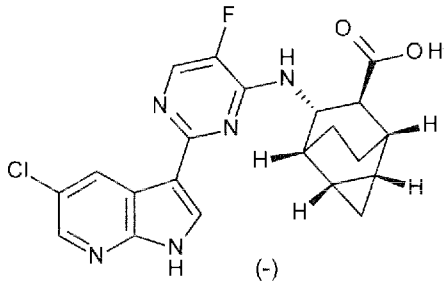
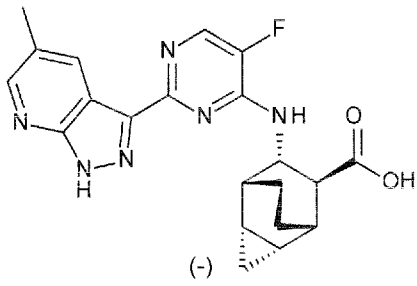
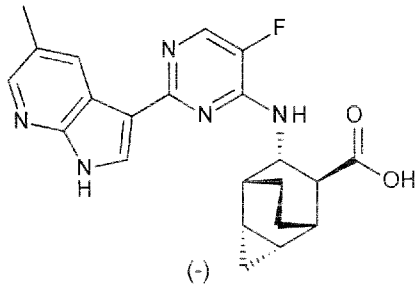
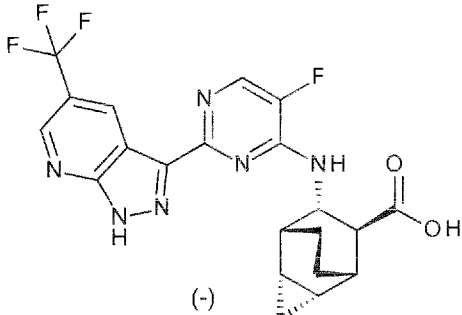
Example 58  (+)	0.07	0.055
Example 59  (-)	111.9	23.6
Example 60  (-)	2.183	2.368
Example 61  (-)	0.565	1.839

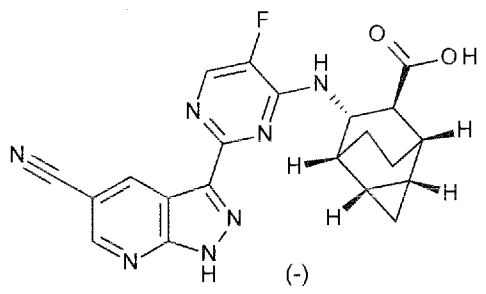
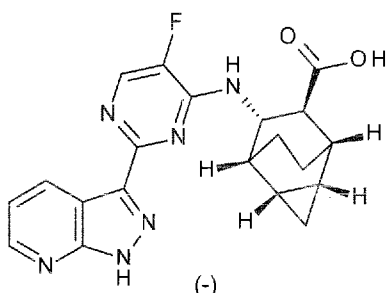
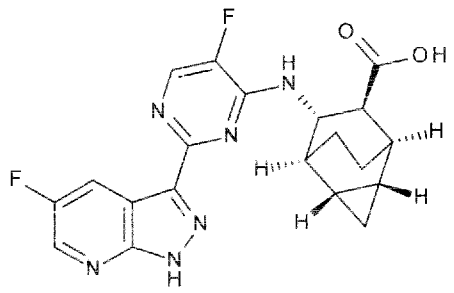
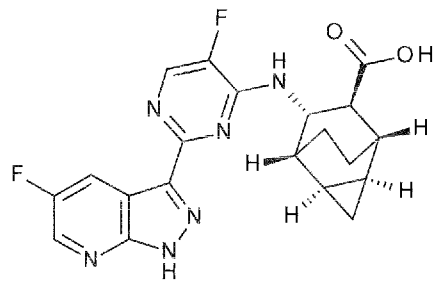
Example 62  (+)	0.0004	0.019
Example 63  (+)	0.156	0.075
Example 64  (+)	50.63	0.218
Example 65  (+)	5.74	0.062

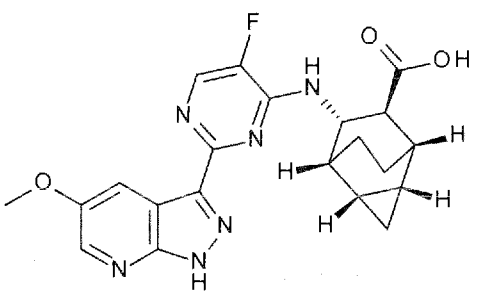
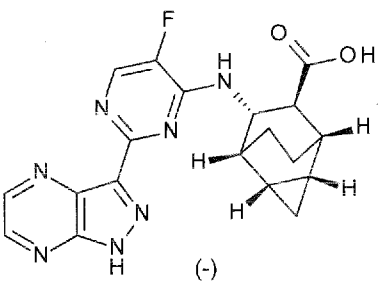
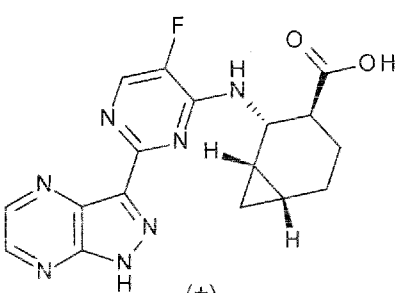
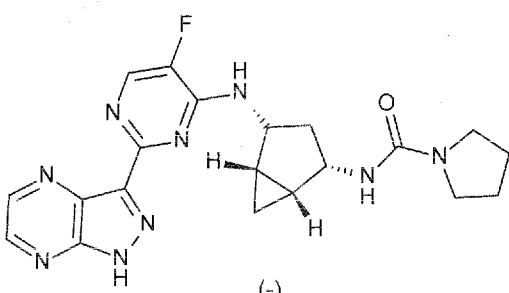
Example 66  (+)	62.13	0.046
Example 67  (+)	0.049	0.025
Example 68  (+)	36.62	0.74
Example 69  (-)	0.115	0.025

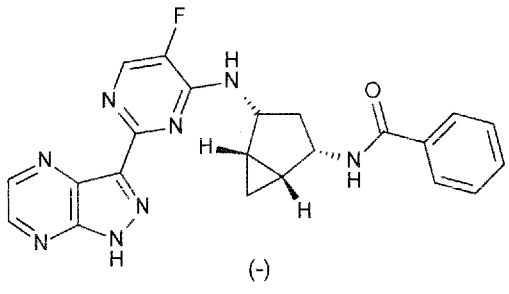
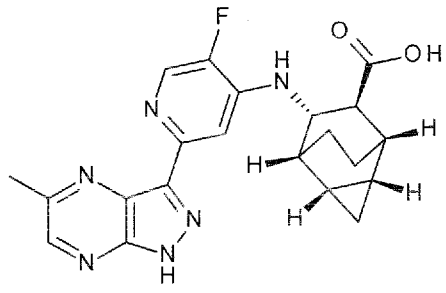
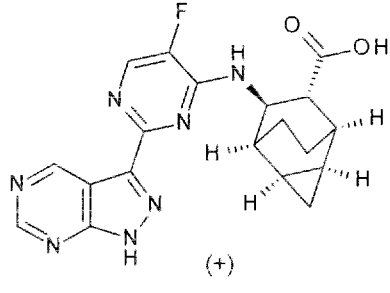
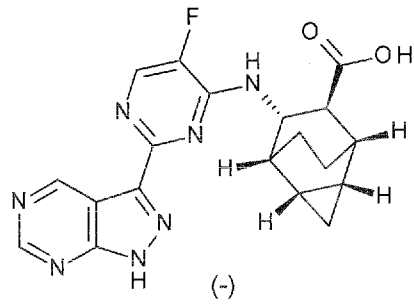
Example 70  (+)	26.7	5.07
Example 71  (-)	0.0006	0.012
Example 72  (+)	3	4.38
Example 73  (+)	0.018	0.007

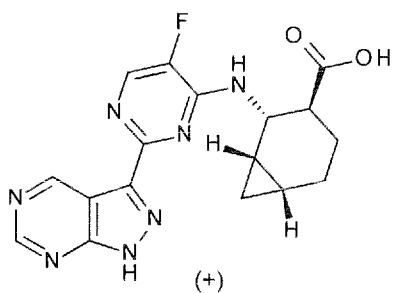
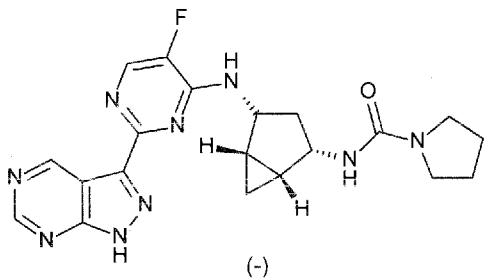
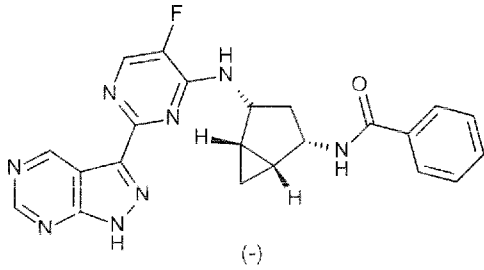
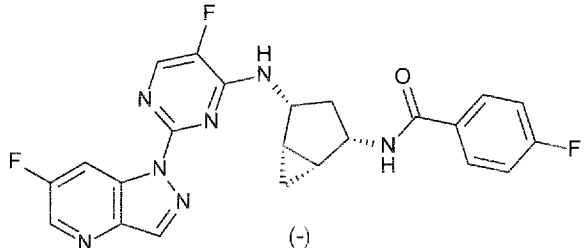
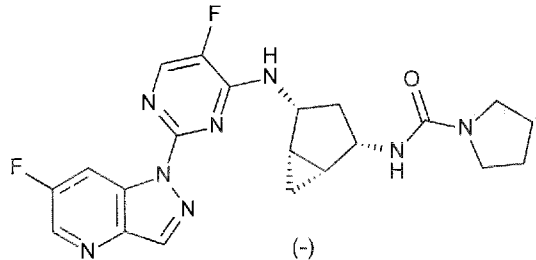
Example 74  (+)	0.111	0.467
Example 75  (-)	0.0002	0.0014
Example 76  (-)	0.0015	0.007
Example 77  (-)	0.0002	0.0006

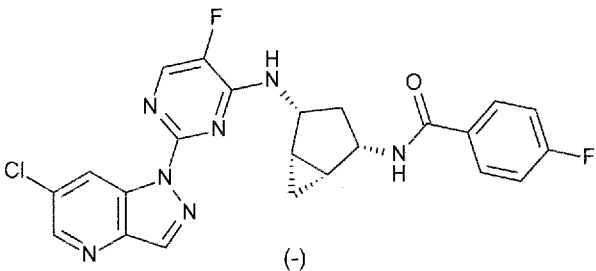
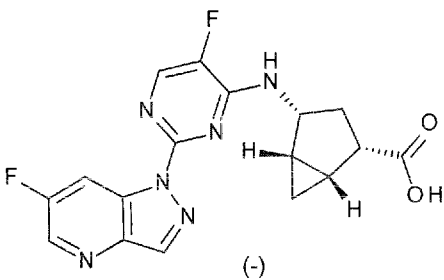
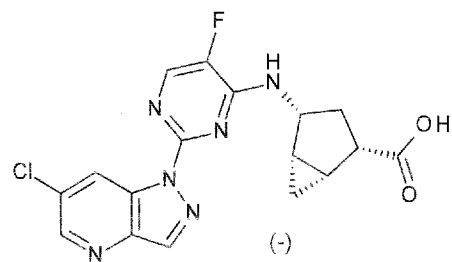
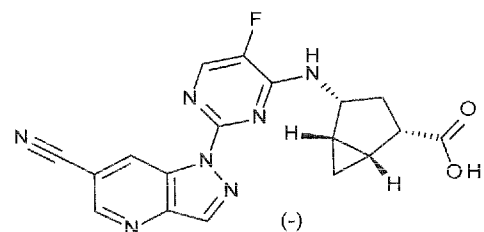
Example 78  (-)	0.0001	0.002
Example 79  (-)	0.0002	0.003
Example 80  (-)	0.0004	0.0012
Example 81  (-)	0.0011	0.0058

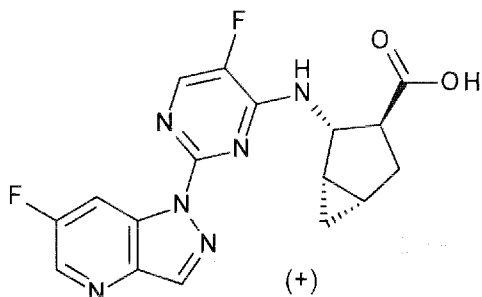
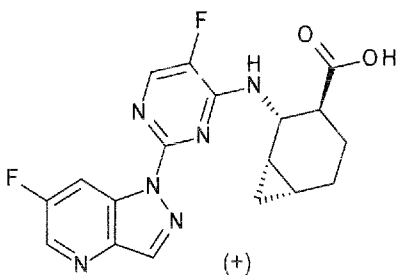
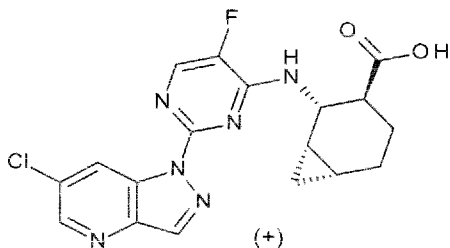
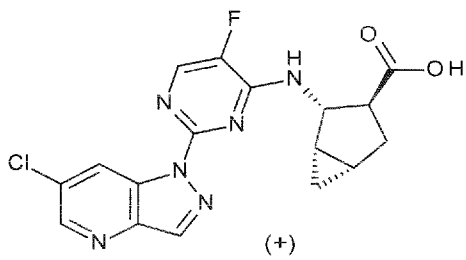
Example 82  (-)	0.0002	0.005
Example 83  (-)	0.0003	0.012
Example 84 	0.0572	0.004
Example 85 	0.0027	0.007

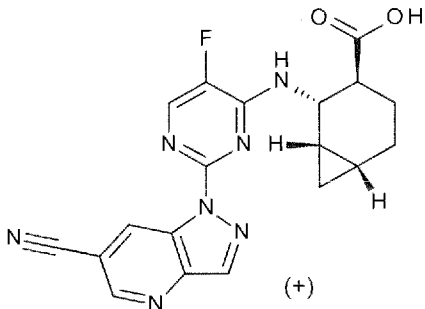
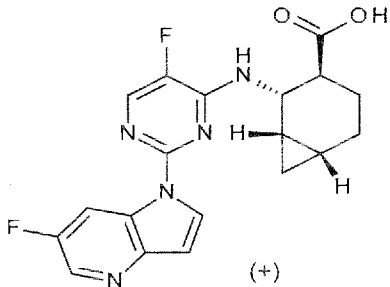
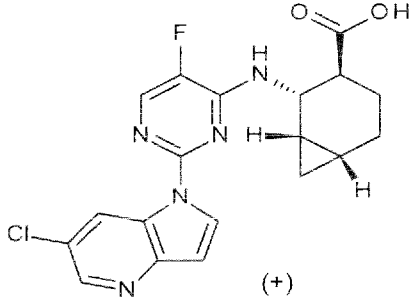
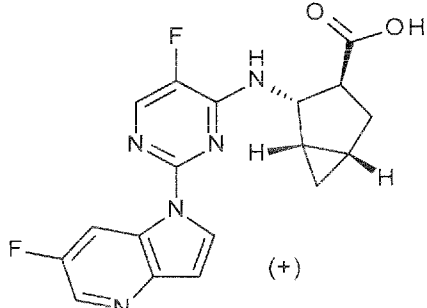
Example 86 	0.1782	0.1455
Example 87  (-)	0.031	0.083
Example 88  (+)	3.228	1.324
Example 89  (-)	9.78	3.393

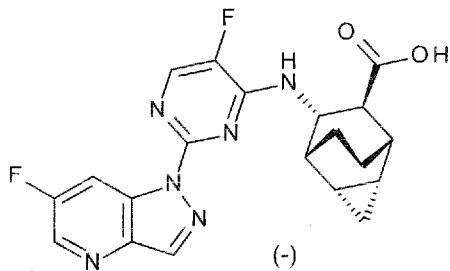
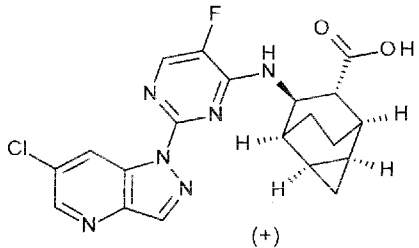
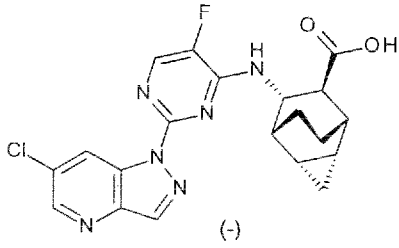
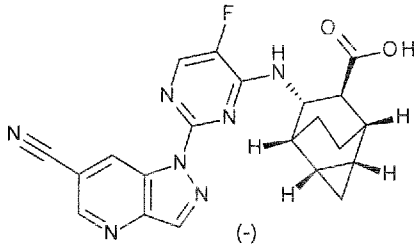
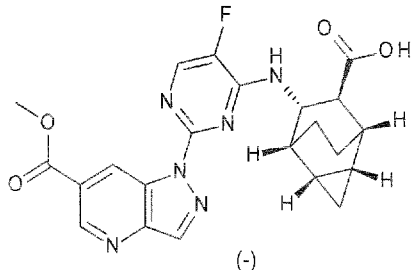
Example 90  (-)	0.69	0.061
Example 91  (-)	0.0027	0.056
Example 92  (+)	2.2	5.4
Example 93  (-)	0.06	0.066

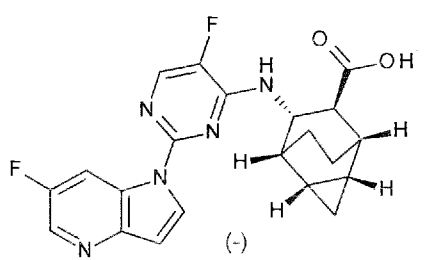
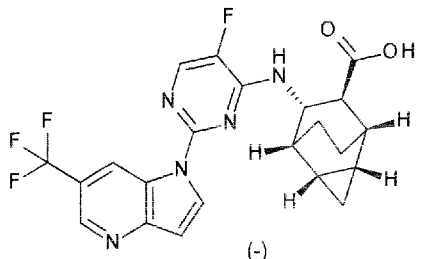
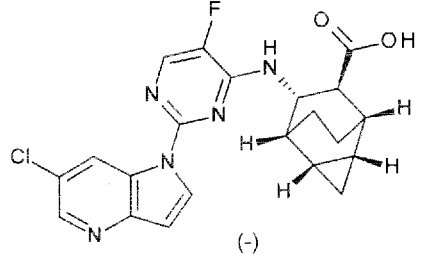
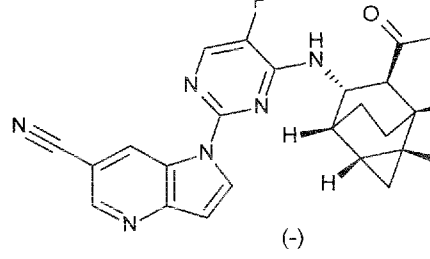
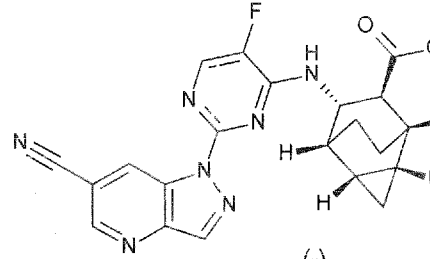
Example 94  (+)	3.77	1.94
Example 95  (-)	5.49	1.755
Example 96  (-)	0.66	0.043
Example 97  (-)	> 200	0.322
Example 98  (-)	56.9	1.04

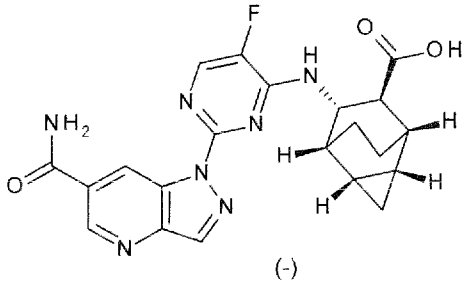
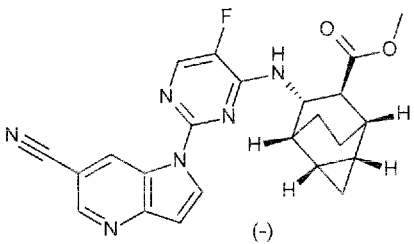
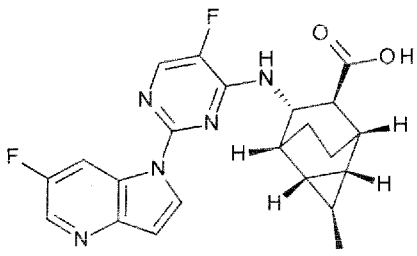
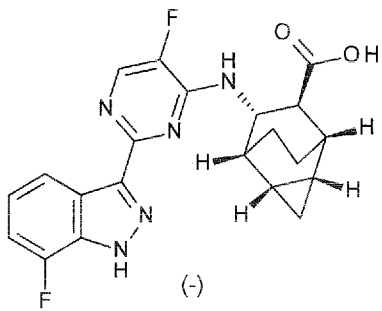
Example 99  (-)	49.77	0.141
Example 100  (-)	113	> 100
Example 101  (-)	16.5	11.2
Example 102  (-)	15.4	> 100

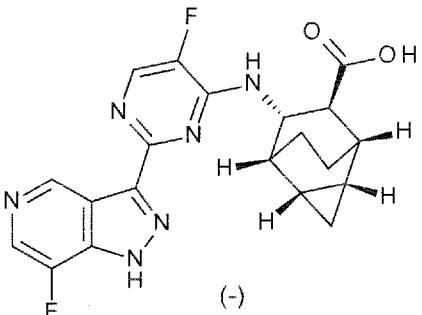
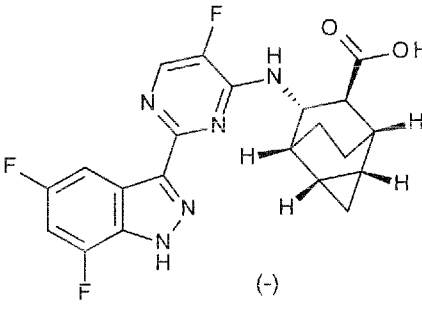
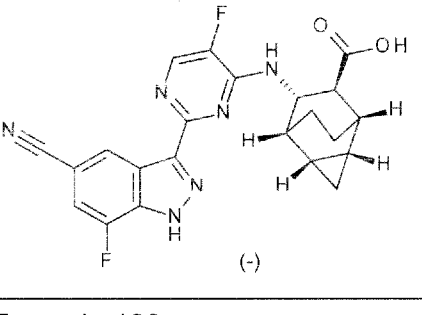
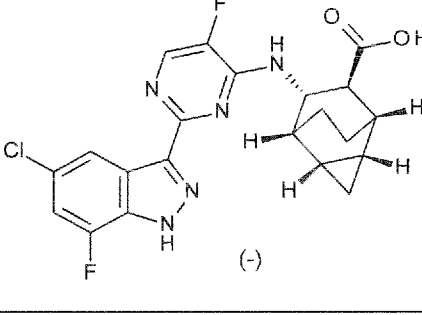
Example 103  (+)	28.3	2.84
Example 104  (+)	27.5	0.94
Example 105  (+)	8.56	0.477
Example 106  (+)	4.91	1.89

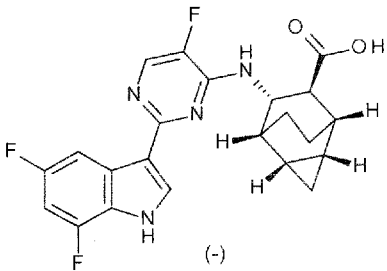
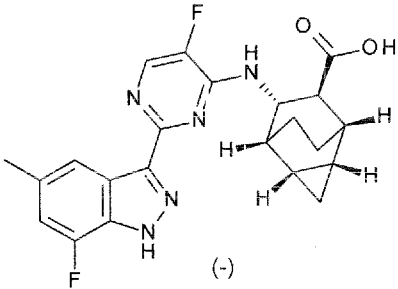
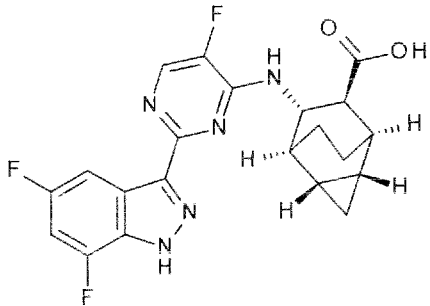
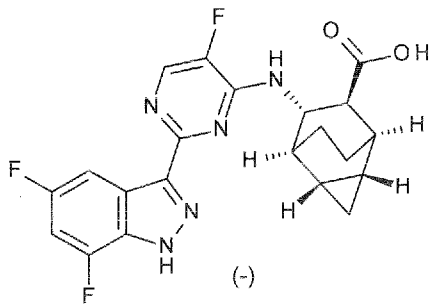
Example 107  (+)	11.1	3.37
Example 108  (+)	60.6	4.21
Example 109  (+)	35.1	2.12
Example 110  (+)	> 200	22.22

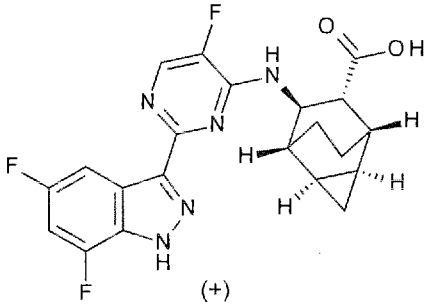
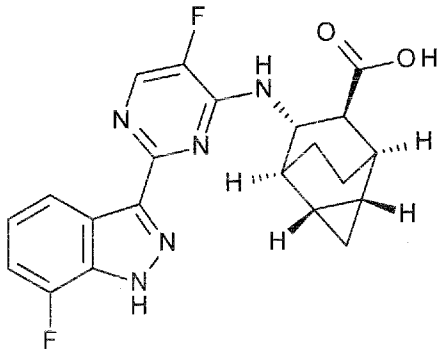
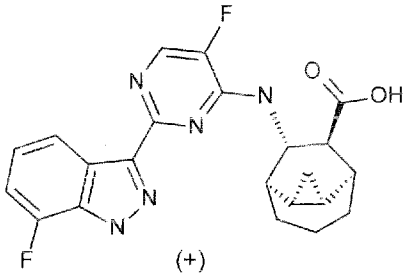
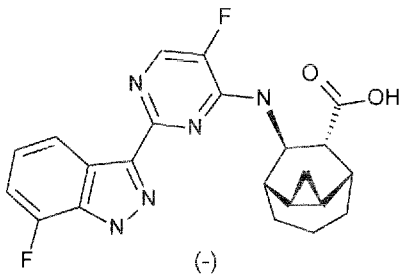
Example 111  (-)	0.161	0.047
Example 112  (+)	> 200	35.63
Example 113  (-)	0.132	0.028
Example 114  (-)	0.71	0.227
Example 115  (-)	34.21	5.23

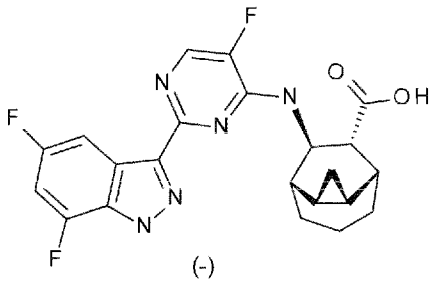
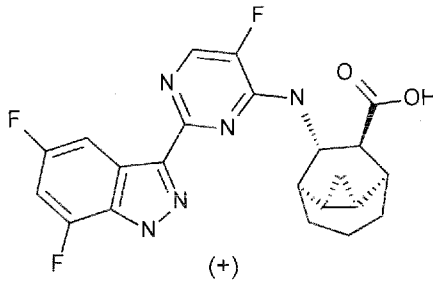
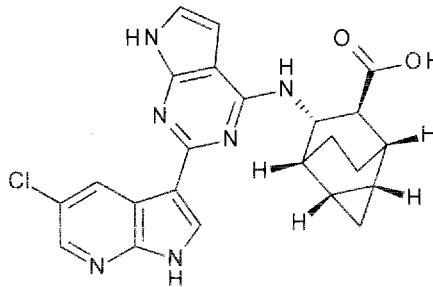
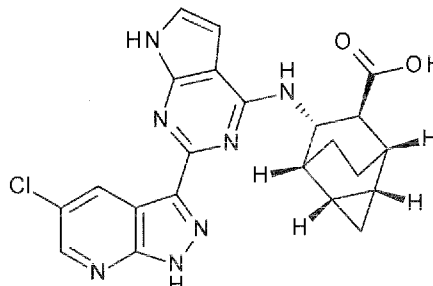
Example 116  (-)	0.479	0.253
Example 117  (-)	24.86	1.783
Example 118  (-)	0.933	0.19
Example 119  (-)	8.32	0.551
Example 120  (-)	30.12	0.172

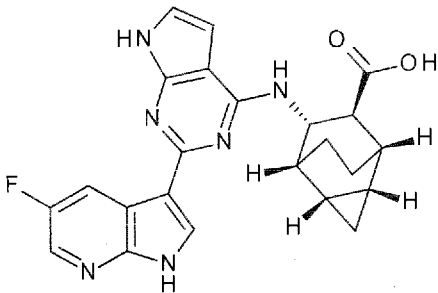
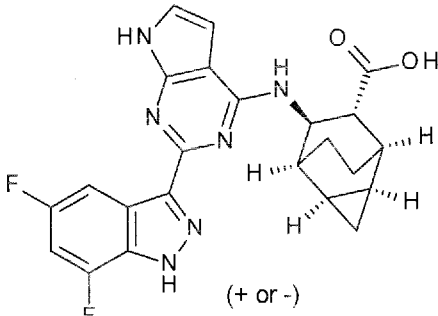
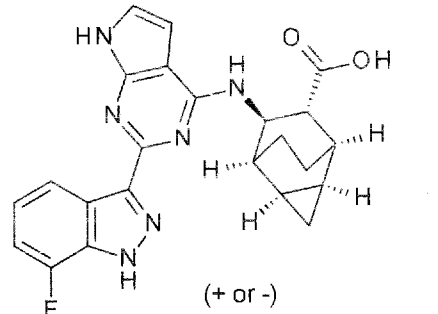
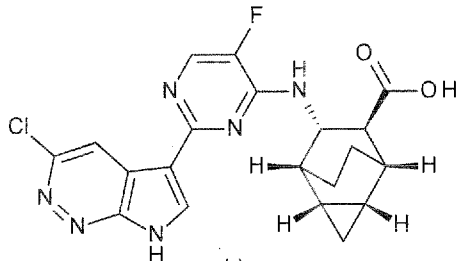
Example 121  (-)	2.182	42.82
Example 122  (-)	> 200	10.25
Example 123 	78.29	2.662
Example 124  (-)	0.198	0.021

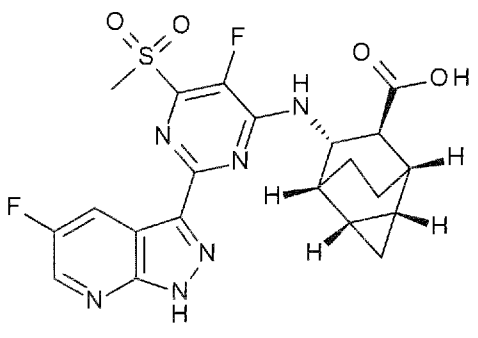
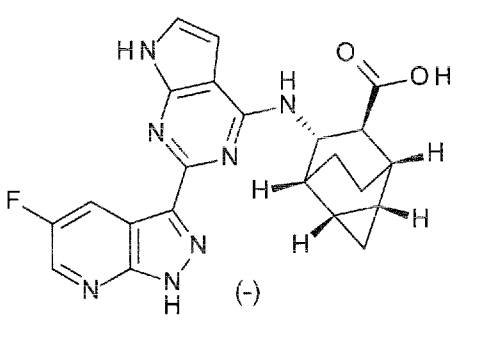
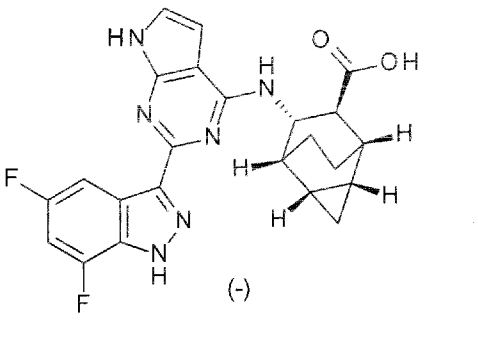
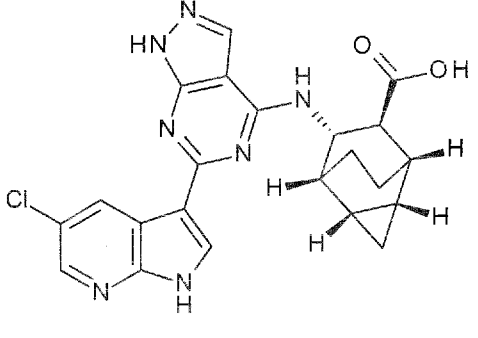
Example 125  (-)	0.211	0.096
Example 126  (-)	0.002	0.003
Example 127  (-)	0.0022	0.012
Example 128  (-)	0.0004	0.0015

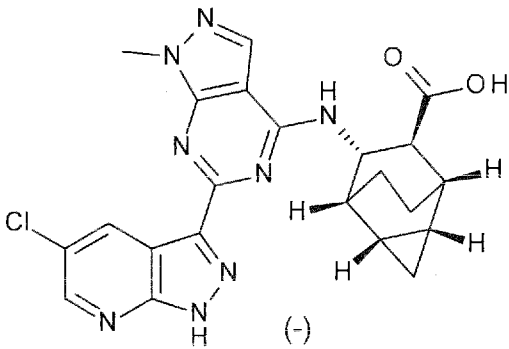
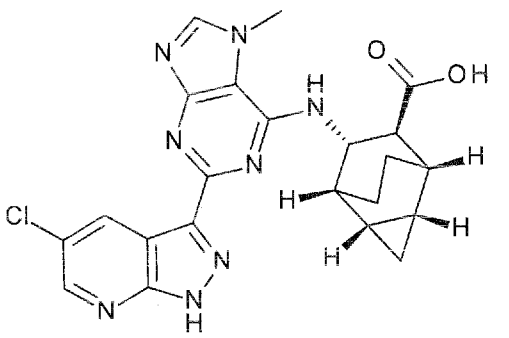
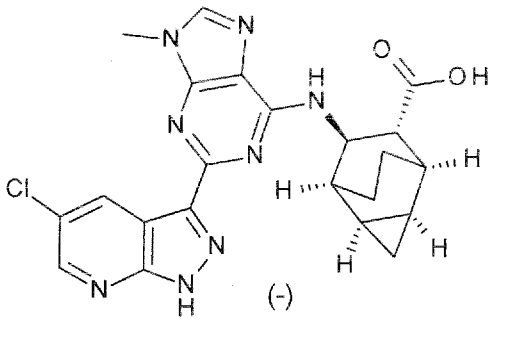
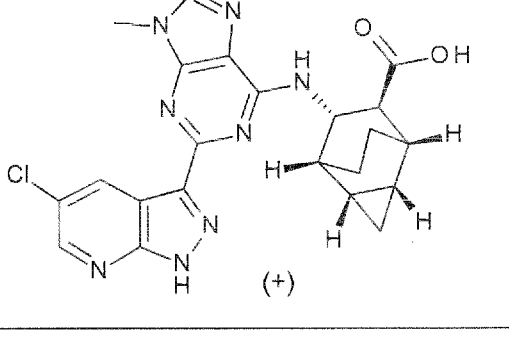
Example 129  (-)	0.321	na
Example 130  (-)	0.0043	0.0048
Example 131  (-)	0.954	0.01
Example 132  (-)	0.081	0.0055

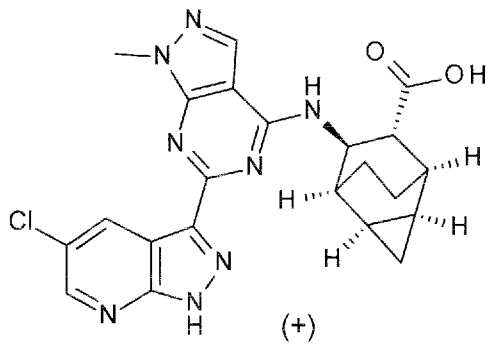
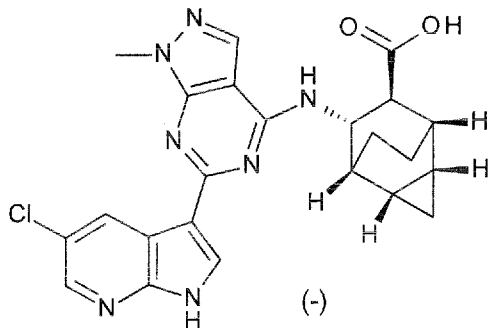
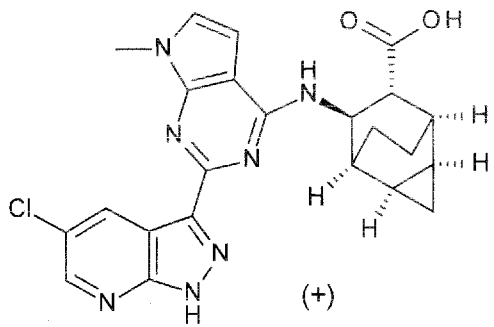
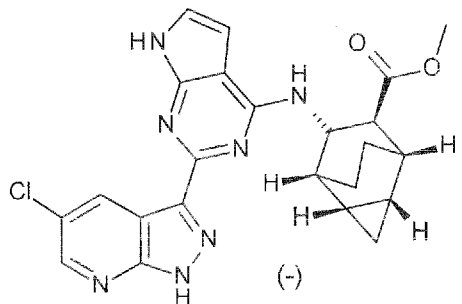
Example 133  (+)	14.1	0.857
Example 134 	2.0189	0.0645
Example 135  (+)	0.0071	0.0042
Example 136  (-)	> 12.5	2.87

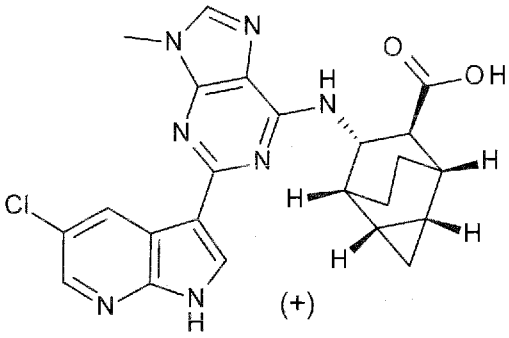
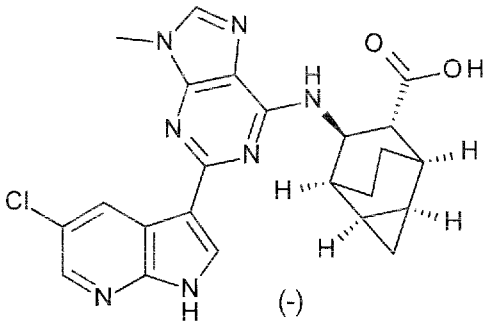
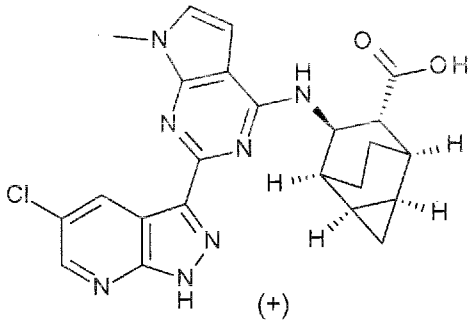
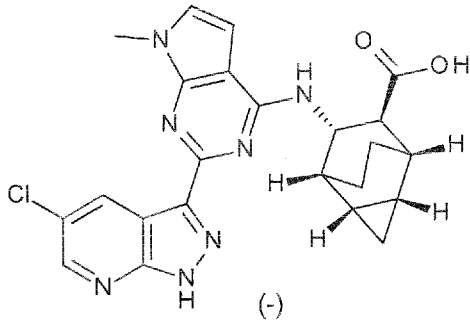
Example 137  (-)	0.614	0.51 1
Example 138  (+)	0.0002	0.001 178
Example 139 	0.0016	0.045
Example 140 	0.0003	0.006

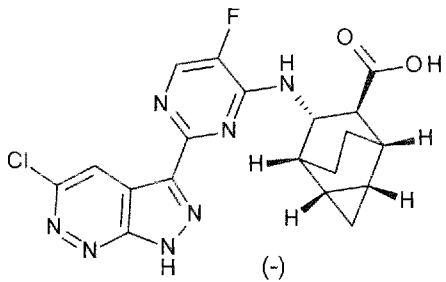
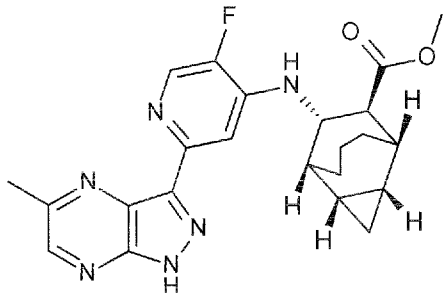
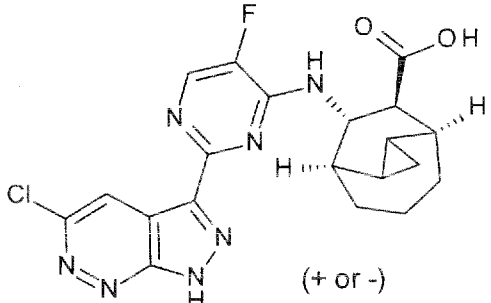
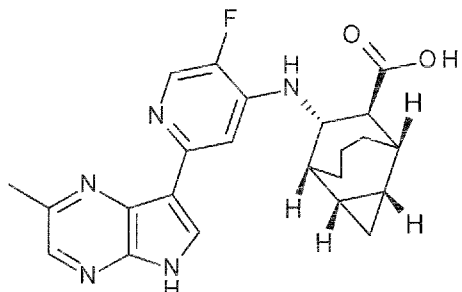
Example 141 	0.915	0.112
Example 142  (+ or -)	> 12.5	3.238
Example 143  (+ or -)	> 12.5	9.98
Example 144  (-)		0.031

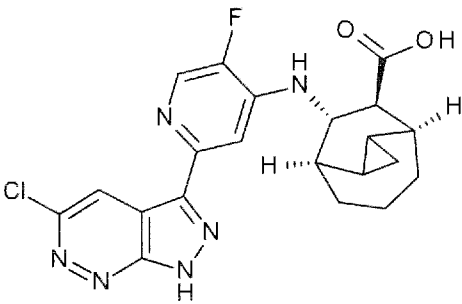
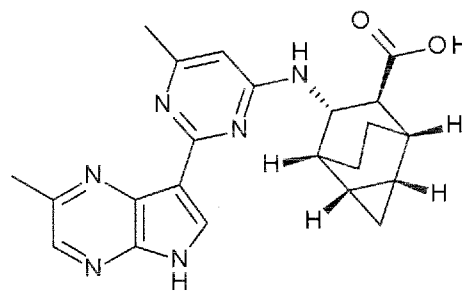
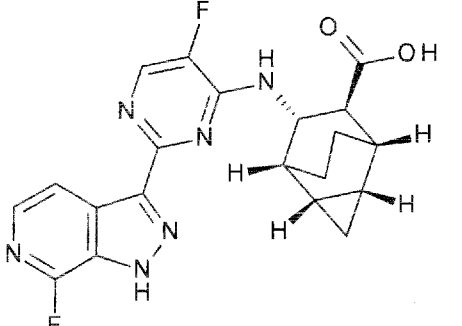
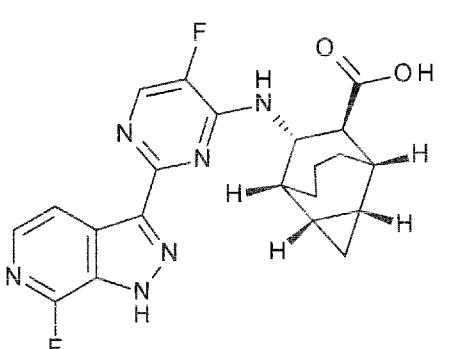
Example 145  Chemical structure of Example 145: A bicyclic molecule (bicyclo[2.2.1]heptane derivative) with a carboxylic acid group and a sulfonamide group. The sulfonamide group is substituted with a fluorine atom and a pyridine ring.	0.002	0.035
Example 146  Chemical structure of Example 146: A bicyclic molecule (bicyclo[2.2.1]heptane derivative) with a carboxylic acid group and a sulfonamide group. The sulfonamide group is substituted with a fluorine atom and a pyridine ring. The structure is labeled with a minus sign (-).	0.0005	0.008
Example 147  Chemical structure of Example 147: A bicyclic molecule (bicyclo[2.2.1]heptane derivative) with a carboxylic acid group and a sulfonamide group. The sulfonamide group is substituted with a fluorine atom and a pyridine ring. The structure is labeled with a minus sign (-).	0.003	0.006
Example 148  Chemical structure of Example 148: A bicyclic molecule (bicyclo[2.2.1]heptane derivative) with a carboxylic acid group and a sulfonamide group. The sulfonamide group is substituted with a fluorine atom and a pyridine ring.	0.001	0.243

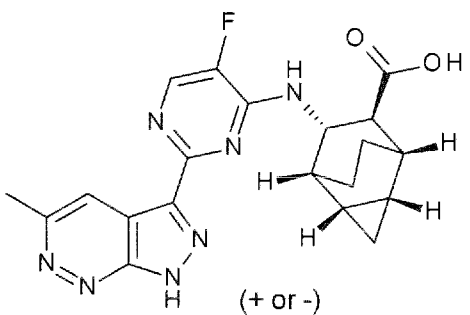
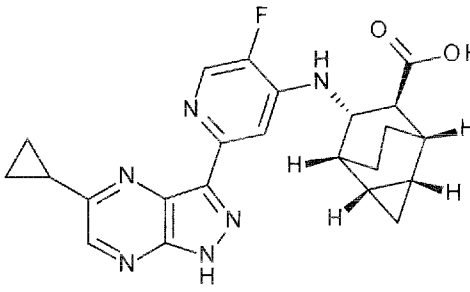
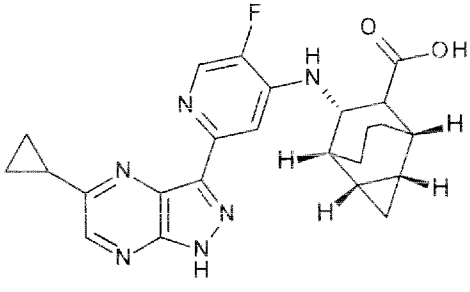
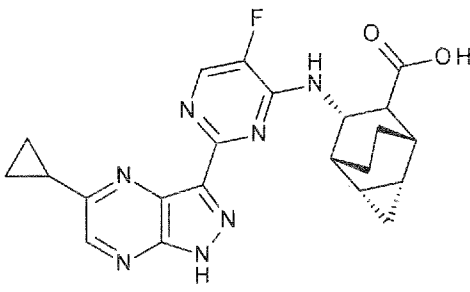
Example 149  (-)	0.106	0.509
Example 150  (-)	0.038	0.637
Example 151  (-)	0.040	0.032
Example 152  (+)	0.426	1.675

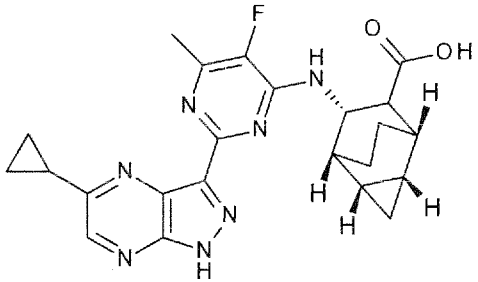
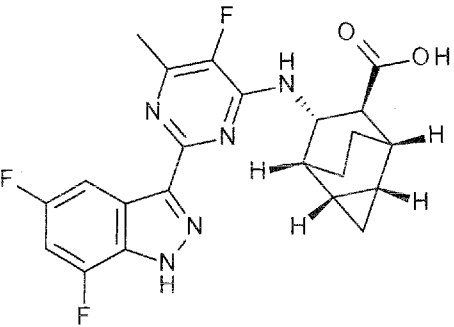
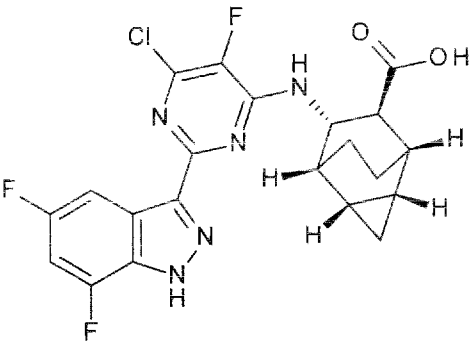
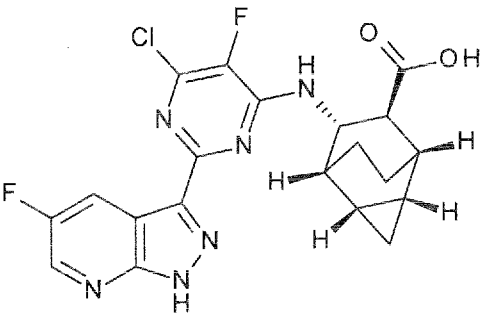
Example 153  (+)	na	0.004
Example 154  (-)	0.078	0.336
Example 155  (+)	0.066	0.886
Example 156  (-)	0.0003	0.007

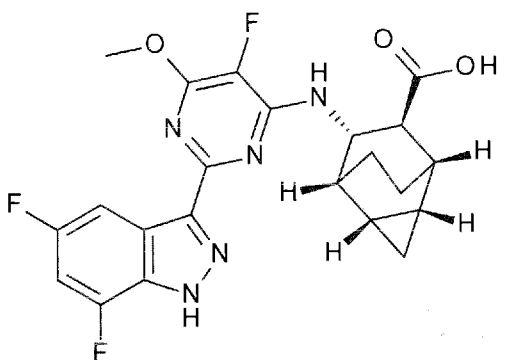
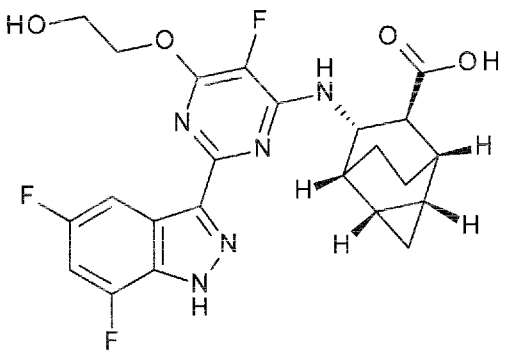
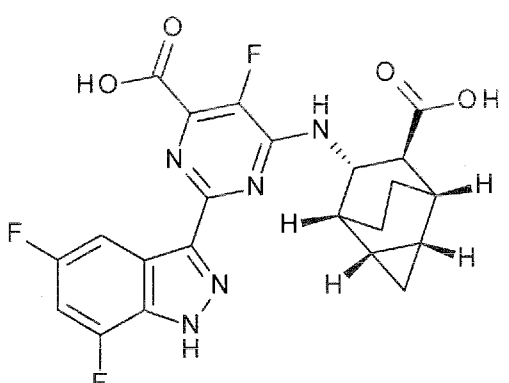
Example 157	> 12.5	1.337
 (+)		
Example 158	0.519	0.077
 (-)		
Example 159	0.037	0.062
 (+)		
Example 160	0.0002	0.0005
 (-)		

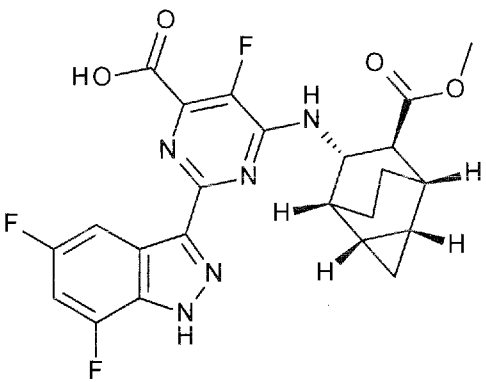
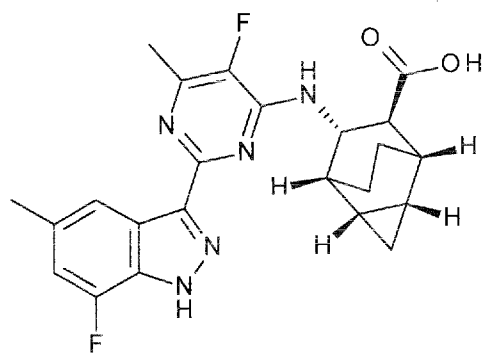
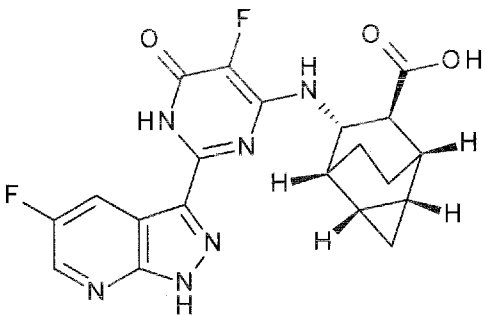
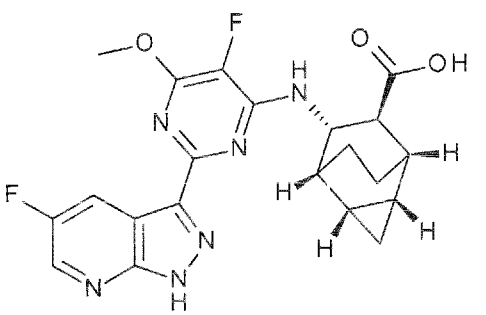
Example 161  (-)	0.003	0.026
Example 162  (+ or -)	0.0004	0.004
Example 163  (+ or -)	0.0005	0.014
Example 164  (+ or -)	0.0006	0.001

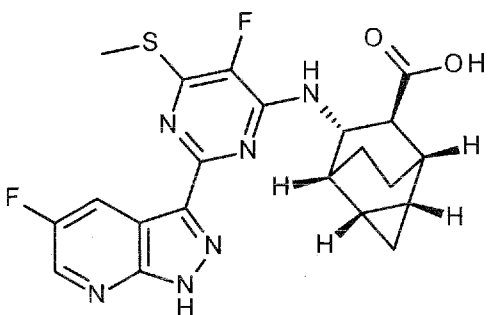
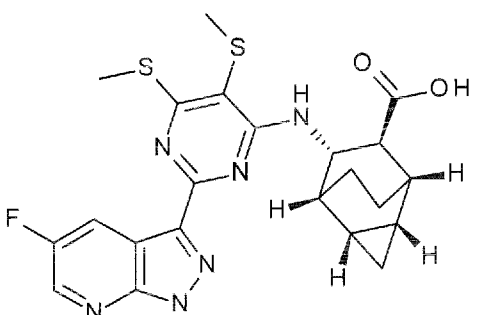
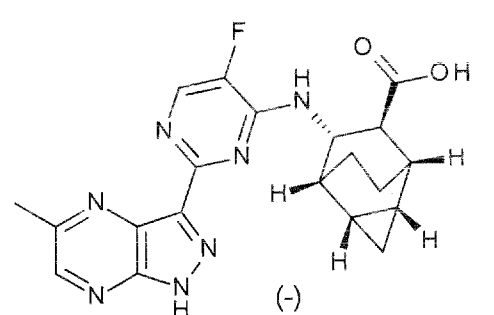
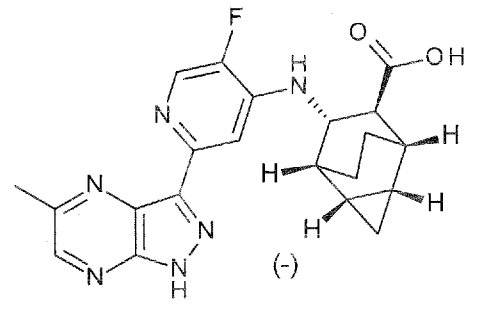
Example 165	0.548	0.144
		
Example 166	0.958	1.091
		
Example 167	8.479	0.347
		
Example 168	6.106	0.141
		

Example 169  (+ or -)	0.008	0.127
Example 170 	0.023	0.118
Example 171  (+ or -)	0.050	0.039
Example 172 	8.259	0.464

Example 173	5.290	0.227
		
Example 174	0.003	0.005
		
Example 175	0.002	0.001
		
Example 176	0.001	0.0002
		

Example 177	0.004	0.007
		
Example 178	0.003	0.076
		
Example 179	0.004	0.116
		

Example 180	0.723	0.281
		
Example 181	0.019	0.005
		
Example 182	0.001	0.141
		
Example 183	0.001	0.003
		

Example 184	0.001	0.028
		
Example 185	9.185	1.672
		
Example 186	0.011	0.039
		
Example 187	0.0005	0.014
		

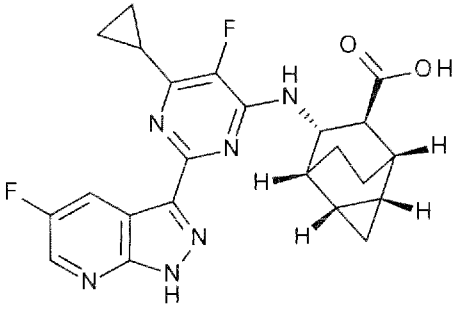
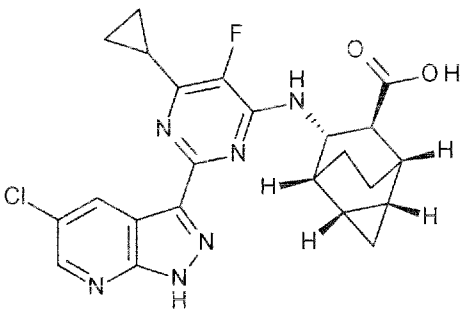
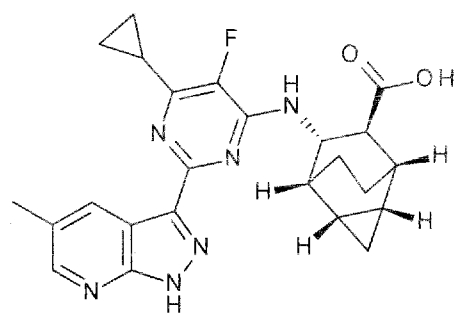
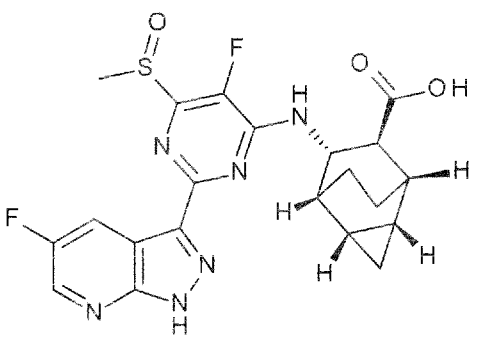
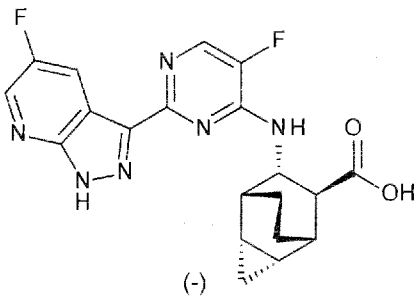
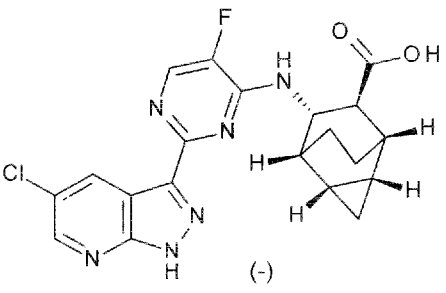
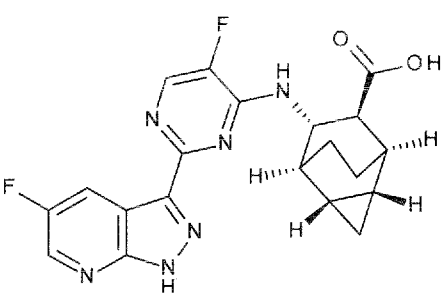
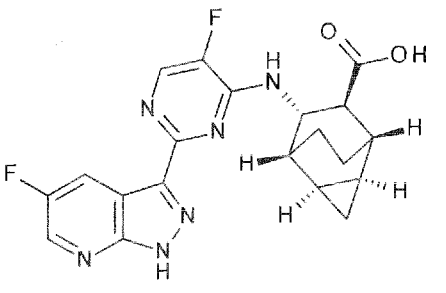
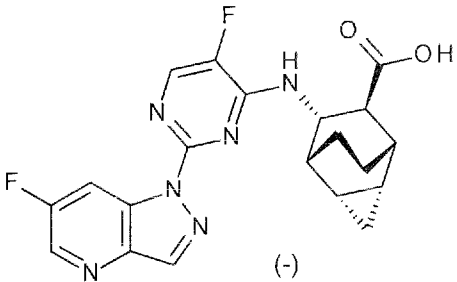
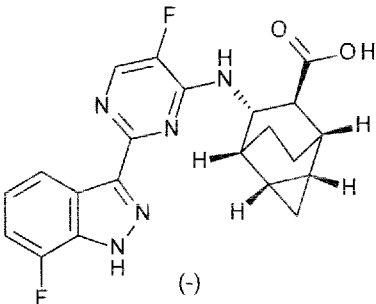
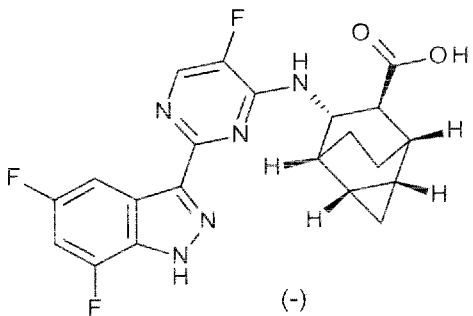
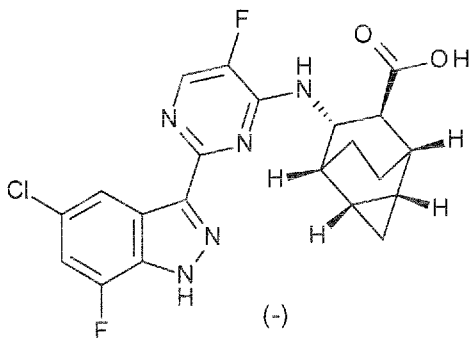
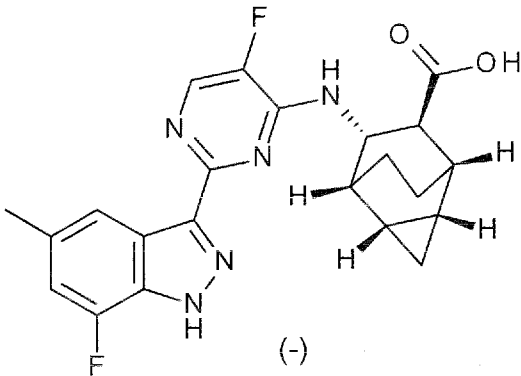
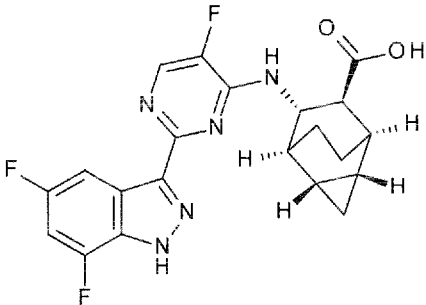
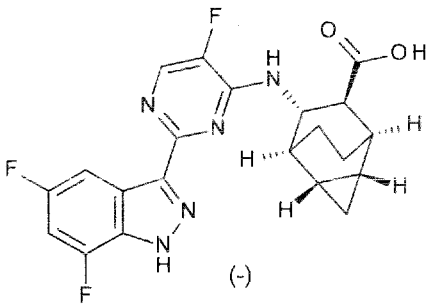
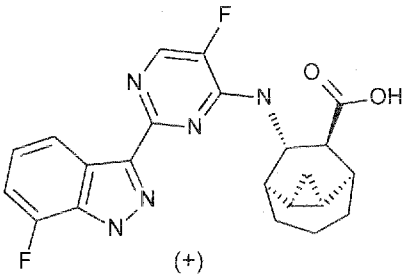
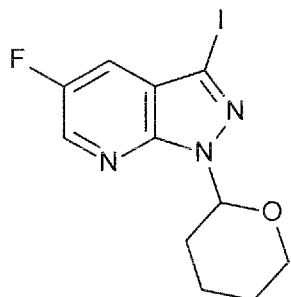
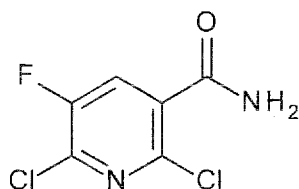
Example 188	0.0004	0.01
		
Example 189	0.001	0.003
		
Example 190	0.001	0.005
		
Example 191	0.002	0.016
		

Table 2.

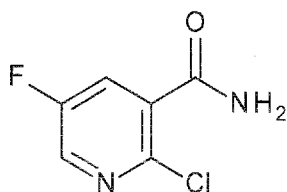
Example	RNP IC ₅₀ [μM]	Replication IC ₅₀ [μM]	LRA IC ₅₀ [μM]
Example 75  (-)	0.0002	0.0001	0.0014
Example 77  (-)	0.0002	0.0001	0.00058
Example 84  (-)	0.0572	0.0015	0.004
Example 85  (-)	0.0027	0.0045	0.007

Example 111  (-)	0.1609	0.046	0.044
Example 124  (-)	0.2288	0.011	0.020
Example 126  (-)	0.0006	0.0014	0.0047
Example 128  (-)	0.0004	0.0025	0.0015

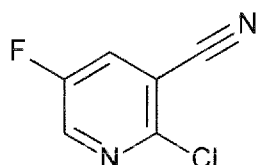
Example 130  (-)	0.0043	0.0013	0.0048
Example 131  (-)	0.954	0.0167	0.010
Example 132  (-)	0.0806	0.0176	0.0055
Example 135  (+)	0.0071	0.0037	0.0042

Intermediate A-1a**5-Fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine**5 fA] 2,6-Dichloro-5-fluoro-pyridine-3-carboxamide

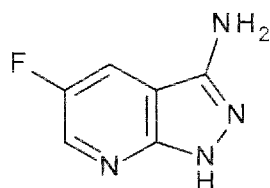
A stirred solution of 2,6-dichloro-5-fluoronicotinonitrile (100 g, 0.526 mol) in conc. H_2SO_4 (1000 mL) was heated at 60°C for 2 h. After cooling to room temperature, the mixture was poured into ice water, and extracted with EtOAc (300 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The crude residue, after being washed with hexane several times gave the title compound (90 g, 83% yield) as a yellow solid. MS: 207.0 [M-H] $^-$

B] 2-Chloro-5-fluoro-pyridine-3-carboxamide

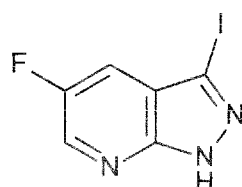
To a stirred solution of 2,6-dichloro-5-fluoro-pyridine-3-carboxamide (95 g, 0.45 mol) in MeOH (45mL) and AcOH (450 mL) was added Zn powder (41.92 g, 0.645 mol). The resulting reaction mixture was heated at 85°C for 15 h. After TLC (petroleum ether: EtOAc = 1:1) showed the completion of the reaction, the reaction mixture was diluted with satd. aq. NaHCO_3 solution and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The residue, after being washed with hexane several times gave the title compound (70 g, 88% yield) as a solid. MS: 173.0 [M-H] $^-$

fC] 2-Chloro-5-fluoro-pyridine-3-carbonitrile

To a stirred solution of 2-chloro-5-fluoro-pyridine-3-carboxamide (60 g, 0.34 mol) and Et₃N (105.6 mL) in DCM (400 mL) was added TFAA (60 mL) dropwise at OX and resulting reaction mixture was stirred at OX for 1.5 h. The reaction was quenched with satd. aq. NaHCO₃ solution and extracted with DCM (400 mL three times). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford a crude title compound (55 g, 87% yield) as a brown solid. MS: 157.1 [M+H]⁺

[DI 5-Fluoro-1H-pyrazolo[3,4-b]pyridin-3-amine

A stirred solution of 2-chloro-5-fluoro-pyridine-3-carbonitrile (50 g, 3.30 mol) and N₂H₄·H₂O (100 mL) in EtOH (500 mL) was heated at 100°C for 2 h. After TLC (petroleum ether: EtOAc = 2:1) showed the completion of the reaction, the solvent was removed under reduced pressure. The residue, after being washed with EtOAc several times afforded the title compound (30.6 g, 62% yield) as a solid. MS: 153.0 [M+H]⁺.

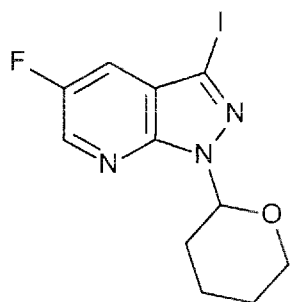
[E] 5-Fluoro-3-iodo-1H-pyrazolo[3,4-b]pyridine

To a stirred solution of 5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-amine (30.6 g, 0.2 mol) in MeCN (500 mL) was added isopentyl nitrite (27.11 g, 0.24 mol) and CH₂I₂ (164 g, 0.60 mol) at OX. After the addition, the resulting reaction mixture was stirred first at OX for 2 h and then at 100°C for 20 h. After TLC (petroleum ether: EtOAc = 5:1) showed the completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was diluted

with water and then extracted with EtOAc. The organic layer was washed with brine (100 mL three times), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 20:1) to afford the title compound (18 g, 34% yield) as a solid. MS: 263.9 $[\text{M}+\text{H}]^+$.

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5-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-pyrazolo[3,4-b]pyridine



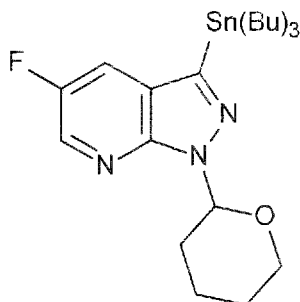
To a stirred solution of 5-fluoro-3-iodo-1H-pyrazolo[3,4-b]pyridine (18 g, 68.4 mmol) in THF (500 mL) was added TsOH (0.1 g) at 0°C and stirred for 30 min. 3,4-Dihydro-2H-pyran (6.9 g, 82.1 mmol) was added dropwise to the above mixture at 0°C and the resulting reaction mixture was then heated at 80°C for 6 h before it was concentrated under vacuum. The residue was diluted with water and extracted with EtOAc (200 mL three times). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 8:1) to afford the title compound (16.8 g, 63% yield) as a yellow solid. MS: 348.0 $[\text{M}+\text{H}]^+$.

10

15

Intermediate A-1b

Tributyl-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)stannane



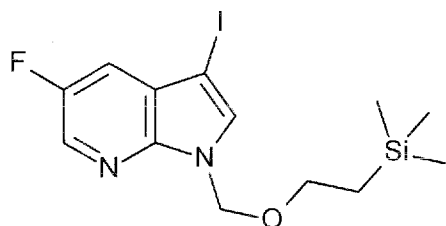
A stirred mixture solution of 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 0.7 g, 2 mmol), Bu_3SnI (1.0 g, 3.0 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.24 g, 0.2 mmol) in dioxane (10 mL) was heated to reflux for 1 h. After TLC showed the

20

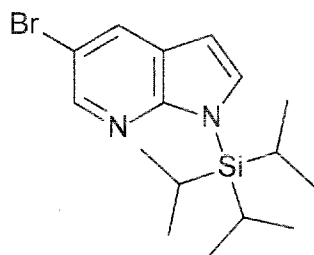
completion of the reaction, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 50:1 to 20:1) to afford the title compound (0.2 g, 29% yield) as an oil. MS: 512.3 $[M+H]^+$.

5 Intermediate A-2

2-[(5-Fluoro-3-iodo-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane

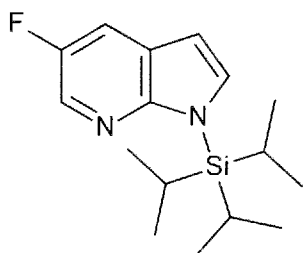


[A] (5-Bromopyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



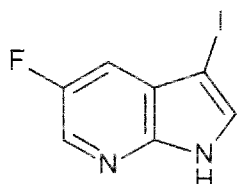
- 10 To a stirred solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (6 g, 0.03 mol) in THF (400 mL) was added NaH (1.8 g, 60% dispersion in mineral oil, 0.045 mol) at 0°C and stirred for 1 h before TIPSCI (8.7 g, 0.045 mol) was added slowly to the above solution at OX. The resulting mixture was allowed to warm up to room temperature and stirred for 4 h before the reaction was quenched by the addition of water. The mixture was subsequently
- 15 concentrated under vacuum and the residue was re-dissolved in EtOAc and washed with brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (8 g, 76% yield) as a white solid. MS: 353.0 $[M+H]^+$.

20 1-(5-Fluoropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



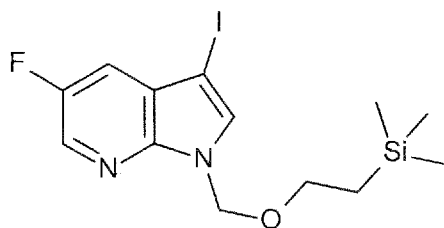
Under N_2 protection, to a stirred solution of (5-bromopyrrolo[2,3-b]pyridin-1-yl)-triisopropylsilane (7.7 g, 0.022 mol) in THF (400 mL) was added slowly n-BuLi (13.2 mL, 0.033 mol) at -78°C . The mixture was stirred at -78°C for 1 h before $(\text{PhSO}_2)_2\text{NF}$ (13.9 g, 0.044 mol) was added. The resulting reaction mixture was stirred at -78°C for 2 h before warmed up to room temperature. The reaction was then quenched by the addition of water and subsequently concentrated under vacuum. The residue was extracted with EtOAc and separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatograph (petroleum ether: EtOAc = 10:1) to afford the title compound (4 g, 63% yield) as a white solid. MS: 293.0 [M+Hf.

[C] 5-Fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine



A stirred mixture solution of (5-fluoropyrrolo[2,3-b]pyridin-1-yl)-triisopropylsilane (3.9 g, 0.013 mol), I_2 (3.3 g, 0.013 mol) and KOH (2.9 g, 0.052 mol) in DMF (150 mL) was heated at 25°C for 12 h before it was poured into water and extracted with EtOAc (50 mL three times). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (3 g, 86% yield) as a solid. MS: 263.0 [M+Hf. This crude product was used directly in the next step without further purification.

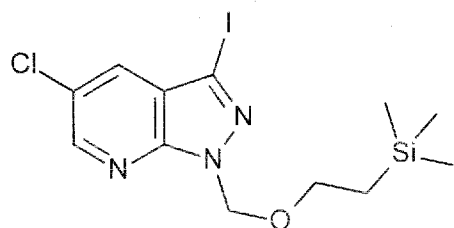
[D] 2-[(5-Fluoro-3-iodo-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane



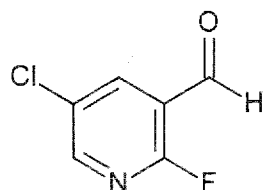
To a stirred solution of 5-fluoro-3-iodo-1H-pyrrolo[2,3-b]pyridine (5 g, 19 mmol) and Cs_2CO_3 (10 g, 30.7 mmol) in DMF (100 mL) was added SEMCI (5 g, 30 mmol) dropwise at 0°C . After the addition, the resulting reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched with ice-water, and then extracted with Et_2O . The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography to afford the title compound (6 g, 80% yield) as colorless oil. MS: 393.4 $[\text{M}+\text{H}]^+$

Intermediate A-3

2-[(5-Chloro-3-iodo-pyrazolo[3,4-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane



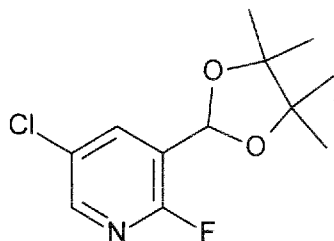
[A] 5-Chloro-2-fluoro-pyridine-3-carbaldehyde



To a stirred solution of 5-chloro-2-fluoropyridine (15 g, 114.5 mmol) in THF (150 mL) was added LDA (85.6 mL, 171.7 mmol) dropwise at -78°C . After stirred for 1.5 h, the morpholine-4-carbaldehyde was added to the above solution and the mixture solution was stirred at -78°C for another 2 h. After TLC (petroleum ether: EtOAc = 5:1) showed the completion of the reaction, the reaction was quenched by the addition of 10% citric acid. The reaction mixture was then allowed to warm up to room temperature and adjusted to pH = 5-6. The mixture was extracted with DCM (100 mL * 3) and the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude title

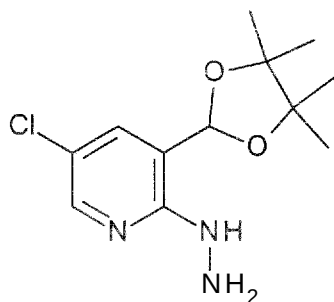
compound (2.8 g, 15% yield) as a white solid. MS: 160.0 $[M+H]^+$. This crude product was used directly in the next step without further purification.

15-Chloro-2-fluoro-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)pyridine

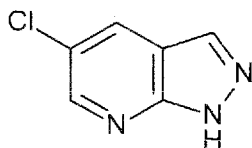


A flask fitted with a Dean-Stark trap was charged with a solution of 5-chloro-2-fluoropyridine-3-carbaldehyde (2.8 g, 17.36 mmol), 2,3-dimethylbutane-2,3-diol (1.3 g, 21 mmol) and PTS (0.14 g, 0.86 mmol) in toluene (50 mL). The reaction mixture was heated to 120°C for 4 h. After TLC (petroleum ether/EtOAc = 5:1) showed the completion of the reaction, the reaction mixture was cooled to room temperature and diluted with EtOAc (20 mL). The organic layer was washed with satd. aq. NaHCO_3 (20 mL x 2), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (3 g, 67% yield) as a white solid. MS: 260.0 $[M+H]^+$. This crude product was used directly in the next step without further purification.

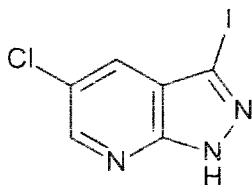
15-Chloro-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-2-pyridylhydrazine



To a stirred solution of 5-chloro-2-fluoro-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)pyridine (3 g, 14.7 mmol) and DIPEA (3.8 g, 29.4 mmol) in isopropanol (20 mL) was added hydrazine (5.1 g, 102.9 mmol) and the resulting reaction mixture was heated to 65 °C for 12 h. After TLC (petroleum ether: EtOAc = 5:1) showed the completion of the reaction, the mixture was concentrated in vacuo to give a crude title compound (3.1 g, 78% yield) as a white solid. MS: 272.1 $[M+H]^+$. This crude product was used directly in the next step without further purification.

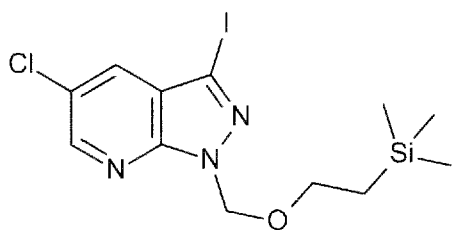
[P] 5-Chloro-1H-pyrazolo[3,4-b]pyridine

To a stirred solution of [5-chloro-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-2-pyridyl]hydrazine (3.1 g, 14.3 mol) in 40 mL of water and 16 mL of EtOH was added 6 N HCl (8 mL). The resulting reaction mixture was heated to 45°C for 6 h. After TLC (petroleum ether: EtOAc = 2:1) showed the completion of the reaction, the reaction mixture was neutralized with 6 N NaOH (8 mL) and adjusted pH = 8. The mixture was concentrated in vacuo to remove volatile EtOH and the residue was extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (2.5 g) as a yellow solid. MS: 154.0 [M+H]⁺. This crude product was used directly in the next step without further purification.

[E] 5-Chloro-3-iodo-1H-pyrazolo[3,4-b]pyridine

A stirred mixture solution 5-chloro-1H-pyrazolo[3,4-b]pyridine (2.5 g, 16.2 mmol) and NIS (4 g, 18 mmol) in DCE (10 mL) was heated to 50°C for 12 h. After TLC (petroleum ether: EtOAc = 2:1) showed the completion of the reaction, the mixture was cooled to room temperature and diluted with EtOAc (20 mL). It was washed with satd. aq. NaHCO₃ solution (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (2 g, 44% yield) as a yellow solid. MS; 279.9 [M+H]⁺. This crude product was used directly in the next step without further purification.

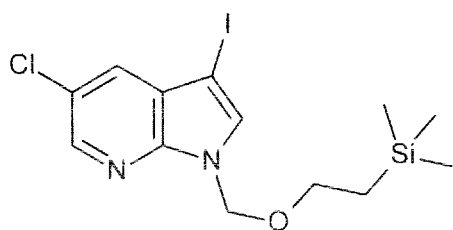
[F] 2-(5-Chloro-3-iodo-pyrazolo[3,4-b]pyridin-1-yl)methoxyethyl-trimethyl-silane



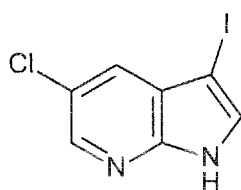
To a stirred solution of 5-chloro-3-iodo-1H-pyrazolo[3,4-b]pyridine (2 g, 13 mmol), NaH (0.56 g, 23.4 mmol) in DMF (5 mL) was added SEMCl (3.9 g, 23.4 mmol) dropwise at room temperature and stirred for 1 h. After TLC (petroleum ether: EtOAc = 10:1) showed the completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (10 mL x2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (0.3 g, 41% yield) as a white solid. MS: 410.0 [M+H]⁺

Intermediate A-4a

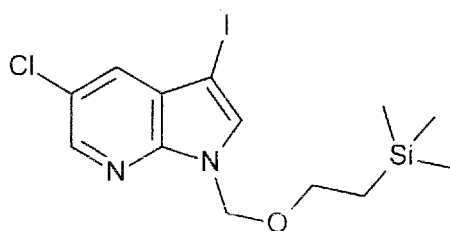
2-[(5-Chloro-3-iodo-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyltrimethylsilane



[A] 5-Chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine



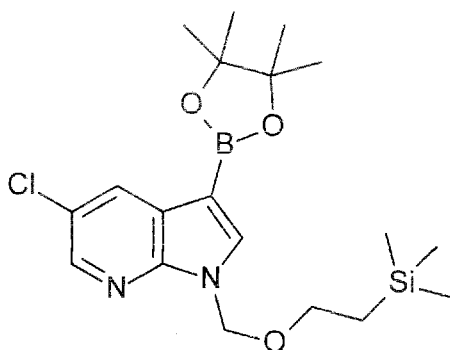
A mixture solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine (20 g, 131.5 mmol), I₂ (33.4 g, 131.5 mmol) and KOH (29.4 g, 526 mmol) in DMF (300 mL) was stirred at room temperature for 12 h before it was poured into water and extracted with EtOAc (150 mL three times). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (18 g, 49% yield) as a solid. MS: 278.9 [M+H]⁺. This crude product was used directly in the next step without further purification.

IB 124(5-Chloro-3-iodo-pyrrolo[2,3-b]pyridin-1-yl)methoxyethyl-trimethyl-silane

To a stirred solution of 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (16 g, 57.5 mmol) and NaH (4.2 g, 172.4 mol) in DMF (100 mL) was added (2-(chloromethoxy)ethyl)trimethylsilane (9.57 g, 172.4 mmol) dropwise at 0°C and stirred for 0.5 h. Afterwards, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL twice). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (10 g, 43% yield) as a solid. MS: 409.0 [M+H]⁺

Intermediate A-4b

2-[[5-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-1-yl]methoxy]ethyl-trimethyl-silane

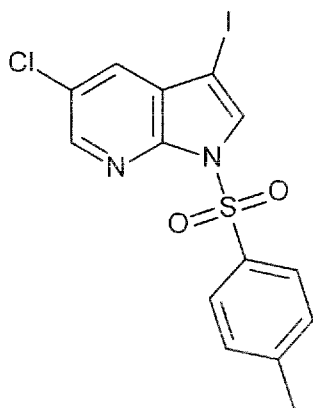


A stirred mixture solution of 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (intermediate A-4a, 1 g, 2.4 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.65 g, 2.5 mmol), AcOK (0.47 g, 4.8 mmol) and PdCl₂(dppf) (0.084 g, 0.12 mmol) in DMSO (10 mL) was heated at 70°C for 2 h before it was diluted with water (20 mL) and extracted with EtOAc (20 mL twice). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography

(petroleum ether: EtOAc = 10:1) to give the title compound (0.3 g, 31% yield) as a white solid. MS: 409.1 $[M+H]^+$.

Intermediate A-4c

5 5-Chloro-3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine

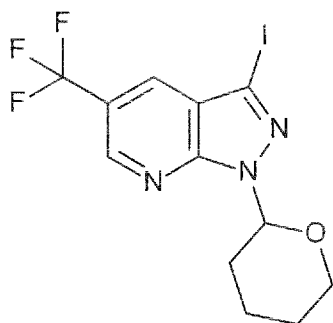


A mixture of 5-chloro-3-iodo-1H-pyrrolo[2,3-b]pyridine (Intermediate A-4a/step A, 22 g, 79 mmol), cesium carbonate (51.5 g, 158 mmol) and 4-toluenesulfonyl chloride (22.5 g, 119 mmol) in DMF (200 mL) was stirred at room temperature for 4 h. After LC-MS showed that the reaction was completed, the mixture was poured into water and the suspension was collected by filtration to afford the crude product (30 g, 87.8% yield) as a light brown solid. MS: 433.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.44 (d, $J=2.20$ Hz, 1H), 8.24 (s, 1H), 8.00 (d, $J=8.44$ Hz, 2H), 7.90 (d, $J=2.32$ Hz, 1H), 7.44 (d, $J=8.19$ Hz, 2H), 2.35 (s, 3H).

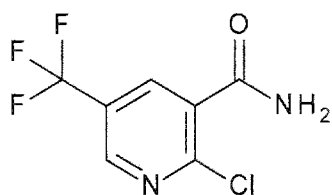
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Intermediate A-5

3-Iodo-1-tetrahydropyran-2-yl-5-(trifluoromethyl)pyrazolo[3,4-b]pyridine

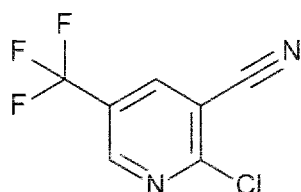


[A] 2-Chloro-5-(trifluoromethyl)pyridine-3-carboxamide



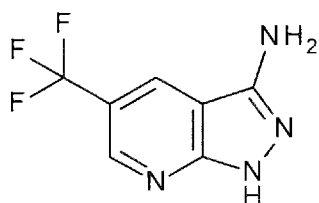
Under N_2 protection, to a stirred solution of 2-chloro-5-(trifluoromethyl)nicotinic acid (20 g, 17.7 mmol) in DCM (60 mL) was added oxalyl chloride (22.5 g, 35.4 mmol) followed by the slow addition of DMF (1 mL). The resulting reaction mixture was stirred at room temperature for 2 h before volatile solvent was removed under reduced pressure. The residue was re-dissolved in DCM (60 mL) and cooled to 0°C . Ammonia (60 mL, 28% in H_2O) was added in one portion to the above solution and resulting mixture was stirred at 0°C for 15 min. The mixture was then diluted with EtOAc (40 mL) and washed with water (30 mL) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (19.6 g, 94% yield) as a white solid. MS: 225.0 [M+H]⁺. This crude product was used directly in the next step without further purification.

[B] 2-Chloro-5-(trifluoromethyl)pyridine-3-carbonitrile



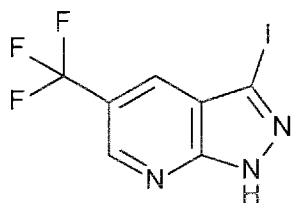
To a stirred solution of 2-chloro-5-(trifluoromethyl)pyridine-3-carboxamide (18 g, 80.1 mmol) and Et_3N (16.4 mL, 160.2 mmol) in DCM (100 mL) was added TFAA (18.5 g, 88.2 mmol) slowly over a period of 15 min at 0°C . The resulting reaction mixture was stirred for at 0°C 90 min before it was diluted with additional DCM (100 mL). The organic layer was then washed with satd. aq. $NaHCO_3$ solution (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (15.2 g, 92% yield) as a yellow solid. MS: 207.0 [M+H]⁺. This crude product was used directly in the next step without further purification.

[C] 5-(Trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine-3-amine



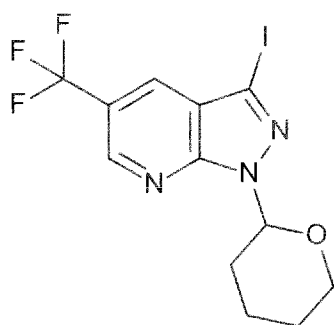
A stirred solution of 2-chloro-5-(trifluoromethyl)pyridine-3-carbonitrile (13.7 g, 87.6 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (10 mL) in EtOH (50 mL) was heated at 100°C for 2 h. After TLC showed the completion of the reaction, the solvent was removed under reduced pressure. The crude product collected by filtration was washed with EtOAc several times to afford the title compound (5 g, 37% yield) as a solid. MS: 203.0 $[\text{M}+\text{H}]^+$.

[D] 3-Iodo-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine



To a stirred solution of 5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine-3-amine (5 g, 24.7 mmol) in acetonitrile (50 mL) was added isoamyl nitrite (4.35 g, 37.1 mmol) and diiodomethane (19.9 g, 74.2 mmol) at 0°C . The resulting mixture solution was stirred first at 0°C for 20 min and then at 100°C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue was diluted with water and extracted with EtOAc (100 mL three times). The combined organics were washed with brine (100 mL three times), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was washed with hexane several times to afford the title compound (5.5 g, 71% yield) as a yellow solid. MS: 313.8 $[\text{M}+\text{H}]^+$

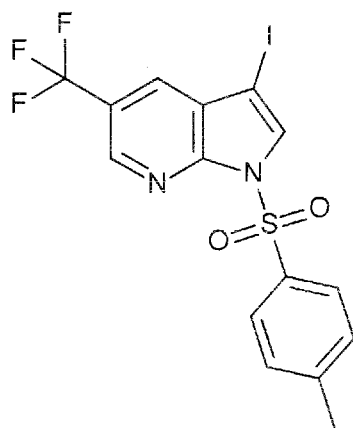
[E] 3-Iodo-1-(tetrahydropyran-2-yl)-5-(trifluoromethyl)pyrazolo[3,4-b]pyridine



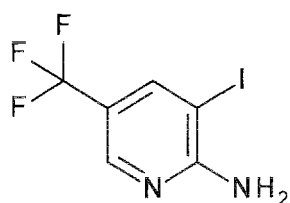
To a stirred mixture solution of 3-iodo-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine (5.5 g, 17.6 mmol) and DHP (14.8 g, 16.1 mL, 176 mmol) in toluene (40 mL) was added 2,2,2-trifluoroacetic acid (401 mg, 3.51 mmol) at room temperature and the resulting reaction mixture solution was heated at 100°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc in hexane) to afford the title compound (3.6 g, 52% yield) as a light yellow solid. MS: 397.5 [M+H]⁺

Intermediate A-6

3-Iodo-1-(p-tolylsulfonyl)-5-(trifluoromethyl)pyrrolo[2,3-b]pyridine



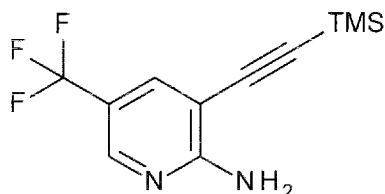
[A] 3-Iodo-5-(trifluoromethyl)pyridin-2-amine



To a mixture solution of 5-(trifluoromethyl)pyridin-2-amine (10 g, 61.69 mmol) and KIO₃ (5.28 g, 24.67 mmol) in 2 N H₂SO₄ (67 mL) was added KI (10.24 g, 61.69 mmol) in H₂O (41 mL) at 100 °C and the resulting reaction mixture was heated at 100 °C for 12 h. Afterwards, the reaction was cooled to room temperature and adjusted to pH = 7 with satd. aq. NaHCO₃ solution (200 mL) and NaHSO₃ until the solution became colorless. The mixture solution was then extracted with DCM (100 mL three times) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum

ether: EtOAc = 5:1) to afford the title compound (10.8 g, 61% yield) as a yellow solid. MS: 288.9 $[M+H]^+$

[B1 5-(Trifluoromethyl)-3-((trimethylsilyl)ethynyl)pyridin-2-amine

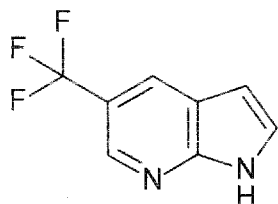


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To a stirred mixture solution of 3-iodo-5-(trifluoromethyl)pyridin-2-amine (10 g, 39.7 mmol), ethynyltrimethylsilane (5.1 g, 72.1 mmol), Et_3N (10.5 g, 104.1 mmol) and CuI (182.2 mg, 0.7 mmol) in THF (50 mL) was added $Pd(Ph_3P)Cl_2$ (305.3 mg, 0.7 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. After TLC (petroleum ether: EtOAc = 10:1) showed the completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 50:1 to 10:1) to afford the title compound (7.5 g, 98% yield) as a yellow solid. MS: 217.0 $[M+H]^+$

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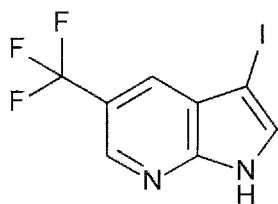
15 [C1 5-(Trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine



To a stirred solution of $t-BuOK$ (10 g, 39.7 mmol) in NMP (25 mL) was added 5-(trifluoromethyl)-3-((trimethylsilyl)ethynyl)pyridin-2-amine (7.5 g, 29 mmol) and the resulting reaction mixture was stirred at 80°C for 12 h. After TLC (petroleum ether: EtOAc = 5:1) showed the completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) to afford the title compound (5 g, 69% yield) as a yellow solid. MS: 187.0 $[M+H]^+$

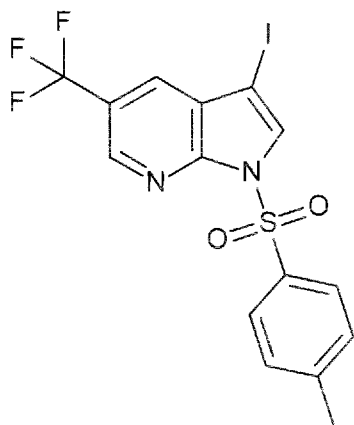
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25 [D] 3-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-2-yl]pyridine



A mixture solution of 5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine (5 g, 26.8 mmol), I₂ (6.8 g, 26.8 mmol) and KOH (4.5 g, 80.4 mmol) in DMF (50 mL) was stirred at room temperature for 12 h. After TLC (petroleum ether: EtOAc = 5:1) showed the completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 50:1 to 10:1) to afford the title compound (1.6 g, 20% yield) as a yellow solid. MS: 312.9 [M+H]⁺

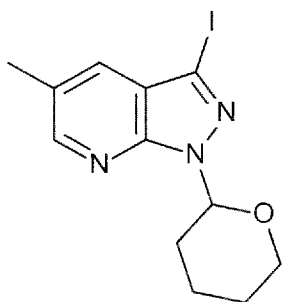
[E] 3-Iodo-1-(p-tolylsulfonyl)-5-(trifluoromethyl)pyrrolo[2,3-b]pyridine



To a stirred solution of 3-iodo-5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine (1.6 g, 5.1 mmol) and NaH (0.36 g, 15.3 mmol) in DMF (10 mL) was added TsCl (1.45 g, 7.65 mmol) dropwise at 0°C and the resulting reaction mixture was stirred at 0°C for 30 min. Afterwards, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL twice). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (petroleum ether: EtOAc = 20:1) to afford the title compound (1.6 g, 68% yield) as a yellow solid. MS: 467.0 [M+H]⁺

Intermediate A-7

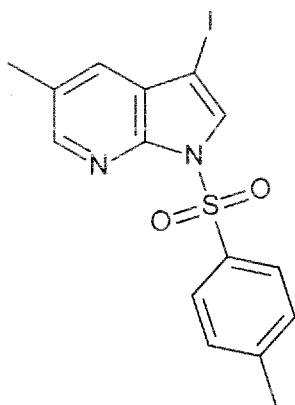
3-Iodo-1-(p-tolylsulfonyl)-5-(trifluoromethyl)pyrrolo[2,3-b]pyridine



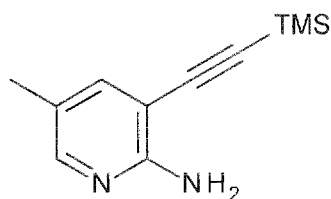
To a stirred mixture solution of 3-iodo-5-methyl-1H-pyrazolo[3,4-b]pyridine (2 g, 7.72 mmol) and DHP (3.9 g, 4.24 mL, 46.3 mmol) in toluene (20 mL) was added TFA (176 mg, 1.54 mmol) at room temperature and the resulting reaction mixture solution was heated at 100°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc in hexane) to afford the title compound (2.6 g, 94% yield) as light yellow oil. MS: 343.9 [M+H]⁺

Intermediate A-8

3-Iodo-5-methyl-1-{p-tolylsulfonyl}pyrrolo[2,3-b]pyridine



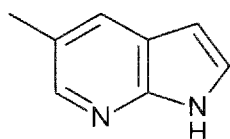
1A] 5-Methyl-3-(2-trimethylsilylvinyl)pyridin-2-amine



To a stirred solution of 3-bromo-5-methylpyridin-2-amine (18 g, 96.2 mmol), ethynyltrimethylsilane (16.54 g, 168.35 mmol) and Et₃N (60 mL) in DMF (5 mL) was added Pd(OAc)₂ (0.43 g, 1.9 mmol) and Ph₃P (0.96 g, 3.8 mmol). The resulting reaction mixture was

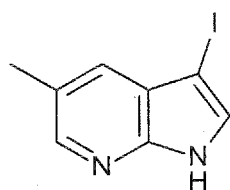
heated to 100°C for 12 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (200 mL three times). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether; EtOAc = 10:1) to afford the title compound (10 g, 51% yield) as a solid. MS: 147.0 [M+H]⁺.

15-Methyl-1H-pyrrolo[2,3-b]pyridine



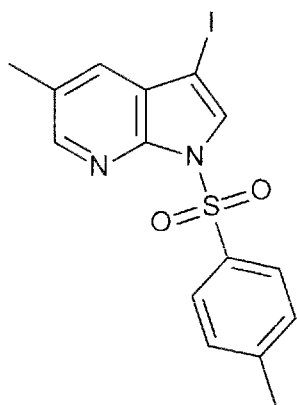
- 10 To a stirred solution of t-BuOK (7.68 g, 68.6 mmol) in NMP (30 mL) was added 5-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-amine (8 g, 39.2 mmol) in NMP (30 mL). The resulting reaction mixture was heated at 80°C for 12 h. After cooling to room temperature, the reaction was quenched by the addition of water (10 mL) at 0 °C and then extracted with EtOAc (5 mL three times). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) to afford the title compound (2.5 g, 48% yield) as a solid. MS: 133.0 [M+H]⁺.

[C] 3-Iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine



- 20 A mixture solution of 5-methyl-1H-pyrrolo[2,3-b]pyridine (2.5 g, 18.9 mmol), I₂ (4.8 g, 18.9 mmol), KOH (4.2 g, 75.6 mmol) in DMF (50 mL) was stirred at room temperature for 12 h before it was poured into water and extracted with EtOAc (10 mL three times). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (2.1 g, 48% yield) as a solid. MS: 259.0 [M+H]⁺.

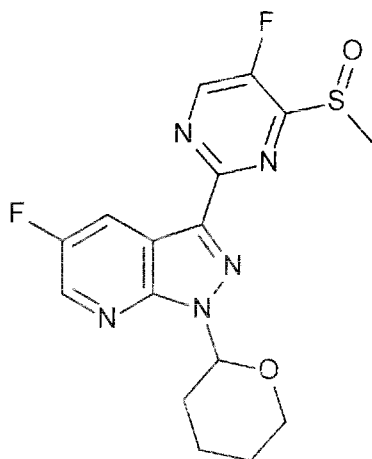
[D1] 3-Iodo-5-methyl-1-(P-tolylsulfonyl)pyrrolo[2,3-b]pyridine



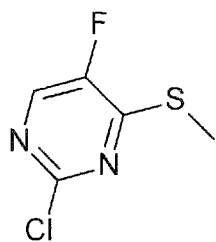
To a stirred solution of 3-iodo-5-methyl-1H-pyrrolo[2,3-b]pyridine (2.0 g, 7.6 mmol) and NaH (0.4 g, 15.2 mmol) in DMF (8 mL) was added TsCl (1.8 g, 9.2 mmol) in DMF (2 mL) at 0°C. The resulting reaction mixture was stirred at room temperature for 12 h before it was concentrated under reduced pressure. The residue was re-dissolved in EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (2.36 g, 74% yield) as a solid. MS: 413.0 [M+H]⁺.

Intermediate A-9

5-Fluoro-3-{5-fluoro-4-methylsulfinyl-pyrimidin-2-yl}-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine

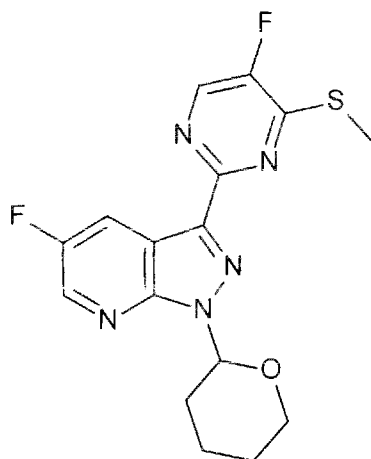


1-Amino-2-chloro-5-fluoro-4-methylsulfinyl-pyrimidine



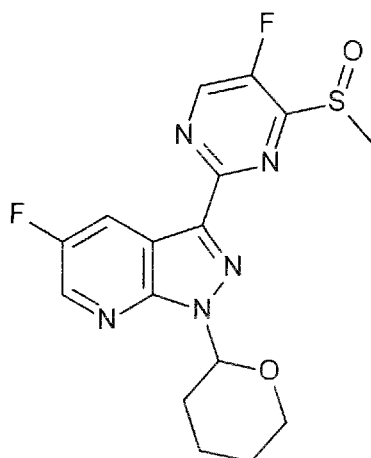
To a stirred solution of 2,4-dichloro-5-fluoropyrimidine (10 g, 60 mmol) in THF (110 mL), was added NaSMe (5.7 g, 81.5 mmol) slowly at 0°C. The mixture was stirred at room temperature for 12 h before it was poured into H₂O (100 mL) and extracted with EtOAc (100 mL twice). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude title compound (10.2 g, 74% yield) as a solid. MS: 179.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

[B] 5-Fluoro-3-(5-fluoro-4-methylsulfanylpyrimidin-2-yl)-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine



A stirred mixture solution of 2-chloro-5-fluoro-4-methylsulfanylpyrimidine (243.7 mg, 1.37 mmol), (5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)-trimethylstannane (Intermediate A-1b, 480 mg, 1.25 mmol), Pd₂(dba)₃ (95 mg, 0.13 mmol) and Xphos (119 mg, 0.25 mmol) in dioxane (3 mL) was heated to 140°C under microwave heating for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the crude product was purified by silica gel flash chromatography column (petroleum ether: EtOAc ≈ 15:1) to afford the title compound (270 mg, 59% yield) as a white solid. MS: 280.0 [M-THP+H]⁺.

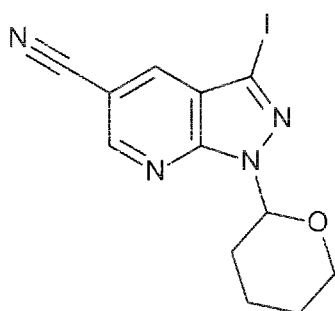
[C] 5-Fluoro-3-(5-fluoro-4-methylsulfinyl-pyrimidin-2-yl)-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine



To a stirred solution of 5-fluoro-3-(5-fluoro-4-methylsulfinyl-pyrimidin-2-yl)-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (270 mg, 0.74 mmol) in DCM (10 mL) was added m-CPBA (150.4 mg, 0.74 mmol) at 0°C and the reaction mixture was stirred at 0°C for 2 hour. After TLC (petroleum ether: EtOAc = 1:1) showed the completion of the reaction, the mixture was quenched with aq. Na₂SO₃ solution (10 mL) and extracted with DCM (10 mL twice). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the title compound (78 mg, 28% yield) as a white solid. MS: 380.1 [M+H]⁺.

Intermediate A-10

3-Iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile



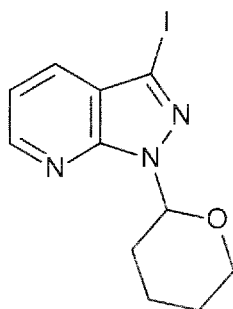
To a stirred mixture solution of 3-iodo-1,4-pyrazolo[3,4-b]pyridine-5-carbonitrile (2 g, 7.41 mmol) and DHP (3.74 g, 44.4 mmol) in toluene (20 mL) was added 2,2,2-trifluoroacetic acid (169 mg, 1.48 mmol) and the resulting reaction mixture solution was stirred at 100°C for 2 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and

extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-50% EtOAc-hexane gradient) to afford the title compound (1.6 g, 61% yield) as a white solid. MS: 355.1 [M+H]⁺

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Intermediate A-11

3-Iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine

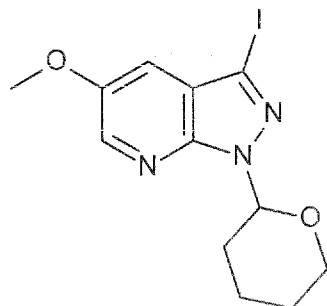


To a stirred mixture solution of 3-iodo-1H-pyrazolo[3,4-b]pyridine (5 g, 20.4 mmol) and DHP (13.7 g, 163 mmol) in toluene (20 mL) was added 2,2,2-trifluoroacetic acid (465 mg, 4.08 mmol) and the resulting reaction mixture solution was stirred at 100°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (5.1 g, 75.9% yield) as a light yellow solid. MS: 330.1 [M+H]⁺

15

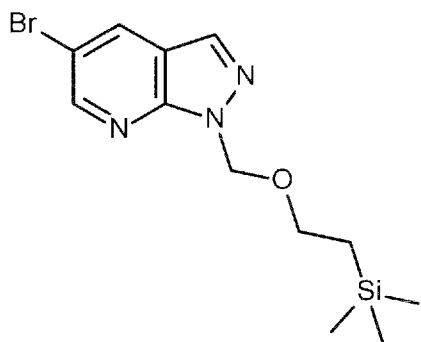
Intermediate A-12a

3-Iodo-5-methoxy-1-(tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridine



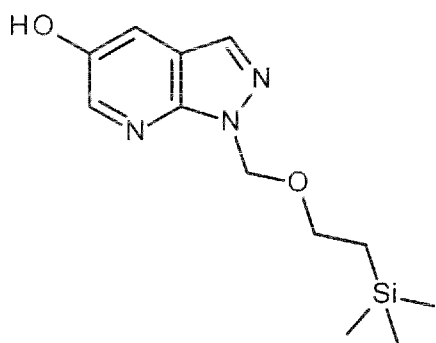
20

[A] 5-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine



To a solution of 5-bromo-1H-pyrazolo[3,4-b]pyridine (4 g, 20 mmol) in DMF (50 mL) was added NaH (1.2 g, 30 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min before SEMCI (4 g, 30 mmol) was added. After the addition, the reaction mixture was allowed to warm up to room temperature and stirred for 0.5 h. The reaction was quenched with satd. aq. NH₄Cl Solution (100 mL) and the mixture was extracted with EtOAc (100 mL). The organic layer was washed with water (100 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether; EtOAc = 1.1) to afford the title compound (4.7 g, 73% yield) as colorless oil. MS: 330.0 [M+2+H]⁺.

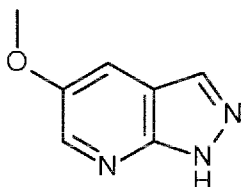
fB] 1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-5-ol



To a stirred solution of 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (9 g, 27.4 mmol), 4,4,4',4',5,5,5,5-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (12.7 g, 50 mmol) in dioxane (50 mL) was added KOAc (5 g, 50 mmol) and Pd(dppf)Cl₂ (430 mg, 0.5 mmol) and the reaction mixture was stirred at 80°C for 16 h. After cooling to room temperature, the mixture solution was concentrated under reduced pressure to give a residue, which was re-suspended in MeOH (80 mL) and filtered to remove the Pd salt. To the filtrate was then added H₂O₂ (20 mL) and the resulting mixture was stirred at 25°C for 5 h. After TLC showed that the reaction was completed, the mixture was diluted with EtOAc (500 mL), washed with water and brine. The organic layer was dried over anhydrous

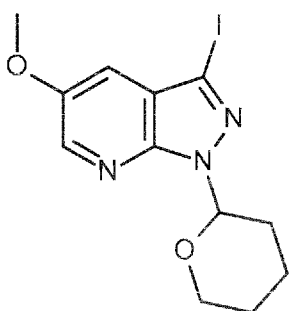
Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the title compound (5.3 g, 73% yield) as yellow oil.

5 [C] 5-Methoxy-1H-pyrazolo[3,4-b]pyridine



To a stirred solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-5-ol (5.3 g, 20 mmol) in DMF (50 mL) was added K₂CO₃ (8.28 g, 60 mmol) and MeI (4.26 g, 30 mmol) and the resulting reaction mixture was stirred at room temperature for 1 h. After TLC showed that the reaction was completed, the reaction mixture was diluted with EtOAc (250 mL), and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude residue, which was re-dissolved in 3 M TBAF/THF (50 mL) and stirred at room temperature for 2 h. After dilution with EtOAc (300 mL), the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to afford the crude title compound (2.5 g) as yellow oil. This crude product was used directly in the next step without further purification.

[D1] 3-iodo-5-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine

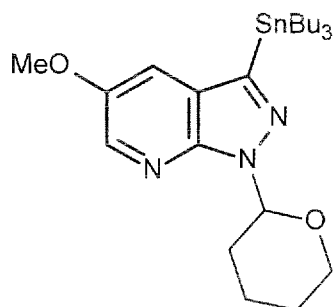


To a stirred solution of 5-methoxy-1H-pyrazolo[3,4-b]pyridine (2.2 g, 15 mmol) in DMF (50 mL) was added NaOH (2.4 g, 60 mmol) and I₂ (7.6 g, 30 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h before the reaction was quenched by the addition of water (50 mL) and extracted with EtOAc (50 mL three times). The combined organic extracts were concentrated under reduced pressure to give a crude residue, which was re-dissolved in DCM (50 mL). To the above solution was then added

TsOH (3.9 g, 7.5 mmol) and DHP (0.64 g, 7.5 mmol) and the resulting mixture solution was stirred at room temperature for 1 h before dilution with satd. aq. NaHCO_3 solution and extracted with DCM (50 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (2.5 g, 40% yield) as a yellow solid. MS: 360.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{CHCl}_3\text{-d}_1$): δ 8.36 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.02 (dd, J = 1.2, 10.4 Hz, 1H), 4.15-4.10 (m, 1H), 3.93 (s, 3H), 3.83-3.77 (m, 1H), 2.65-2.49 (m, 1H), 2.15-1.50 (m, 5H).

Intermediate A-12b

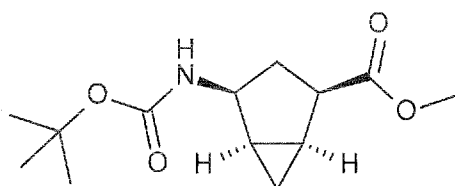
5-Methoxy-1-(tetrahydro-2H-pyran-2-yl)-3-(tributylstannyl)-1H-pyrazolo[3,4-b]pyridine



To a stirred solution of 3-iodo-5-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (500 mg, 1.35 mmol) in dioxane (15 mL) was added Sn_2Bu_6 (2.9 g, 2.5 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (175 mg, 0.15 mmol) and the reaction mixture was stirred at 45°C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 30:1) to afford the title compound (400 mg, 55% yield) as colorless oil. MS: 524.0 $[\text{M}+\text{H}]^+$.

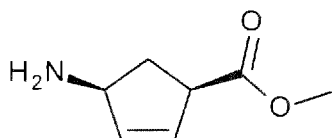
Intermediate B-1

(+)-Methyl (1R,2S,4R,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate



(+)

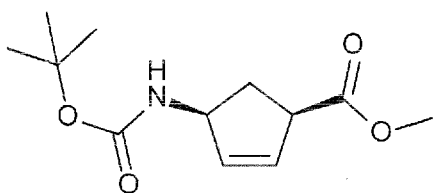
fAl (+)-Methyl (1R,4S)-4-aminocyclopent-2-ene-1-carboxylate hydrochloride



(+)

To a stirred solution of (+)-(1R,4S)-4-aminocyclopent-2-ene-1-carboxylic acid hydrochloride (10 g, 61.1 mmol) in MeOH (100 mL) was added AcCl (27 mL) dropwise at 0°C. After the addition, the resulting mixture was refluxed at 80°C for 16 h. After cooling to room temperature, the mixture was concentrated under vacuum to afford a crude title compound (11 g) as a white solid. MS: 142.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

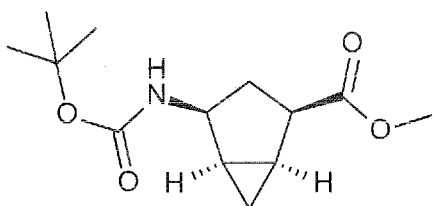
10 [B] (+)-Methyl (1R,4S)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate



(+)

To a stirred solution of (+)-methyl (1R,4S)-4-aminocyclopent-2-ene-1-carboxylate hydrochloride (5.5 g, 30.5 mmol). TEA (9 g, 90 mmol) in DCM (250 mL) was added Boc anhydride (9 g, 42 mmol) portion-wise at 0 °C. After the addition, the resulting mixture was slowly warmed up to room temperature and stirred for 3 h. The reaction mixture was then washed with satd. aq. NaHCO₃ solution, and the separated organic layer is dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-10% gradient) to afford the title compound (7 g, 95% yield) as a white solid. MS: 242.1 [M+H]⁺.

20 [C] (+)-Methyl (1R,2S,4R,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate

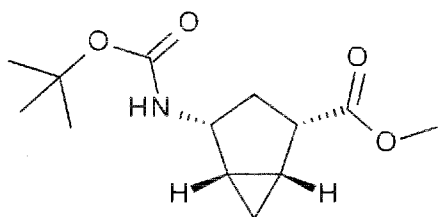


(+)

To a stirred solution of (+)-methyl (1R,4S)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate (2.1 g, 8.7 mmol) in DCM (60 mL) was added ZnEt_2 (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 15 min, CH_2I_2 (2.7 mL, 33.5 mmol) and additional ZnEt_2 (1 M in hexane, 16.3 mL) were added dropwise to the
 5 above mixture and 5 min later, one additional portion of CH_2I_2 (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 16 h. The reaction was quenched with satd. aq. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was
 10 purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0 to 20% gradient) to afford the title compound (400 mg, 16% yield) as a white solid. MS: 256.1 $[\text{M}+\text{H}]^+$.

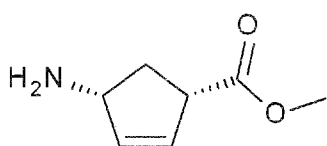
Intermediate B-2

(-)-Methyl (1S,2R,4S,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate
 15



(-)

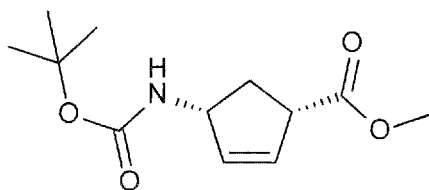
[A] (-)-Methyl (1S,4R)-4-aminocyclopent-2-ene-1-carboxylate hydrochloride



(-)

To a stirred solution of (-)-(1S,4R)-4-aminocyclopent-2-ene-1-carboxylic acid hydrochloride (10 g, 61.1 mmol) in MeOH (150 mL) was added AcCl (27 mL) dropwise at 0°C. After the
 20 addition, the resulting mixture was refluxed at 80°C for 16 h. After cooling to room temperature, the solvent was evaporated under vacuum to afford a crude title compound (12 g) as a white solid. MS: 142.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

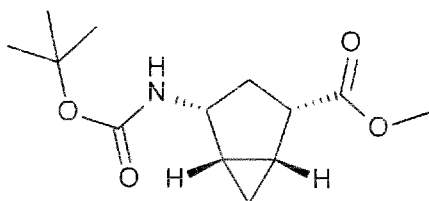
[B] (-)-Methyl (1S,4R)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate



(-)

To a stirred solution of (-)-methyl (1S,4R)-4-aminocyclopent-2-ene-1-carboxylate hydrochloride (12 g, 61.1 mmol), TEA (20 g, 198 mmol) in DCM (250 mL) was added Boc anhydride (17.2 g, 79.6 mmol) portion-wise at 0°C. After the addition, the resulting mixture was slowly warmed up to room temperature and stirred for 3 h. The reaction mixture was then washed with satd. aq. NaHCO₃ solution, and the separated organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-10% gradient) to afford the title compound (10 g, 67% yield) as a white solid. MS: 242.1 [M+H]⁺.

id (-)-Methyl (1S,2R,4S,5R) -2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate

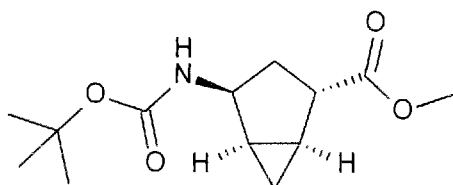


(-)

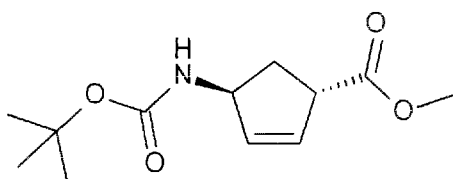
To a stirred solution of (-)-methyl (1S,4R)-4-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-2-carboxylate (2 g, 8.2 mmol) in DCM (50 mL) was added ZnEt₂ (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 15 min, CH₂I₂ (2.7 mL, 33.5 mmol) and additional ZnEt₂ (1 M in hexane, 16.3 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH₂I₂ (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 16 h. The reaction was quenched with satd. aq. NH₄Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-10% gradient) to afford the title compound (900 mg, 44% yield) as a white solid. MS: 256.1 [M+H]⁺.

Intermediate B-3

(+ or -)-Methyl (1R,2S,4S,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate



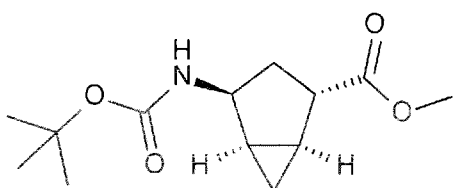
1A1 (+ or -)-Methyl (1S,4S)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate



5 (+ or -)

To a stirred solution of (+)-methyl (1R,4S)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate (Intermediate B-1/step B, 8 g, 33 mmol) in methanol (100 mL) was added sodium methoxide (14 g, 260 mmol) portion-wise at -10°C and stirred for 1 h. The reaction mixture was acidified by AcOH to pH = 7 and concentrated under vacuum to about 30 mL. It was then diluted with water, and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-10% gradient) to afford the title compound (1.5 g, 18% yield) as a white solid. MS: 242.1 [M+H]⁺.

15 1B1 (+ or -)-Methyl (1R,2S,4S,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate



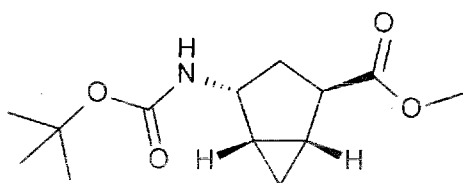
(+ or -)

To a stirred solution of (+ or -)-methyl (1S,4S)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate (2.5 g, 10.3 mmol) in DCM (50 mL, anhydrous) was added ZnEt₂ (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 15 min, CH₂I₂ (2.7 mL, 33.5 mmol) and additional ZnEt₂ (1 M in hexane, 16.3 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH₂I₂ (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room

temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (EtOAc/ petroleum ether, 0~20% gradient) to afford the title compound (900 mg, 34% yield) as a white solid. MS: 256.1 $[\text{M}+\text{H}]^+$.

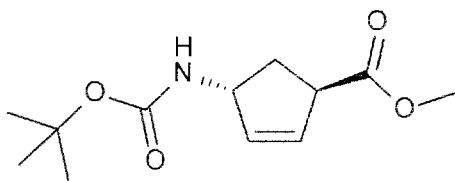
Intermediate B-4

(- or +)-Methyl (1S,2R,4R,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate



(- or +)

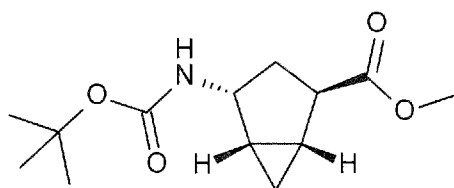
[A] (- or +)-Methyl (1R,4R)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate



(- or +)

To a stirred solution of (- or +)-methyl (1S,4R)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate (Intermediate 6-2/step B, 7.5 g, 31 mmol) in methanol (100 mL) was added sodium methoxide (1.8 g, 31 mmol) portion-wise at -10°C and stirred for 1 h. The reaction mixture was acidified by AcOH to pH = 7 and concentrated under vacuum to about 30 mL. It was then diluted with water, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-10% gradient) to afford the title compound (3.8 g, 50% yield) as a white solid. MS: 242.1 $[\text{M}+\text{H}]^+$.

[B] (- or +)-Methyl (1S,2R,4R,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate

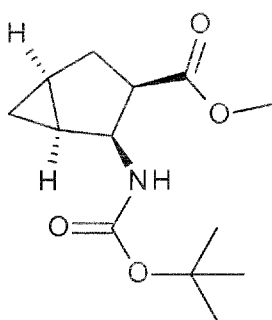


(- or +)

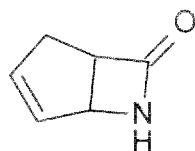
To a stirred solution of (- or +)-methyl (1R,4R)-4-(tert-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate (2 g, 8.2 mmol) in DCM (50 mL, anhydrous) was added ZnEt_2 (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 15 min, CH_2I_2 (2.7 mL, 33.5 mmol) and additional ZnEt_2 (1 M in hexane, 16.3 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH_2I_2 (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the title compound (500 mg, 23% yield) as a white solid. MS. 256.1 [M+H]⁺

Intermediate B-5

15 **(rac)-Methyl (1S,2S,3R,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-3-carboxylate**



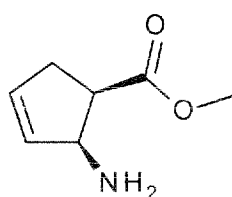
[A] 6-Azabicyclo[3.2.0]hept-3-en-7-one



20 A solution of chlorosulfonyl isocyanate (40 g, 0.28 mol) in dry Et_2O (100 mL) was added dropwise to a solution of freshly distilled cyclopentadiene (20 g, 0.30 mol) in dry Et_2O at -10°C. After the addition, the resulting colorless solution was stirred at -10°C for 1 h before

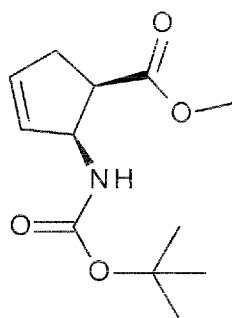
Na₂SO₃ solution (41 g in 150 mL water) was added dropwise to quench the reaction at 0°C. The resulting mixture was then neutralized with aq. KOH solution to pH = 8 and allowed to slowly warm up room temperature. The mixture was then extracted with Et₂O (300 mL twice) and EtOAc (100 mL twice). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (8 g, 24% yield) as yellow gum. MS: 110.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

[B] (rac)-Methyl (1R,2S)-2-aminocyclopent-3-ene-1-carboxylate



To a stirred solution of 6-azabicyclo[3.2.0]hept-3-en-7-one (8.5 g, 77.3 mmol) in MeOH (150 mL) was added AcCl (20 mL) dropwise at 0°C. After the addition, the resulting mixture was heated at 75°C for 16 h. The solvent was evaporated under vacuum to afford a crude racemic mixture of title compound (14 g) as a brown solid. MS: 141.9 [M+H]⁺. This crude product was used directly in the next step without further purification.

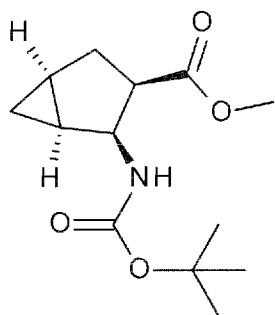
[d] (rac)-Methyl (1R,2S)-2-(tert-butoxycarbonylamino)cyclopent-3-ene-1-carboxylate



To a stirred solution of (rac)-methyl (1R,2S)-2-aminocyclopent-3-ene-1-carboxylate (14 g, 77.3 mmol) and TEA (20 g, 0.20 mol) in DCM (200 mL) was added Boc anhydride (20 g, 92.6 mmol) dropwise at 0°C. The mixture was allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NaHCO₃ solution, and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the title racemic

mixture of compounds (14.5 g, 77% yield) as a white solid. MS: 242.1 $[M+H]^+$.

ID1 (rac)-Methyl (1S,2S,3R,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-3-carboxylate

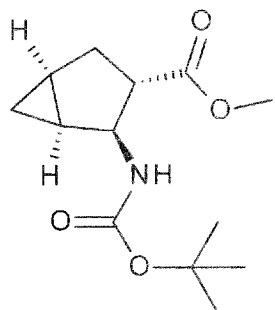


5

To a stirred solution of (rac)-methyl (1R,2S)-2-(tert-butoxycarbonylamino)-cyclopent-3-ene-1-carboxylate (2 g, 8.3 mmol) in DCM (50 mL) was added $Zn^{+}I_2$ (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 5 min, CH_2I_2 (2.7 mL, 33.5 mmol) and additional $ZnEt_2$ (1 M in hexane, 16.3 mL) were added dropwise to the
 10 above mixture and 5 min later, one additional portion of CH_2I_2 (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude racemic mixture of
 15 title compound (4 g, 100% yield) as a white solid. MS: 256.1 $[M+H]^+$. This crude product was used directly in the next step without further purification.

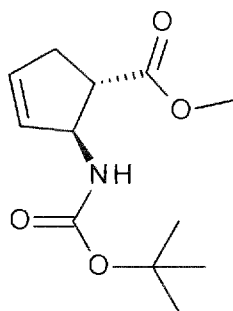
Intermediate B-6

Methyl (1S,2S,3S,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-3-carboxylate



20

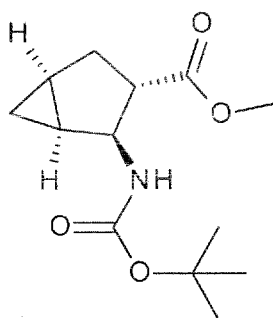
[A] (rac)-Methyl (1S,2S)-2-(tert-butoxycarbonylamino)-cyclopent-3-ene-1-carboxylate



A stirred solution of (rac)-methyl (1R,2S)-2-(tert-butoxycarbonylamino)cyclopent-3-ene-1-carboxylate (Intermediate B-5, step C, 6.2 g, 25.6 mmol) and sodium methoxide (2.7 g, 50 mmol) in MeOH (80 mL) was stirred at room temperature for 24 h before the solution was
 5 acidified with AcOH at 0 °C to pH = 7. The reaction mixture was then diluted with water, and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the racemic mixture of title compound (3.8 g, 63% yield) as white solids. MS: 242.1 [M+H].

10

1B] (rac)-Methyl (1S,2S,3S,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-3-carboxylate

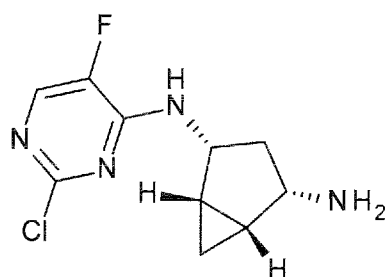


To a stirred solution of (rac)-methyl (1S,2S)-2-(tert-butoxycarbonylamino)- bicyclo[3.1.0]hex-3-ene-1-carboxylate (2 g, 8.3 mmol) in DCM (50 mL) was added ZnEt₂ (1 M in hexane, 16.3 mL)
 15 dropwise at 0 °C. After the resulting mixture was stirred at 0 °C for 5 min, CH₂I₂ (2.7 mL, 33.5 mmol) and additional ZnEt₂ (1 M in hexane, 16.3 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH₂I₂ (2.7 mL, 33.5 mmol) was added at 0 °C. The reaction mixture was then allowed to slowly warm up to room
 20 temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH₄Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude racemic mixture of title compound (4 g, 100% yield) as a white solid. MS: 256.1 [M+H]. This crude product

was used directly in the next step without further purification.

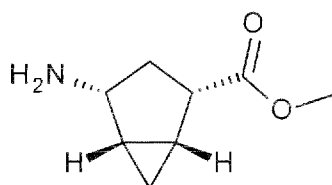
Intermediate B-7

(-)-(1S,2R,4S,5R)-A/2-(2-Chloro-5-fluoro-pyrimidin-4-yl)bicyclo[3.1.0]hexane-2,4-diamine



(-)

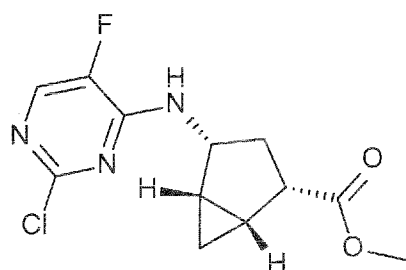
IA] (-)-Methyl (1S,2R,4S,5R)-2-aminobicyclo[3.1.0]hexane-4-carboxylate



(-)

A solution of (-)-methyl (1S,2R,4S,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-2, 900 mg, 3.5 mmol) in TFA/DCM (15 mL, 2:1) was stirred at room temperature for 3 h. Afterwards, the solvent was evaporated to dryness under reduced pressure to give a crude title compound (900 mg) as yellow gum. MS: 156.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

IB] (-)-Methyl (1S,2R,4S,5R)-2-(2-chloro-5-fluoro-pyrimidin-4-yl)aminobicyclo[3.1.0]hexane-4-carboxylate



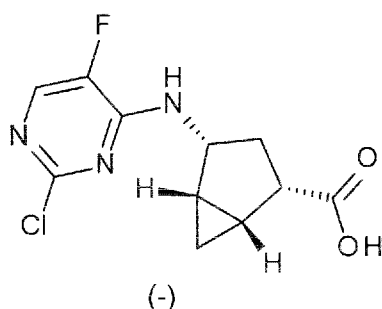
(-)

A round-bottom flask charged with (-)-methyl (1S,2R,4S,5R)-2-aminobicyclo[3.1.0]hexane-4-carboxylate (900 mg, 3.5 mmol), 2,4-dichloro-5-fluoro-pyrimidine (1.5 g, 8.9 mmol) and DIPEA (10.0 g, 77.5 mmol) in THF (20 mL) was heated at 60°C for 16 h. Afterwards, the

reaction was cooled to room temperature, the solvent was removed under vacuum and the residue was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the title compound (500 mg, 50% yield) as a yellow solid. MS: 286.2 [M+H]⁺.

5

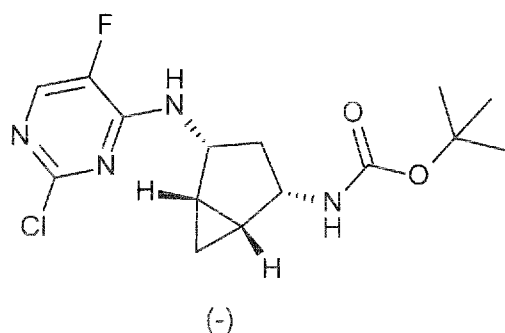
[C] (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylic acid



A mixture solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate (550 mg, 1.9 mmol) and LiOH monohydrate (200 mg, 4.76 mmol) in THF/water (20 mL, 1:1) was stirred at room temperature for 2 h. Afterwards, the reaction mixture was neutralized with 1N HCl to pH = 7 and then extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (500 mg, 96% yield) as a white solid. MS: 272.1 [M+H]⁺. It was used directly in the next step reaction without further purification.

15

[D] (-)-tert-butyl 2-[(1R,2S,4R,5S)-4-(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-bicyclo[3.1.0]hexan-2-ylcarbamate

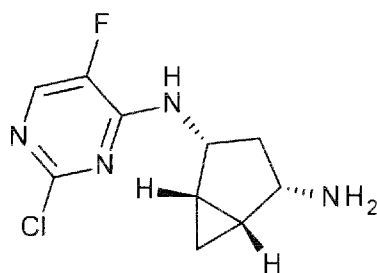


A stirred solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylic acid (600 mg, 2.2 mmol), DPPA (1.2 g, 4.4 mmol), and TEA (263 mg, 2.6 mmol) in toluene (10 mL) was heated at 90°C for 1 h before *tert*-BuOH (1.6 g, 22 mmol) was added to the reaction mixture and stirred for another 2 h at 90°C. After cooling to room temperature, the reaction mixture was concentrated under vacuum to give a

20

crude product, which was purified by silica gel column chromatography (EtOAc/ petroleum ether, 0-30% gradient) to afford the title compound (260 mg, 34% yield) as a white solid. MS: 343.2 [M+Hf.

5 [E1(-)-(1S,2R,4S,5R)-A/2-(2-Chloro-5-fluoro-pyrimidin-4-yl)bicyclo[3.1.0]hexane-2,4-diamine

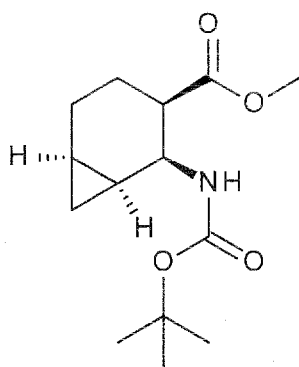


(-)

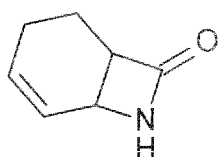
A solution of (-)-tert-butyl N-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]carbamate (260 mg, 0.76 mmol) in TFA/DCM (4mL/8 mL) was stirred at room temperature for 2 h. Afterwards, the solvent was evaporated under vacuum to afford a crude title compound (300 mg) as brown gum. MS: 243.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

Intermediate B-8

(rac)-Methyl (1R,2R,3S,6S)-2-(tert-butoxycarbonylamino)norcaradiene-3-carboxylate



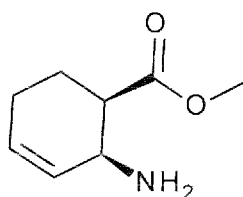
[A] 7-Azabicyclo[4.2.0]oct-4-en-5-one



To a stirred solution of chlorosulfonyl isocyanate (7.7 mL, 89 mmol) in dry Et₂O (100 mL) was added cyclohexa-1,3-diene (8 g, 99 mmol) in dry Et₂O (100 mL) at 0°C. The resulting

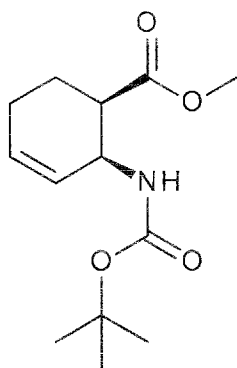
reaction mixture was stirred at room temperature for 30 min before it was poured into aqueous solution of K_2CO_3/Na_2SO_3 (36 g/1.1 g in 300 mL of water) and extracted with Et_2O (300 mL twice) and $EtOAc$ (100 mL twice). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (8 g, 65% yield) as yellow gum. MS: 124.1 $[M+H]^+$. This crude product was used directly in the next step without further purification.

[B] (rac)-Methyl (1R,2S)-2-aminocyclohex-3-ene-1-carboxylate



- 10 To a stirred solution of 7-azabicyclo[4.2.0]oct-4-en-8-one (8 g, 64 mmol) in MeOH (150 mL) was added $AcCl$ (20 mL) dropwise at $0^\circ C$. After the addition, the resulting reaction mixture was heated at $75^\circ C$ for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to afford a crude racemic mixture of title compounds (12 g) as a brown solid. MS: 156.2 $[M+H]^+$. This crude product was used directly in the next step without further purification.

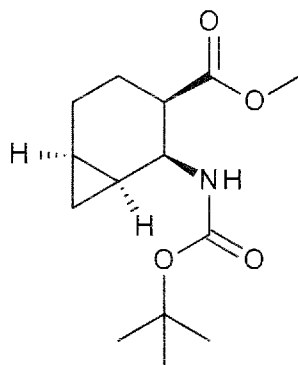
[C] (rac)-Methyl (1R,2S)-2-(tert-butoxycarbonylamino)cyclohex-3-ene-1-carboxylate



- 20 To a stirred solution of (rac)-methyl (1R,2S)-2-aminocyclohex-3-ene-1-carboxylate (12 g, 64 mmol) and TEA (30 g, 0.29 mol) in DCM (200 mL) was added Boc anhydride (20 g, 92.6 mmol) dropwise at $0^\circ C$. After the addition, the resulting reaction mixture was slowly warmed up to room temperature and stirred for 2 h before it was quenched with satd. aq. $NaHCO_3$ solution and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel

flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford a racemic mixture of title compound (13 g, 79% yield) as a white solid. MS: 256.1 $[M+H]^+$.

[PI (rac)-Methyl (1S,2S,3R,6R)-2-(tert-butoxycarbonylamino)norcarane-3-carboxylate



5

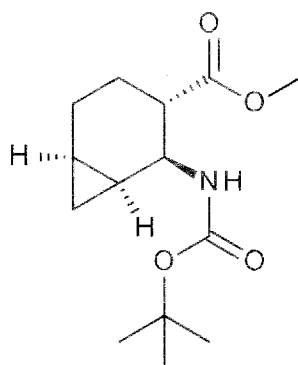
To a stirred solution of (rac)-methyl (1R,2S)-2-(tert-butoxycarbonylamino)cyclohex-3-ene-1-carboxylate (2.2 g, 8.7 mmol) in DCM (50 mL) was added $ZnEt_2$ (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 5 min, CH_2I_2 (2.7 mL, 33.5 mmol) and additional $ZnEt_2$ (1 M in hexane, 16.3 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH_2I_2 (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude mixture of two pairs of racemic compounds (4 g, 100% yield) as a white solid. MS: 270.2 $[M+H]^+$. This crude product was used directly in the next step without further purification. The title pair of racemic compounds was obtained as the major product.

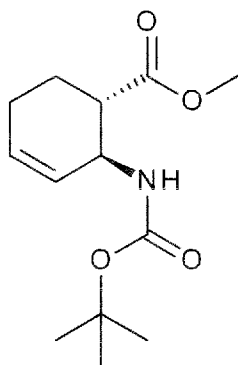
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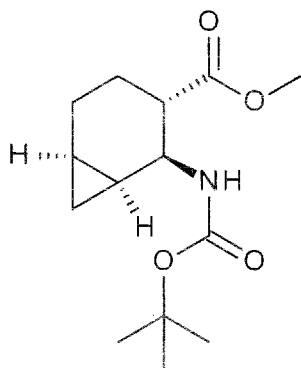
Intermediate B-9

20 **(rac)-Methyl (1S,2S,3S,6R)-2-(tert-butoxycarbonylamino)norcarane-3-carboxylate**



[A] (rac)-Methyl (1S,2S)-2-(tert-butoxycarbonylamino)cyclohex-3-ene-1-carboxylate

A stirred solution of (rac)-methyl (1R,2S)-2-(tert-butoxycarbonylamino)cyclohex-3-ene-1-carboxylate (Intermediate B-8/step C, 6 g, 22 mmol) and sodium methoxide (6 g, 110 mmol) in dry MeOH (150 mL) was stirred at room temperature for 72 h before it was acidified with AcOH at 0°C to pH = 7. The reaction mixture was then diluted with water, and extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the racemic mixture of title compound (5 g, 83% yield) as a white solid. MS: 256.1 [M+Hf].

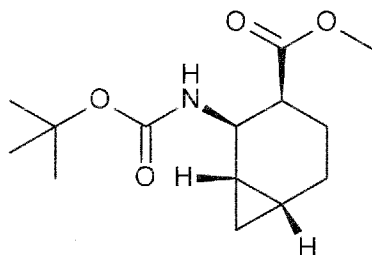
[B] (rac)-Methyl (1S,2S,3S,6R)-2-(tert-butoxycarbonylamino)norcaradiene-3-carboxylate

To a stirred solution of (rac)-methyl (1S,2S)-2-(tert-butoxycarbonylamino)-cyclohex-3-ene-1-carboxylate (2.3 g, 9 mmol) in DCM (50 mL) was added ZnEt₂ (1 M in hexane, 16.3 mL) dropwise at 0°C. After the resulting mixture was stirred at 0°C for 15 min, CH₂I₂ (2.7 mL, 33.5 mmol) and additional ZnEt₂ (1 M in hexane, 16.3 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH₂I₂ (2.7 mL, 33.5 mmol) was added at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH₄Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over

anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude racemic mixture of title compound (3 g) as a white solid. MS: 270.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

5 Intermediate B-10

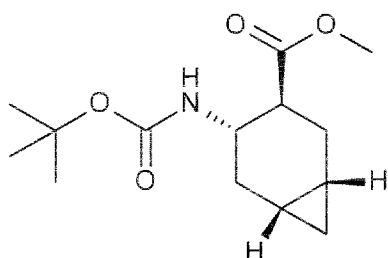
(rac)-Methyl (1S,2R,3S,6R)-2-(tert-butoxycarbonylamino)norcarane-3-carboxylate



In the synthesis of intermediate B-8/step D, the title pair of racemic compound was obtained as the minor product. MS: 270.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next
10 step without further purification.

Intermediate B-11

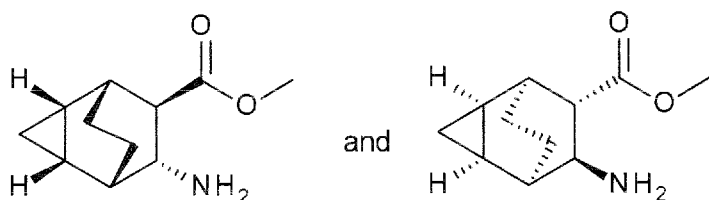
(rac)-Methyl (1S,3S,4S,6R)-4-(tert-butoxycarbonylamino)norcarane-3-carboxylate



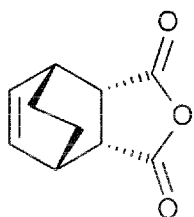
- 15 To a stirred solution of (rac)-methyl (1S,6S)-6-(tert-butoxycarbonylamino)-cyclohex-3-ene-1-carboxylate (1 g, 3.9 mmol) in DCM (50 mL) was added ZnEt_2 (1 M in hexane, 8.1 mL) dropwise at 0°C . After the resulting mixture was stirred at 0°C for 5 min, CH_2I_2 (1.5 mL, 18.6 mmol) and additional ZnEt_2 (1 M in hexane, 8.1 mL) were added dropwise to the above mixture and 5 min later, one additional portion of CH_2I_2 (1.5 mL, 18.6 mmol) was added at
20 0°C . The reaction mixture was then allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude racemic mixture of title compound (3 g) as a white solid. MS: 270.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without
25 further purification.

Intermediate B-12

(1S,2R,4S,5R,6R,7R)-Methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

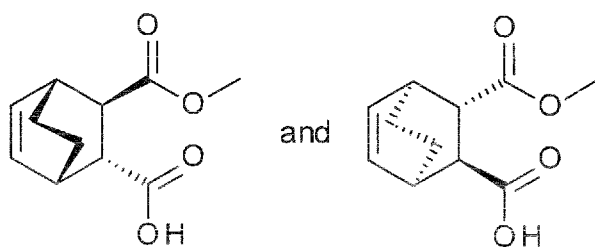


5 [A] *meso*-endo-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione



To a stirred solution of maleic anhydride (24 g, 0.24 mol) in chloroform (200 mL) was added cyclohexa-1,3-diene (25 mL, 0.26 mol) dropwise at 0°C in the dark. After the addition, the mixture was allowed to slowly warm up to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and the residue was washed with cold MeOH (200 mL). Vacuum filtration then afforded a crude title compound (30 g, 70% yield) as a white solid. This crude product was used directly in the next step without further purification.

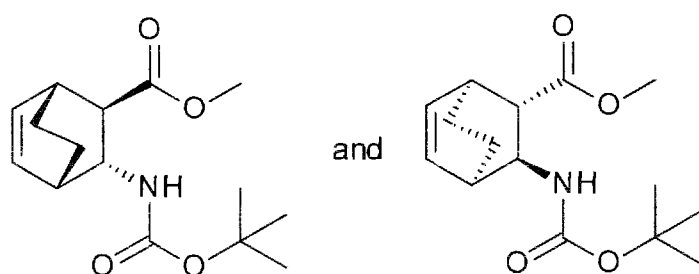
10 [B] (rac)-trans-3-(Methoxycarbonyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid



15 To a stirred solution of sodium methoxide (40 g, 0.74 mol) in MeOH (250 mL) was added *meso*-endo-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione (15 g, 84.6 mmol) portion-wise at 0°C. After the addition, the reaction mixture was allowed to slowly warm up to room temperature and stirred for 60 h. The solvent was removed under reduced pressure and the residue was poured into 1 N HCl solution, and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc, 0~100% gradient) to afford a racemic mixture of title compounds (10 g, 67% yield) as white solids.

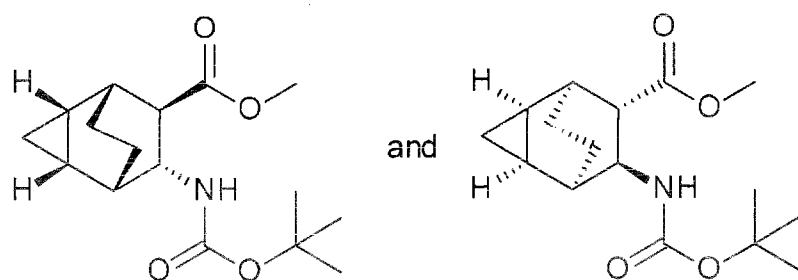
MS: 209.1 [M-H]⁻

(1R,2R,3R,4S)-Methyl 3-((tert-butoxycarbonyl)amino)bicyclo[2.2.1]oct-5-ene-2-carboxylate and (1S,2S,3S,4R)-methyl 3-((tert-butoxycarbonyl)amino)bicyclo[2.2.1]oct-5-ene-2-carboxylate



To a stirred solution of (rac)-frans-3-(methoxycabonyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid (10 g, 47.6 mmol). TEA (9.8 g, 97 mmol) in toluene (120 mL) was added DPPA (20 g, 77.8 mmol) dropwise at 0°C. After the addition, the reaction mixture was slowly heated to 100°C for 2 h and when no gas evolving was observed, t-BuOH (20 g, 270 mmol) was added to the mixture and heated at 100°C for another 10 h. After cooling down, the solvent was evaporated under reduced pressure and the residue was purified by silica gel flash chromatography (petroleum ether: EtOAc, 0-20% gradient) to afford a racemic mixture of title compound as a white solid (2 g, 15% yield). MS: 282.2 [M+H]⁺.

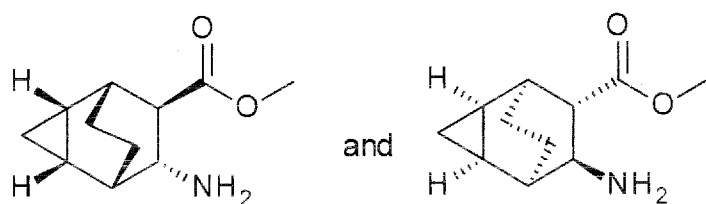
(1S,2R,4S,5R,6R,7R)-Methyl 7-((tert-butoxycarbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-((tert-butoxycarbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of racemic mixture of (1R,2R,3R,4S)-methyl 3-((tert-butoxycarbonyl)amino)bicyclo[2.2.2]oct-5-ene-2-carboxylate and (1S,2S,3S,4R)-methyl 3-((tert-butoxycarbonyl)amino)bicyclo[2.2.2]oct-5-ene-2-carboxylate (1 g, 3.5 mmol) in DCM (20 mL) was added ZnEt₂ (1 M in hexane, 8.0 mL) dropwise at 0°C. After the mixture was stirred for 5 min, CH₂I₂ (1.5 mL, 18.5 mmol) and additional ZnEt₂ (1 M in hexane, 8.0 mL) were added dropwise to the above mixture and 5 min later, one additional portion of

CH₂I₂ (1.5 mL, 18.5 mmol) was added at 0°C. The resulting reaction mixture was then allowed to slowly warm up to room temperature and stirred for 2 h. The reaction was quenched with satd. aq. NH₄Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude racemic mixture of title compound (2 g) as a white solid. MS: 296.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

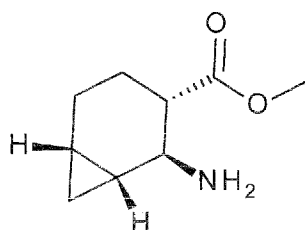
(1S,2R,4S,5R,6R,7R)-Methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of racemic mixture of (1S,2R,4S,5R,6R,7R)-methyl 7-((tert-butoxycarbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-((tert-butoxycarbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (19.5 g, 66 mmol) in DCM (100 mL) was added TFA (118 g, 80 mL, 1.04 mol) and the resulting reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure to give a crude racemic mixture of title compound (20.4 g) as yellow oil. MS: 196.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

Intermediate B-13

(rac)-Methyl (1R,2S,3S,6S)-2-aminonorcaradiene-3-carboxylate

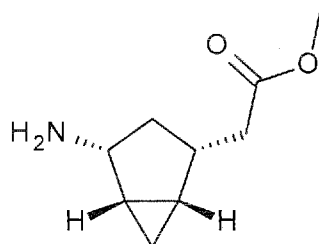


To a stirred solution of ZnEt₂ (1 M in hexane, 16 mL) in DCM (6 mL) was added CH₂I₂ (2.6 mL, 32 mmol) dropwise at -50°C and the resulting solution was stirred at 0°C for 15 min before TFA (1.2 mL, 16 mmol) was added. After the solution was stirred for 15 min, a solution of (rac)-methyl (1S,2S)-2-((tert-butoxycarbonyl)amino)-cyclohex-3-ene-1-carboxylate (Intermediate B-9/step A, 1 g, 4 mmol) in DCM (5 mL) was added dropwise at 0°C. After the addition, the reaction mixture was allowed to slowly warm up to room temperature and

stirred for 16 h. The solvent was evaporated under reduced pressure to afford a crude racemic mixture of title compound (4 g) as yellow oil. MS: 170.2 $[M+H]^+$. This crude product was used directly in the next step without further purification.

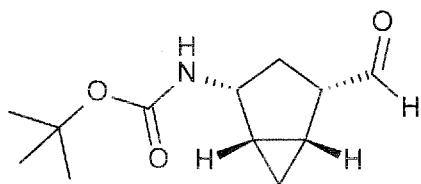
5 Intermediate B-14

(-)-Methyl 2-[(1S,2R,4R,5S)-2-amino-4-bicyclo[3.1.0]hexanyl]acetate



(-)

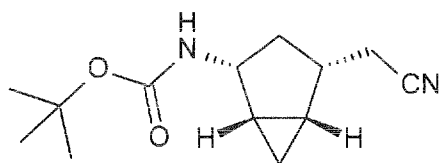
[A] (-)-tert-Butyl N-[(1S,2R,4S,5R)-4-formyl-2-bicyclo[3.1.0]hexanyl]carbamate



(-)

- 10 To a stirred solution of (-)-methyl [(1S,2R,4S,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-2, 2 g, 7.8 mmol) in toluene (30 mL) was added DIBAL (8.6 mL, 8.6 mmol) at -60°C and stirred for 0.5 h. After TLC showed the completion of the reaction, the reaction was quenched by the addition of satd. aq. NH_4Cl solution. The reaction mixture was extracted with EtOAc (20 mL twice) and the organic layer was washed
- 15 with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude title compound (1.2 g, 68% yield). This crude product was used directly in the next step without further purification.

[B] (-)-tert-Butyl N-[(1S,2R,4R,5S)-4-(cyanomethyl)-2-bicyclo[3.1.0]hexanyl]carbamate

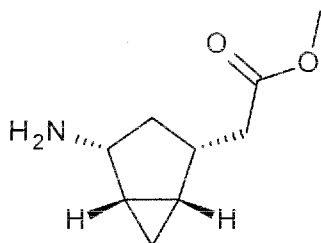


(-)

To a suspension of potassium tert-butoxide (2.2 g, 20 mmol) in THF (20 mL) was added

TOSMIC (2.1 g, 10 mmol) in THF (5 mL) dropwise over a period of 10 min at -60°C. The resulting dark brown solution was stirred at -60°C for 20 min before (-)-ferf-butyl ((1S,2R,4R,5S)-4-(cyanomethyl)bicyclo[3.1.0]hexan-2-yl)carbamate (1.1 g, 5 mmol) in THF (5 mL) was added slowly over a period of 15 min and the mixture solution was stirred for additional 30 min. MeOH (50 mL) was added to the above solution dropwise before it was allowed to warm up to room temperature and heated to 80°C for 90 min. After TLC showed the completion of the reaction, the dark brown suspension was cooled to room temperature and concentrated in vacuo to give a crude title compound (0.3 g, 28% yield). This crude product was used directly in the next step without further purification.

fCl (-)-Methyl 2-*r*-(1S,2R,4R,5S)-2-amino-4-bicyclo[3.1.0]hexanyllacetate

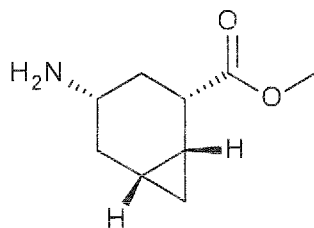


(-)

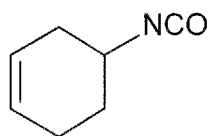
A stirred solution of (-)-ferf-butyl *A*-[(1S,2R,4R,5S)-4-(cyanomethyl)-2-bicyclo[3.1.0]hexanyll]carbamate (0.15 g, 0.63 mmol) in concentrated hydrochloric acid (10 mL) was heated at 100°C for 2 h before it was cooled down and concentrated under reduced pressure. The residue was re-dissolved in a solution of dioxane (5 mL) and MeOH (5 mL) and stirred at room temperature for 12 h. The volatiles were removed under reduced pressure to give a crude title compound (0.1 g, 77% yield) as a solid. MS: 170.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

Intermediate B-15

(rac)-Methyl (1R,2S,4S,6R)-4-aminonorcaradiene-2-carboxylate

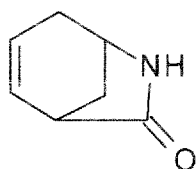


[A1 4-Isocyanatocyclohexene]



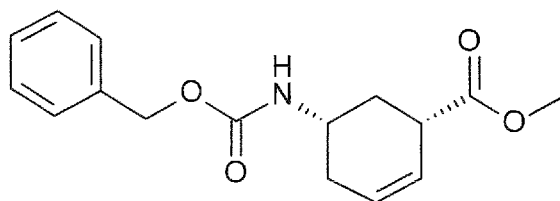
To a solution of 4-isocyanatocyclohexene (20 g, 158.6 mmol) in DCM (100 mL) was added oxalyi chloride (40.2 g, 317.2 mmol) at 0°C, followed by the addition of DMF (0.1 mL) slowly. After wards, the temperature was allowed to warm up to room temperature and stirred for 5 16 h. The reaction was quenched with MeOH, and then the solvent was removed under reduced pressure to give a crude product as brown oil, which was used in the next step without further purification. The crude product was re-dissolved in acetone (60 mL) and followed by the addition of a solution of NaN₃ (20.7 g, 318.5 mmol) in H₂O (40 mL) slowly at 10 0°C, and the resulting mixture solution was stirred at 0°C for 2 additional 2 h. The reaction mixture was poured into ice water (100 mL). and extracted with toluene (50 mL * 2). The combined organics were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The crude product was re-dissolved in toluene (100 mL) and the solution was heated to 60-70°C for 40 min. After cooling to room temperature, the solvent was removed in vacuo to give the crude title compound (20 g) as brown oil, which was used in the next step without 15 any further purification.

1B 17-Azabicyclo[3.2.1]oct-3-en-6-one



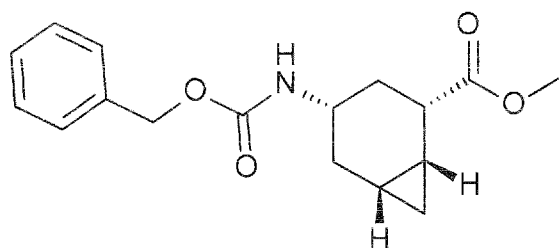
4-Isocyanatocyclohexene (20 g, 162 mmol) were added into 20 mL of PPA at 100 °C, and 20 the resulting mixture was stirred for 20 min. After the mixture was cooled to room temperature. 100 mL water was added in one portion and the solution was extracted with DCM (50 mL * 3). The organic layers were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (DCM: MeOH = 10: 1) to afford the title compound (4.2 g, 26.9% 25 yield) as a white solid. ¹H NMR (400MHz, CHCl₃-d₁) δ 6.12 (t, J=8.0 Hz, 1H), 5.91 (br. s., 1H), 5.67 (d, J=9.5 Hz, 1H), 3.87 (br. s., 1H), 2.82 - 2.73 (m, 1H), 2.46 - 2.38 (m, 1H), 2.30 (td, J=4.9, 10.1 Hz, 1H), 2.17 (d, J=18.6 Hz, 1H), 1.83 (d, J=10.0 Hz, 1H).

[C] (rac)-Methyl (1S,5S)-5-(benzyloxycarbonylamino)cyclohex-2-ene-1-carboxylate



To a solution of 7-azabicyclo[3.2.1]oct-3-en-6-one (6 g, 47.6 mmol) in MeOH (100 mL) was added SOCl_2 (11.3 g, 95.2 mmol) at 0°C , and then the mixture was stirred at 60°C for 3 h. The solution was cooled to room temperature, and concentrated in vacuo to give the crude product (8 g) as colorless oil, which was used in the next step without any further purification. To a solution of the crude product and TEA (8.9 g, 52.3 mmol) in DCM (200 mL) was added CbzCl (8.9 g, 52.3 mmol) at 0°C , and the mixture was stirred at room temperature for 16 h. The mixture was washed with brine (20 mL), and then dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed in vacuo and the crude product was purified by silica gel flash chromatography (petroleum ether: EtOAc = 5: 1) to give the title compound (6.1 g, 44.5% yield) as colorless oil. ^1H NMR (400MHz, CHCl_3-d_1) δ 7.43 - 7.31 (m, 5H), 5.87 - 5.68 (m, 2H), 5.12 (s, 2H), 5.04 (br. s., 1H), 3.89 (br. s., 1H), 3.71 (s, 3H), 3.34 (br. s., 1H), 2.49 - 2.37 (m, 1H), 2.27 (dd, $J=5.5, 8.8$ Hz, 1H), 2.02 - 1.90 (m, 1H), 1.79 (td, $J=10.2, 12.4$ Hz, 1H).

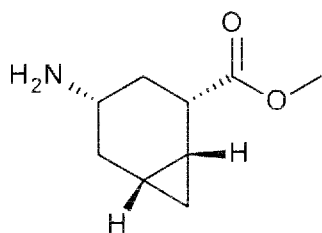
[D] (rac-Methyl (1R,2S,4S,6R)-4-(benzyloxycarbonylamino)norcaradiene-2-carboxylate



To a stirred solution of (rac)-methyl (1S,5S)-5-(benzyloxycarbonylamino)cyclohex-2-ene-1-carboxylate (3 g, 10.4 mmol) in DCM (30 mL) was added Et_2Zn (20.8 mL, 20.8 mmol) dropwise at 0°C under N_2 atmosphere. 15 min later, CH_2I_2 (11.1 g, 41.6 mmol) was added dropwise at 0°C . 15 min later, another batch of Et_2Zn (20.8 mL, 20.8 mmol) and CH_2I_2 (11.1 g, 41.6 mmol) were added slowly at 0°C . The mixture was slowly warmed to room temperature and stirred for another 4 h. 10 mL of satd. aq. NH_4Cl solution was added to quench the reaction, and the solution was extracted with DCM (10 mL *2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed in vacuo to give the crude product, which was purified by

silica gel flash chromatography (petroleum ether : EtOAc = 10: 1) to give the title compound (1.2 g, 38% yield) as a white solid of racemic mixture. ^1H NMR (400 MHz, MeOH- d_4) δ 7.40 - 7.28 (m, 5H), 5.12 - 5.01 (m, 2H), 3.70 (s, 3H), 3.44 - 3.34 (m, 1H), 3.18 - 3.02 (m, 1H), 2.36 - 2.22 (m, 1H), 1.85 - 1.69 (m, 1H), 1.29 - 1.15 (m, 3H), 1.12 - 1.01 (m, 1H), 0.65 (dt, $J=4.9$, 8.8 Hz, 1H), 0.18 (q, $J=5.3$ Hz, 1H).

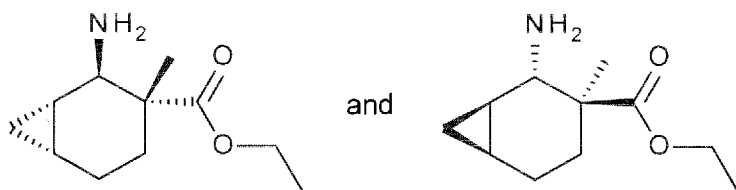
[E] (rac)-Methyl (1R,2S,4S,6R)-4-aminonorcarane-2-carboxylate



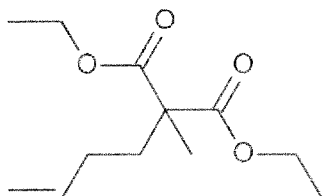
To a stirred solution of (rac)-methyl (1R,2S,4S,6R)-4-(benzyloxycarbonylamino)norcarane-2-carboxylate in MeOH (10 mL) was added Pd/C (0.05 g) at 25°C under H_2 atmosphere (15 psi). and the resulting mixture was stirred for 3 h. The catalyst was filtered off and the filtrate was concentrated to give the crude title compound (0.3 g) as yellow oil, which was used in the next step without any further purification.

Intermediate B-16

Ethyl (1R,2S,3S,6S)-2-amino-3-methyl-norcarane-3-carboxylate and ethyl (1R,2S,3S,6S)-2-amino-3-methyl-norcarane-3-carboxylate



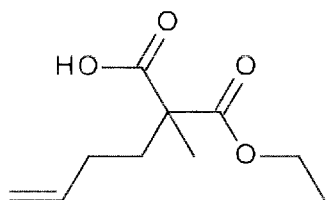
[A] Diethyl 2-but-3-enyl-2-methyl-propanedioate



To a stirred solution of NaH (5.17 g, 60% in mineral oil, 129 mmol) in DMF (60 mL) was added diethyl methylmalonate (14.7 mL, 86 mmol) dropwise at 0°C. The solution was stirred for 15 min before 4-bromo-1-butene (9.62 mL, 97 mmol) was added and stirred at room

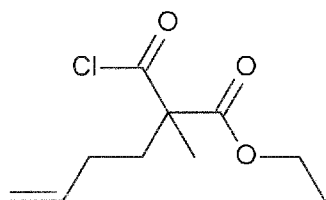
temperature for 12 h. The mixture was then concentrated in vacuo and distilled under vacuum (10 psi, 95°C) to afford the title compound (17 g, 87% yield) as colorless oil. ¹H NMR (400 MHz, CHCl₃-d₁) δ 5.80 (ddt, J = 16.6, 10.2, 6.1 Hz, 1H), 5.04 (d, J = 16.6 Hz, 1H), 4.97 (dd, J = 10.2, 1.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 4H), 2.05 - 1.93 (m, 4H), 1.42 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H).

[BI 2-Ethoxycarbonyl-2-methyl-hex-5-enoic acid



To a stirred solution of diethyl 2-(but-3-en-1-yl)-2-methylmalonate (17 g, 74 mmol) in EtOH (50 mL) was added a solution of KOH (4.5 g, 80 mmol) in EtOH (20 mL) at 0°C. After the addition, the resulting solution was allowed to warm up to room temperature and stirred overnight. The mixture was concentrated under reduced pressure and diluted with H₂O (100 mL) and extracted with EtOAc (40 mL twice). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to have starting material di-ester recovered. The aqueous layer was adjusted to pH = 3 and extracted with EtOAc (50 mL). This organic layer was then washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (10.6 g, 53 mmol) as light yellow oil. This crude product was used directly in the next step without further purification.

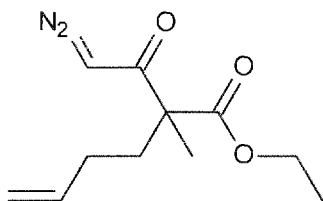
[OJ Ethyl 2-chlorocarbonyl-2-methyl-hex-5-enoate



To a stirred solution of 2-(ethoxycarbonyl)-2-methylhex-5-enoic acid (10.6 g, 53 mmol) in toluene (100 mL) was added pyridine (0.4 mL) followed by the addition of oxalyl chloride (12 mL, 150 mmol), dropwise at 0°C. After the addition, the resulting mixture was allowed to warm up to room temperature and heated at 60°C for 12 h. After cooling to room temperature, the mixture was concentrated and distilled under vacuum (10 psi, 90°C) to give the title compound (9 g, 41 mmol) as colorless oil. ¹H NMR (400 MHz, CHCl₃-d₁) δ 5.79 (ddt, J =

16.6, 10.2, 6.1 Hz, 1H), 5.08 (d, $J = 16.6$ Hz, 1H), 5.02 (dd, $J = 10.3, 1.2$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 2.10 - 2.01 (m, 4H), 1.56 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H).

1D1 Ethyl 2-(2-diazoacetyl)-2-methylhex-5-enoate

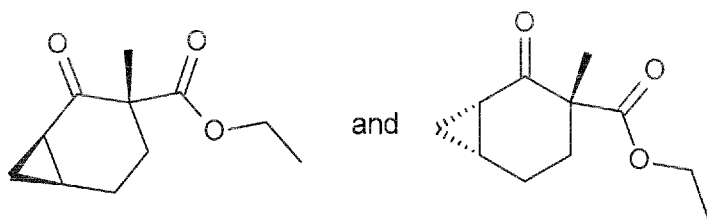


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To a stirred solution of diazomethane (prepared from 1-methyl-1-nitrosourea (15 g), dried over KOH) in Et₂O (100 mL) was added ethyl 2-(chlorocarbonyl)-2-methylhex-5-enoate (5 g, 23 mmol) in Et₂O (50 mL) dropwise at 0°C. The resulting reaction mixture was then warmed up to room temperature and stirred for 2 h. The mixture was first concentrated under reduced pressure, and the residue was dilute with Et₂O and filtered. The filtrate was concentrated in vacuo to give a crude title compound (5 g, 22 mmol) as yellow oil. ¹H NMR (400 MHz, CHCl₃-d₁) δ 5.80 (m, 1H), 5.47 (s, 2H), 5.05 (d, $J = 16.6$ Hz, 1H), 4.99 (dd, $J = 10.3$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.10 - 1.90 (m, 4H), 1.40 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H).

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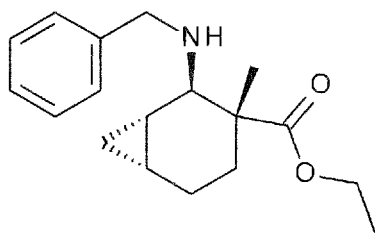
[E] (rac)-Ethyl (1R,3R,6S)-3-methyl-2-oxo-norcarane-3-carboxylate and (rac)-ethyl (1S,3R,6R)-3-methyl-2-oxo-norcarane-3-carboxylate



To a stirred solution of allylpalladium chloride dimer (50 mg, 0.13 mmol) in toluene (20 mL) was added ethyl 2-(2-diazoacetyl)-2-methylhex-5-enoate (5.0 g, 22 mmol) in toluene (10 mL) at 0°C over a period of 30 min. The resulting solution was stirred at room temperature for 12 h before it was concentrated in vacuo. The crude product was purified by silica gel flash chromatography (petroleum ether: EtOAc = 30 : 1) to give the title mixture of compounds (2.2 g, 11 mmol) as colorless oil. The ratio of two diastereomers is 3:2 based on ¹H NMR analysis.

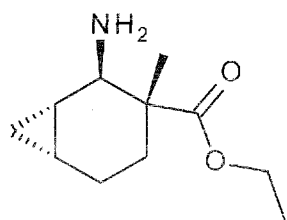
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[F] (rac)-Ethyl(1S^R,3R,6R)-2-(benzylamino)-3-methyl-norcarane-3-carboxylate



To a stirred solution of (rac)-ethyl (1S,3R,6R)-3-methyl-2-oxo-norcarane-3-carboxylate (2 g, 10 mmol) and benzylamine (2.1 mL, 20 mmol) in DCM (20 mL) was added titanium (IV) chloride (1.1 mL, 10 mmol) at room temperature. The resulting solution was stirred for 2 h before NaBH₃CN (1.26 g, 20 mmol) in MeOH (10 mL) was added at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was diluted with EtOAc (100 mL) and then quenched with 1N NaOH (60 mL). After addition of Et₂O (100 mL) to the mixture, the organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo. The crude product was purified by silica gel flash chromatography (DCM:MeOH = 200 : 1) to give the title racemic mixture of compounds (0.86 g, 3.0 mmol) as light green oil. ¹H NMR (400 MHz, CHCl₃-d₁) δ 7.38 - 7.25 (m, 5H), 4.13 - 3.95 (m, 3H), 3.82 (d, J = 13.3 Hz, 1H), 2.86 (d, J = 1.5 Hz, 1H), 1.88 (ddd, J = 19.6, 13.2, 6.1 Hz, 1H), 1.74 (ddd, J = 19.6, 6.4, 2.2 Hz, 1H), 1.45 - 1.30 (m, 2H), 1.20 (s, 3H), 1.17 (t, J = 7.1, 2H), 1.00 (ddd, J = 14.6, 8.7, 6.2 Hz, 1H), 0.80 - 0.71 (m, (dt, J = 6.0, 2.5 Hz, 1H).

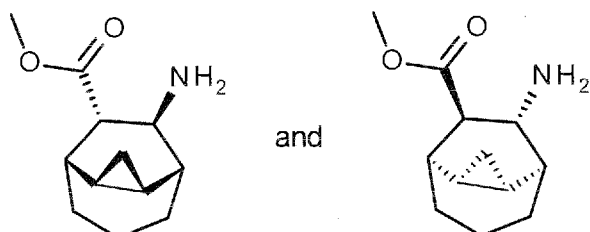
[G] (rac)-Ethyl (1S,2R,3R,6R)-2-amino-3-methyl-norcarane-3-carboxylate



Under N₂, to a stirred solution (rac)-ethyl (1S,2R,3R,6R)-2-(benzylamino)-3-methyl-bicyclo[4.1.0]heptane-3-carboxylate (0.43 g, 1.5 mmol) in formic acid (5 mL) was added 10% palladium hydroxide on carbon (0.1 g). The mixture was then flushed with hydrogen and heated at 50°C for 12 h. After cooling to room temperature, the resulting suspension was filtered off through Celite, and the filtrate was concentrated in vacuo to give a crude title compound as yellow oil. This crude product was used directly in the next step without further purification.

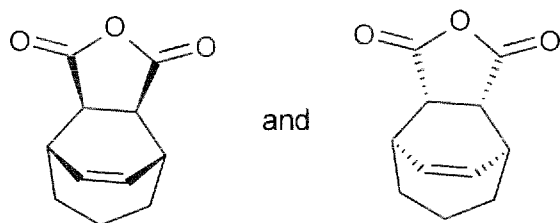
Intermediate B-17

(1S,2R,4S,5R,9S,10S)-Methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate and (1R,2S,4R,5S,9R,10R)-methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



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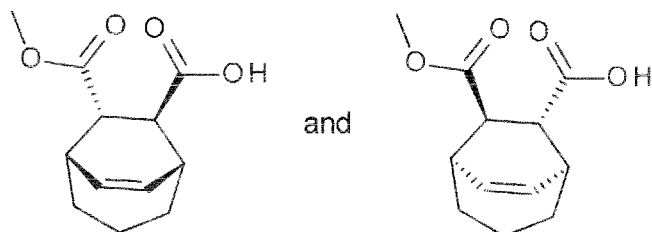
[A] (3aR,4S,8R,8aS)-4,5,6,7,8,8a-hexahydro-1H-4,8-ethenocycloheptafuran-1,3(3aH)-dione and (3aR,4S,8R,8aS)-4,5,6,7,8,8a-hexahydro-1H-4,8-ethenocycloheptafuran-1,3(3aH)-dione



10 A stirred solution of cyclohepta-1,3-diene (15 g, 159 mmol) and maleic anhydride (15.6 g, 159 mmol) in toluene (50 mL) was heated at 120°C for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give a crude title compound (29.4 g, 96% yield) as a white solid. It was used directly in the next step reaction without further purification. MS: 225.1 [M+H⁺].

15

[B] (1R,5S,8S,9S)-9-(Methoxycarbonyl)bicyclo[3.2.2]non-6-ene-8-carboxylic acid and (1S,5R,8R,9R)-9-(methoxycarbonyl)bicyclo[3.2.2]non-6-ene-8-carboxylic acid

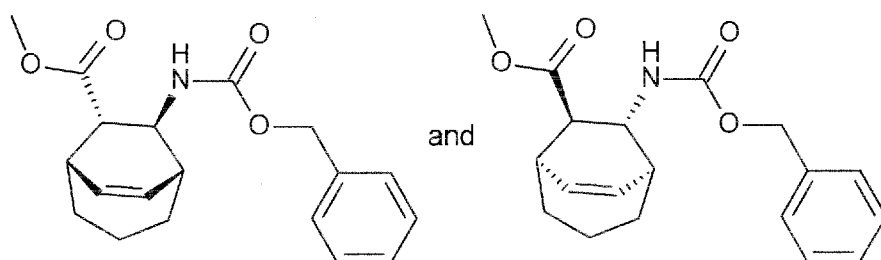


20 (3aR,4S,8R,8aS)-4,5,6,7,8,8a-hexahydro-1H-4,8-ethenocyclohepta[c]furan-1,3(3aH)-dione and (3aR,4S,8R,8aS)-4,5,6,7,8,8a-hexahydro-1H-4,8-ethenocyclohepta[c]furan-1,3(3aH)-dione (50 g, 260 mmol) was treated with sodium methoxide (70.3 g, 1.3 mol) in MeOH (500

mL) at room temperature. After the reaction mixture was stirred at room temperature for 24 h, it was acidified with 2 N HCl solution (300 mL) and extracted with EtOAc (300 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (50 g, 85.7% yield) as a yellow solid.

5 MS: 344.2 $[\text{M}+\text{H}^+]$. It was used directly in the next step reaction without further purification.

[C] (1S,5R,8S,9S)-Methyl 9-(((benzyloxy)carbonyl)amino)bicyclo[3.2.2]non-6-ene-8-carboxylate and (1R,5S,8R,9R)-methyl 9-(((benzyloxy)carbonyl)amino)bicyclo[3.2.2]-non-6-ene-8-carboxylate



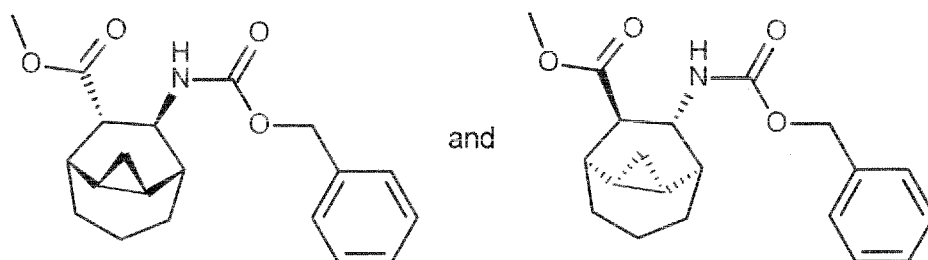
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To a stirred solution of (1R,5S,8S,9S)-9-(methoxycarbonyl)bicyclo[3.2.2]non-6-ene-8-carboxylic acid and (1S,5R,8R,9R)-9-(methoxycarbonyl)bicyclo[3.2.2]non-6-ene-8-carboxylic acid (17.3 g, 77.1 mmol) and Et_3N (23.4 g, 231 mmol) in toluene (100 mL) was added diphenylphosphoryl azide (25.5 g, 92.6 mmol) dropwise at room temperature. After the addition, the reaction mixture was heated at 100°C for 1 h before benzyl alcohol (16.7 g, 154 mmol) was added. The resulting mixture solution was heated at 100°C for another 1 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc: petroleum ether = 0 to 40%) to afford the title compound (13 g, 52% yield) as yellow oil. MS: 330.2 $[\text{M}+\text{H}^+]$.

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20

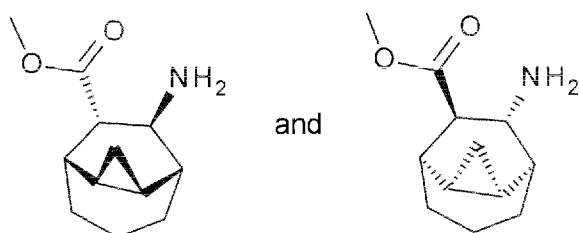
[D] (1S,2R,4S,5R,9S,10S)-Methyl 10-(((benzyloxy)carbonyl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate and (1R,2S,4R,5S,9R,10R)-methyl 10-(((benzyloxy)carbonyl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



25

To a stirred mixture solution of (1S,5R,8S,9S)-methyl 9-(((benzyloxy)carbonyl)amino)-bicyclo[3.2.2]non-6-ene-8-carboxylate and (1R,5S,8R,9R)-methyl 9-(((benzyloxy)carbonyl)amino)bicyclo[3.2.2]non-6-ene-8-carboxylate (4 g, 12.1 mmol) in DCM (20 mL) was added diethylzinc (24.3 mL, 24.3 mmol) at 0°C followed by the addition of diiodomethane (13 g, 48.6 mmol) slowly after 5 min. After the resulting mixture solution was stirred at OX for 10 min, a second batch of diethylzinc (24.3 mL, 24.3 mmol) and diiodomethane (13 g, 48.6 mmol) were added. The mixture solution was stirred at 0°C for another 2 h before it was diluted with water (20 mL), and extracted with DCM (140 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc:petroleum ether= 0 to 30%) to afford the title compound (3.6 g, 90% yield) as yellow oil. MS: 344.2 $[\text{M}+\text{H}]^+$.

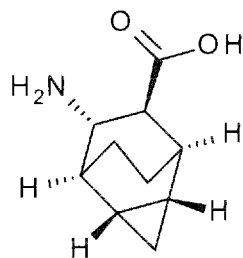
[El] (1S,2R,4S,5R,9S,10S)-Methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate and (1R,2S,4R,5S,9R,10R)-methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



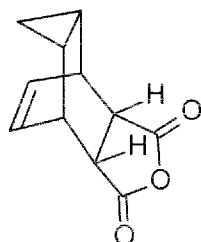
A mixture solution of (1S,2R,4S,5R,9S,10S)-methyl 10-(((benzyloxy)carbonyl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate and (1R,2S,4R,5S,9R,10R)-methyl 10-(((benzyloxy)carbonyl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (12g, 34.9 mmol) and palladium hydroxide on carbon (800 mg, 5.7 mmol) in MeOH (100 mL) was stirred at room temperature for 5 h under H_2 atmosphere (1 atm). Afterwards, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give a crude title compounds (7 g, 95.7% yield) as colorless oil. MS: 210.1 $[\text{M}+\text{H}]^+$. It was used directly in the next step without further purification.

Intermediate B-18

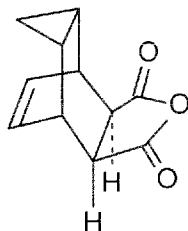
(rac)-(1S,2S,4R,5R,6S,7S)-Meihyl

7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

[AL (3aR,4R,4aR,5aS,6S,6aS)-4,4a,5,5a,6,6a-hexahydro-1 H-4,6-ethenocyclopropa[flisobenzofuran-1 ,3(3a/-)-dione and (3aR,4S,4aS,5aR,6R,6aS)-4,4a,5,5a,6,6a-hexahydro-1H-4,6-ethenocyclopropa[flisobenzofuran-1 ,3(3aH)-dione



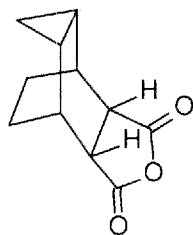
B-18A-1



B-18A-2

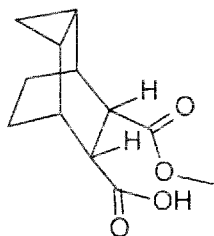
A stirred solution of cyclohepta-1,3,5-triene (60 g, 652.2 mmol) and furan-2,5-dione (63.9 g, 652.2 mmol) in xylene (300 mL) was heated to 130°C for 1 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to give a crude product, which after re-crystallization from petroleum and EtOAc (3:1) afforded the title endo compound (B-18A-1, 65 g, 52% yield) as a white solid. The mother liquid was concentrated and the residue was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title exo compound (2 g, 1.6% yield) as a yellow solid. Endo compound (B-18A-1), ¹H NMR (400 MHz, CHCl₃-cf1) δ 0.28 (dt, J=6.09, 3.67 Hz, 1 H), 0.34 - 0.43 (m, 1 H), 1.05 - 1.19 (m, 2 H), 3.27 (t, J=1.82 Hz, 2 H), 3.44 - 3.57 (m, 2 H), 5.91 (dd, J=4.77, 3.39 Hz, 2 H). Exo compound (B-18A-2). ¹H NMR: (300 MHz, CHCl₃-d1) δ 0.01 - 0.31 (m, 2 H) 1.12 (br. s., 2 H) 3.09 (br. s., 2 H) 3.41 (br. s., 2 H) 5.95 (d, J=2.26 Hz, 2 H).

fBI (3aR,4R,4aR,5aS,6S,6aS)-hexahydro-1/-4,6-ethanocyclopropa[flisobenzofuran-1,3(3aH)-dione



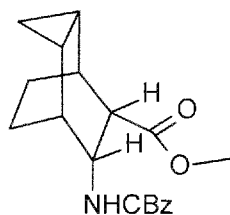
A solution of (3aR,4R,4aR,5aS,6S,6aS)-4,4a,5,5a,6,6a-hexahydro-1H-4,6-ethenocyclopropa[f]isobenzofuran-1,3-dione (20 g, 0.105 mol) and Pd/C (50 g) in EtOAc (200 mL) was hydrogenated under H₂ atmosphere (30 psi) at room temperature for 12 h. After TLC (petroleum ether: EtOAc = 5:1) showed that the reaction was completed, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether: EtOAc = 20:1) to afford the title compound (13 g, 65% yield) as an oil. ¹H NMR (400 MHz, CHCl₃-d₁) δ ppm 0.35 - 0.44 (m, 1 H) 0.55 (dt, J=6.53, 3.51 Hz, 1 H) 0.89 - 0.97 (m, 1 H) 1.25 (d, J=8.41 Hz, 1 H) 1.41 - 1.49 (m, 1 H) 2.56 (br. s., 1 H) 3.03 (s, 1 H).

[C] (rac)-(1S,2S,4R,5R,6R,7S)-7-(Methoxycarbonyl)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



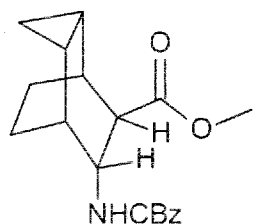
A solution of (3aR,4R,4aR,5aS,6S,6aS)-hexahydro-1H-4,6-ethenocyclopropa[f]isobenzofuran-1,3-dione (25 g, 130 mmol) in MeOH (500 mL) was stirred at 70 °C for 36 h. After TLC (petroleum ether: EtOAc = 5:1) showed the starting material was consumed, the reaction was cooled down and the reaction solution was concentrated in vacuo to give a crude title compound (27 g, 100% yield). ¹H NMR (400 MHz, CHCl₃-d₁) δ 3.64 (s, 3H), 3.11 - 2.98 (m, 2H), 2.33 (d, J=10.4 Hz, 2H), 1.66 (d, J=8.5 Hz, 2H), 1.19 (d, J=8.5 Hz, 2H), 1.07 - 0.93 (m, 2H), 0.83 - 0.77 (m, 1H), 0.50 - 0.42 (m, 1H).

[D] (rac)-(1R,2R,4S,5S,6S,7R)-7-(((benzyloxy)carbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a mixture solution of (rac)-(1R,2R,4S,5S,8R,9S)-9-(methoxycarbonyl)tricyclo[3.2.2.0(2,4)]non-6-ene-8-carboxylic acid (10 g, 44.5 mmol), benzyl alcohol (19.2 g, 178.3 mmol) and Et₃N (18.3 mL, 133.5 mmol) in toluene (100 mL) was added DPPA (14.6 g, 53.4 mmol) slowly and the resulting reaction mixture solution was stirred first at room temperature for 1 h and then at 100°C for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 15:1) to afford the title compound (11.5 g, 82% yield) as an oil.

10 [E] (rac)-(1R,2R,4S,5S,6R,7R)-Methyl 7-(((benzyloxy)carbonyl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate

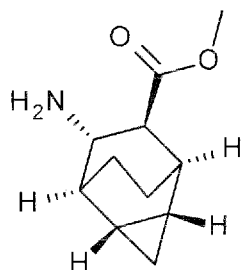


To a stirred solution of Na (1.25 g, 54.6 mmol) in MeOH (60 mL) was added (rac)-(1R,2R,4S,5S)-methyl 7-(((benzyloxy)carbonyl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-

15 carboxylate (6 g, 18.2 mmol) and the reaction mixture was stirred at room temperature for 4 h. After TLC (petroleum ether: EtOAc = 5:1) showed the starting material was consumed, AcOH was added into the reaction mixture to adjust the pH to 7. The mixture solution was then concentrated under reduced pressure, and the residue was partitioned between water (20 mL) and EtOAc (20 mL three times). The combined organics were dried over anhydrous
20 MgSO₄, filtered and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 10 : 1) to afford the title compound (5 g, 83.3% yield) as an oil. ¹H NMR (300 MHz, CHCl₃-d₁) δ 7.43 - 7.29 (m, 7H), 5.10 (br. s., 2H), 4.94 (br. s., 1H), 4.34 (d, J=2.8 Hz, 1H), 3.80 - 3.68 (m, 3H), 2.33 (br. s.,

1H), 2.29 - 2.19 (m, 1H), 2.13 (br. s., 1H), 1.51 - 1.33 (m, 3H), 1.12 - 0.83 (m, 3H), 0.74 - 0.64 (m, 1H), 0.52 - 0.39 (m, 1H).

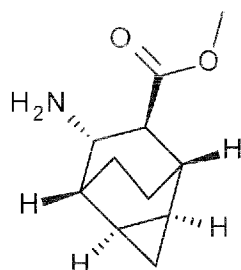
[F] (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



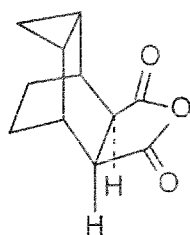
5 To a solution of (rac)-(1R,2R,4S,5S,6R,7R)-methyl 7-(((benzyloxy)carbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (2 g, 6 mmol) in EtOAc (20 ml) was added Pd/C (0.5 g) and the mixture was stirred at room temperature under H₂ (1 atm) for 12 h. After TLC (petroleum ether: EtOAc = 1:1) showed that the reaction was completed, the mixture solution was filtered, and the filtrate was concentrated
10 in vacuo to give a crude title product (1 g) as an oil. This crude product was used directly in the next step without further purification.

Intermediate B-19

(rac)-(1R,2R,4S,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

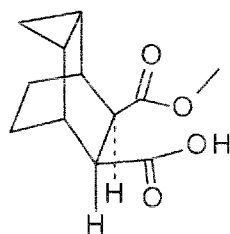


15 1A1 (3aR,4S,4aS,5aR,6R,6aS)-Hexahydro-1H-4,6-ethanocyclopropa[1]isobenzofuran-1,3(1aH)-dione



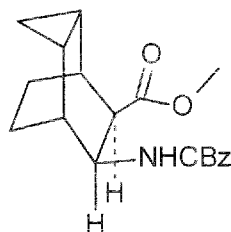
A solution of (3aR,4S,4aS,5aR,6R,6aS)-hexahydro-1H-4,6-ethanocyclopropa[f]isobenzofuran-1,3(3a/-)-dione (1.9 g, 10 mmol) and Pd/C (1 g) in EtOAc (20 mL) was hydrogenated under H₂ atmosphere (30 psi) at 40°C for 2 h. After TLC (petroleum ether: EtOAc = 5:1) showed that the reaction was completed, the mixture solution was filtered and the filtrate was concentrated under reduced pressure to give a crude title compound (1.5 g, 68.1% yield) as an oil. ¹H NMR (400 MHz, CHCl₃-d₁) δ 0.35 - 0.44 (m, 1 H) 0.55 (dt, J=6.53, 3.51 Hz, 1 H) 0.89 - 0.97 (m, 1 H) 1.25 (d, J=8.41 Hz, 1 H) 1.41 - 1.49 (m, 1 H) 2.56 (br. s., 1 H) 3.03 (s, 1 H).

IB 1 (rac)-(1S,2S,4R,5R,6S,7R)-7-(Methoxycarbonyl)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A solution of (3aS,4R,4aR,5aS,6S)-hexahydro-1H-4,6-ethanocyclopropa[f]isobenzofuran-1,3(3aH)-dione (3 g, 15.6 mmol) in MeOH (30 mL) was stirred at 70 °C for 36 h. After TLC (petroleum ether: EtOAc = 5:1) showed the starting material was consumed, the reaction mixture was concentrated under reduced pressure to give a crude title compound (3.3 g). ¹H NMR (400 MHz, CHCl₃-d₁) δ 5.47 (br. s., 2H), 3.63 (s, 3H), 3.04 - 2.84 (m, 2H), 2.41 - 2.27 (m, 2H), 1.43 (d, J=7.4 Hz, 2H), 1.31 - 1.06 (m, 4H), 0.60 - 0.46 (m, 1H), 0.40 - 0.28 (m, 1H).

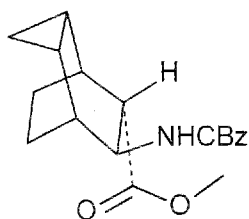
ICL (rac)-(1R,2R,4S,5S,6R,7S)-Methyl 7-(((benzyloxycarbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a mixture solution of (rac)-(1S,2S,4R,5R,6S,7R)-7-(methoxycarbonyl)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (2.8 g, 12.4 mmol), benzyl alcohol (5.36 g, 49.6 mmol) and Et₃N (5.2 mL, 37.4 mmol) in toluene (30 mL) was added

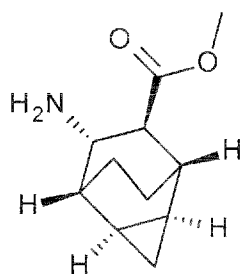
DPPA (4.09 g, 14.9 mmol) slowly and the resulting mixture solution was stirred at room temperature for 1 h before was heated at 100 °C for another 12 h. After cooling to room temperature, the mixture solution was concentrated under reduced pressure to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 15:1) to afford the title compound (1.5 g, 38.4% yield) as an oil.

[C] (rac)-(1 R.2R,4S.5S.6S.7S)-Methyl z-
(((benzyloxy)carbonyl)amino)thcvclor3.2.2.02,4]nonane-6-carboxylate



To a solution of Na (0.35 g, 15 mmol) in MeOH (15 mL) was added (rac)-(1 R.2R,4S.5S.6R,7S)-methyl7-(((benzyloxy)carbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1.7 g, 5 mmol) and the reaction mixture was stirred at room temperature for 4 h. After TLC (petroleum ether: EtOAc = 5:1) showed that the reaction was completed, the AcOH was added to adjust pH to 7. The mixture solution was then concentrated under reduced pressure. The residue was partitioned between water (10 mL) and EtOAc (10 mL three times). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 10: 1) to afford the title compound (1 g, 58.8% yield) as an oil. ¹H NMR (300MHz, CHCl₃-d₁) δ 7.44 - 7.29 (m, 8H), 5.10 (br. s., 2H), 4.71 (s, 1H), 4.31 (br. s., 1H), 3.80 - 3.61 (m, 3H), 3.50 (d, J=5.5 Hz, 1H), 2.42 (br. s., 1H), 2.33 (br. s., 1H), 2.13 (br. s., 1H), 1.36 (d, J=3.8 Hz, 2H), 1.18 (d, J=8.1 Hz, 1H), 1.03 (br. s., 2H), 0.71 (td, J=3.2, 6.0 Hz, 1H), 0.52 - 0.39 (m, 1H).

[D] (rac)-(1 R.2R.4S.5S.6S.7S)-Methyl 7-aminotncvclor3.2.2.02.4]nonane-6-carboxylate

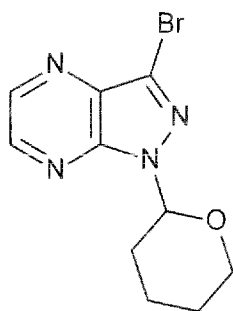


To a solution of (rac)-(1R,2R,4S,5S,6S,7S)-methyl 7-(((benzyloxy)carbonyl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

(0.4 g, 1.2 mmol) in EtOAc (5 mL) was added Pd/C (0.5 g) and the mixture solution was stirred under H₂ (1atm) atmosphere at room temperature for 3 h. After TLC (petroleum ether: EtOAc = 1:1) showed that the reaction was completed, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether; EtOAc = 10:1) to afford the title compound (0.12 g, 52% yield) as an oil. This crude product was used directly in the next step without further purification.

Intermediate C-1

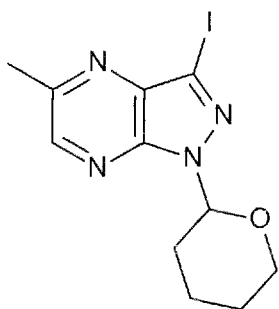
3-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine



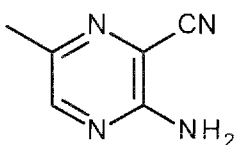
To a stirred mixture solution of 3-bromo-1H-pyrazolo[3,4-b]pyrazine (10 g, 50.2 mmol) and DHP (25.4 g, 301 mmol) in toluene (40 mL) was added 2,2,2-trifluoroacetic acid (1.15 g, 10 mmol) and the reaction mixture solution was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to yield the title compound (11g, 77.3% yield) as a light yellow solid. MS: 283.1&285.1 [M+Hf.

Intermediate C-2a

3-Iodo-5-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyrazine

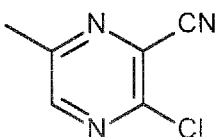


IA1 3-Amino-6-methylpyrazine-2-carbonitrile

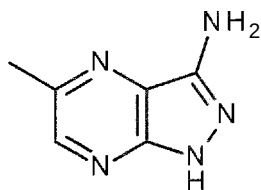


To a stirred solution of 3-bromo-5-methylpyrazin-2-amine (2 g, 18.3 mmol) in 1,4-dioxane
 5 (50 mL) was added pyridine (2.9 g, 36.6 mmol) at 30 °C, followed by the addition of Br₂
 (4.39 g, 27.5 mmol) dropwise at 30 °C, and stirred for 2 h. After TLC (petroleum ether:
 EtOAc = 3: 1) showed the starting material was consumed completely, the reaction was
 quenched by the addition of aq. Na₂SO₃ solution (40 mL) and extracted with EtOAc (40 mL
 three times). The combined organic extracts were washed with brine, dried with anhydrous
 10 Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by
 silica gel flash chromatography (petroleum ether: EtOAc = 8:1 to 3:1) to afford the title
 compound (1.8 g, 52.2% yield) as a white solid. MS: 135.1 [M+H]⁺.

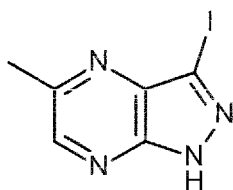
fBI 3-Chloro-6-methylpyrazine-2-carbonitrile



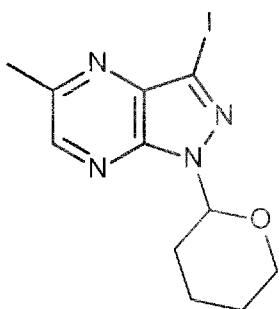
15 To a solution of 3-amino-6-methylpyrazine-2-carbonitrile (1 g, 7.46 mmol) in AcOH (10 mL)
 and HCl (10 mL) was added NaNO₂ (2.57 g, 37.3 mmol) at 0°C and stirred for 1 h. After
 TLC (petroleum ether: EtOAc = 3: 1) showed the starting material was consumed,
 the reaction mixture was poured into satd. aq. NaHCO₃ solution and adjusted pH = 8. The
 20 aqueous solution was extracted with EtOAc (50 mL three times), and the combined organic
 layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and
 concentrated in vacuo to afford the title compound (0.5 g, 43.7% yield) as black oil. MS:
 154.1 [M+H]⁺.

[C] 5-Methyl-1H-pyrazolo[3,4-b]pyrazin-3-amine

To a stirred solution of 3-chloro-6-methylpyrazine-2-carbonitrile (50 mg, 0.326 mmol) in EtOH (5 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (1 mL) and the resulting reaction mixture was stirred at 90 °C for 18 h. After cooling to room temperature, solvent was removed under reduced pressure, and the residue was re-dissolved in EtOAc (20 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude title compound (20 mg, 41.2% yield) as a yellow solid. MS: 150.1 $[\text{M}+\text{H}]^+$.

10 [D] 3-Iodo-5-methyl-1H-pyrazolo[3,4-b]pyrazine

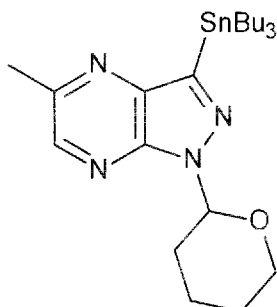
To a stirred mixture solution of 5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-amine (25 mg, 0.164 mmol) and I_2 (54 mg, 0.197 mmol) in MeCN (5 mL) was added isopentyl nitrite (23 mg, 0.213 mmol) at 80 °C and stirred for 1 h. After TLC (petroleum ether: EtOAc = 1: 1) showed the starting material was consumed completely, the reaction was quenched with aq. Na_2SO_3 solution (10 mL), and extracted with EtOAc (10 mL three times). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (10 mg, 22.9% yield) as a white solid. MS: 261.1 $[\text{M}+\text{H}]^+$.

20 [E] 3-Iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine

To a solution of 3-iodo-5-methyl-1 *H*-pyrazolo[3,4-*b*]pyrazine (5 g, 19.0 mmol) in THF (50 mL) was added TsOH (3.27 g, 19.0 mmol) and DHP (4.79 g, 57.0 mmol) and the resulting reaction mixture was stirred at 80 °C for 15 h. After TLC (petroleum ether: EtOAc = 3: 1) showed the starting material was consumed completely, the solvent was removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1 to 1:1) to afford the title compound (5 g, 75.8% yield) as a white solid. MS: 345.1 [M+H]⁺.

Intermediate C-2b

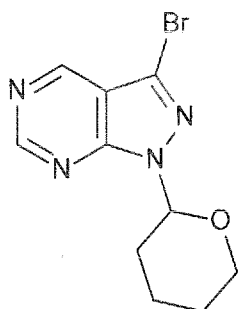
10 Tributyl-(5-methyl-1-(tetrahydropyran-2-yl)-pyrazolo[3,4-*b*]pyrazin-3-yl)stannane



To a stirred solution of 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 *H*-pyrazolo[3,4-*b*]pyrazine (1.1 g, 3.20 mmol) in 1,4-dioxane (15 mL) was added Sn₂(n-Bu)₆ (2.23 g, 3.84 mmol), and Pd(PPh₃)₄ (370 mg, 0.32 mmol). The resulting solution was stirred at 100 °C for 2 h until TLC (petroleum ether: EtOAc = 3: 1) showed the starting material was consumed completely. Solvent was removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 100:1 to 50:1) to afford the title compound (600 mg, 37% yield) as yellow oil. MS: 507.4 [M+H]⁺.

20 Intermediate D-1

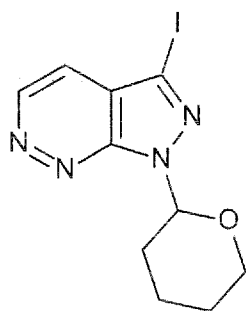
3-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*d*]pyrimidine



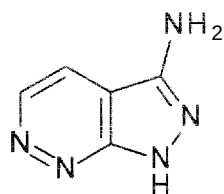
To a stirred mixture solution of 3-bromo-1H-pyrazolo[3,4-d]pyrimidine (5 g, 25.1 mmol) and DHP (12.7 g, 151 mmol) in toluene (40 mL) was added 2,2,2-trifluoroacetic acid (573 mg, 5.02 mmol) and the reaction mixture solution was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to yield the title compound (4.5g, 63.3% yield) as a light yellow solid. MS: 283.1&285.1 $[\text{M}+\text{H}]^+$

10 Intermediate E-1

3-Iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-c]pyridazine

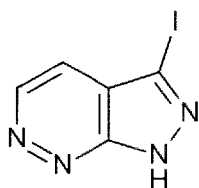


[A] 1H-pyrazolo[3,4-c]pyridazin-3-amine



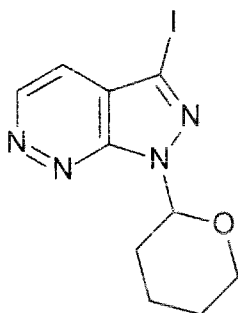
15 A mixture solution of 3-chloropyridazine-4-carbonitrile (4 g, 28.8 mmol) and hydrazine hydrate (7.2 g, 144 mmol) in n-butanol (100 mL) was stirred at 130 °C for 20 h. After TLC (100% EtOAc, $R_f = 0.1$) showed that the reaction was completed, the solvent was removed under reduced pressure to give a crude product, which was crystallized in ethanol (100 mL) to afford the title compound (3 g, 78% yield) as a yellow solid. ^1H NMR (300MHz, $\text{DMSO}-d_6$) δ 12.63 (brs, 1H), 8.91 (d, $J=5.5$ Hz, 2H), 8.02 (d, $J=5.5$ Hz, 2H), 5.98 (s, 4H).

13-Iodo-1H-pyrazolo[3,4-c]pyridazine

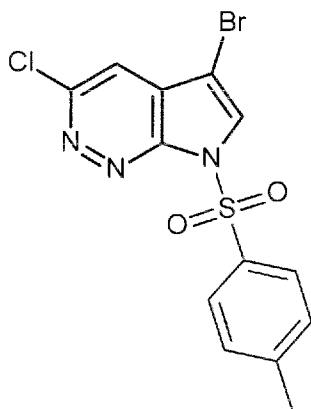
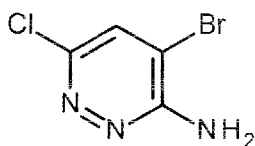


To a stirred solution of 1H-pyrazolo[3,4-c]pyridazin-3-amine (3 g, 22.2 mmol) and I₂ (28.4 g, 111.1 mmol) in MeCN (60 mL) and DMSO (20 mL) was added iso-amyl nitrite (10.4 g, 88.8 mmol) in MeCN (10 mL) dropwise at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 1 h. After TLC (100% EtOAc, R_f = 0.6) showed that the reaction was completed, the reaction was quenched with satd. aq. NaHSC₃ solution until the reaction mixture turned yellow. Water (150 mL) was added and the mixture solution was extracted with EtOAc (100 mL x 4). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (1.8 g, 33% yield) as a grey solid. ¹H NMR (300MHz, DMSO-*d*₆): δ 14.92 (br. s., 1H), 9.18 (d, J=5.7 Hz, 1H), 7.91 (d, J=5.7 Hz, 1H).

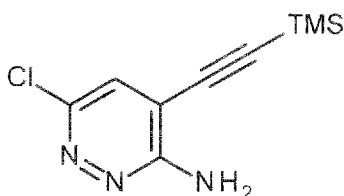
fCl 3-iodo-1-(Tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridazine



A mixture solution of 3-iodo-1H-pyrazolo[3,4-c]pyridazine (1.8 g, 7.3 mmol), 4-methylbenzenesulfonic acid (125.6 mg, 0.73 mmol) and 3,4-dihydro-2H-pyran (3.1 g, 36.5 mmol) in THF (40 mL) and DMSO (10 mL) was stirred at 80 °C for 20 h. After TLC (petroleum ether: EtOAc = 1:1, R_f = 0.6) showed that the reaction was completed, the solvent was removed under reduced pressure. The residue was portioned between water (100 mL) and EtOAc (100 mL twice). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford the title compound (1.7 g, 71% yield) as a yellow solid. MS: 353.0, [M+Na]⁺. ¹H NMR (300MHz, CHCl₃-*d*₁): 8 ppm 9.24 (d, J=5.7 Hz, 1H), 7.56-7.69 (m, 1H), 6.41 (dd, J=10.6, 2.4 Hz, 1H), 4.08-4.23 (m, 1H), 3.87 (td, J=11.5, 2.4 Hz, 1H), 2.64-2.81 (m, 1H), 2.03-2.27 (m, 2H), 1.78-1.92 (m, 2H), 1.63-1.74 (m, 1H).

Intermediate E-2**5-Bromo-3-chloro-7-tosyl-7H-pyrrolo[2,3-c]pyridazine**5 [A] 4-Bromo-6-chloropyridazin-3-amine

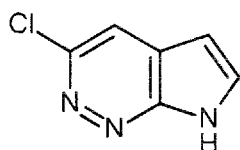
To a stirred mixture solution of 6-chloropyridazin-3-amine (50 g, 387.6 mmol) and NaHCO_3 (74.3 g, 465.1 mmol) in MeOH (500 mL) was added Br_2 dropwise. After the addition, the reaction mixture was stirred at room temperature for 18 h. After TLC (petroleum ether : EtOAc = 1:1) showed that the reaction was completed, the reaction was concentrated under reduced pressure. The residue was re-dissolved in EtOAc, and washed with 10% aq. sodium thiosulfate solution (100 mL twice) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether : EtOAc = 5:1 to 2:1) to afford the title compound (33 g, 41.2% yield) as a solid. MS: 210.0 $[\text{M}+\text{H}]^+$.

[B] 6-Chloro-4-((trimethylsilyl)ethynyl)pyridazin-3-amine

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (20 g, 95.7 mmol) in toluene (250 mL) was added Et_3N (26.2 g, 239.3 mmol), ethynyltrimethylsilane (10.34 g, 105.3 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (6.7 g, 9.57 mmol) and CuI (1.83 g, 9.57 mmol). and the resulting

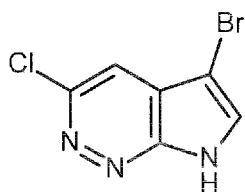
reaction mixture was stirred at room temperature for 3 h under N₂ protection. Afterwards, the reaction was quenched by the addition of H₂O (150 mL). The reaction mixture solution was filtered and the filtrate was extracted with EtOAc (100 mL three times). The combined organics were concentrated in vacuo to give a crude title compound (20.41 g) as a brown solid. MS: 226.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

[C] 3-Chloro-7H-pyrrolo [2.3-c] pyridazine

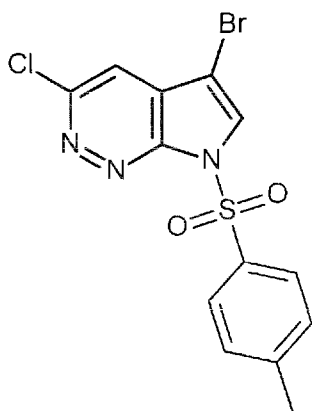


To a stirred solution of 6-chloro-4-((trimethylsilyl)ethynyl)pyridazin-3-amine (10 g, 44.4 mmol) in DMF (150 mL) was added t-BuOK (7.4 g, 66 mmol) and Me₂NH (0.4 g, 8.8 mmol) and the resulting reaction mixture was stirred at 120 °C for 2 h. Afterwards, the reaction was quenched by the addition of satd. aq. NH₄Cl solution (50 mL). The reaction mixture solution was filtered and the filter cake was washed with EtOAc (50 mL) twice. The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude solid, which was purified by silica gel flash chromatography (petroleum ether : EtOAc = 8:1 to 3:1) to afford the title compound (2 g, 30% yield) as a solid. MS: 154.2 [M+H]⁺

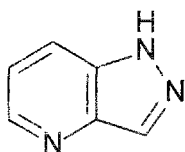
[D] B-bromo-3-chloro-7H-pyrrolo[2.3-c]pyridazine



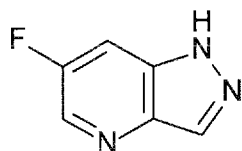
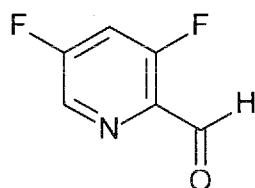
To a stirred solution of 3-chloro-7H-pyrrolo [2.3-c] pyridazine (1.9 g, 12.4 mmol) in DMF (15 mL) was added NBS (2.2 g, 13 mmol) and the resulting reaction mixture was stirred at 30 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc (20 mL three times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether : EtOAc = 20:1 to 4:1) to afford the title compound (1.9 g, 65.9% yield) as a light yellow solid. MS: 234.1 [M+H]⁺.

[E] 5-Bromo-3-chloro-7-tosyl-7H-pyrrolo[2,3-c]pyridazine

To a stirred solution of 5-bromo-3-chloro-7H-pyrrolo[2,3-c]pyridazine (1.8 g, 7.69 mmol) in
 5 DMF (20 mL) was added NaH (0.55 g, 23.0 mmol) at 0 °C. The reaction mixture was stirred
 at 0 °C for 0.5 h before TsCl (2.65 g, 11.53 mmol) was added and the resulting mixture
 solution was stirred for additional 1 h at 0 °C. The reaction was quenched with satd. aq.
 NH₄Cl solution, and extracted with EtOAc (10 mL three times). The combined organics were
 washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a crude
 10 product, which was purified by silica gel flash chromatography (petroleum ether : EtOAc =
 10:1-2:1) to afford the title compound (1.2 g, 42.3% yield) as a yellow solid. MS: 387.9
 [M+H]⁺. ¹H NMR (400MHz, DMSO-d₆) 8.870 (s, 1H), 8.15 (s, 1H), 8.08 (d, J=8.4 Hz, 2H),
 7.49 (d, J=8.4 Hz, 2H), 2.37 (s, 3H).

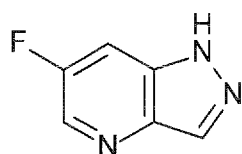
15 Intermediate F-11H-Pyrazolo[4,3-b]pyridine

A solution of 3-fluoropicolinaldehyde (12.5 g, 100 mmol) in N₂H₄·H₂O (80%, 200 mL) was
 stirred at 120 °C for 16 h. After TLC (petroleum ether: EtOAc = 5:1) showed that the
 20 reaction was completed, the mixture solution was poured into water (400 mL) and extracted
 by EtOAc (400 mL). The organic layer was then washed with brine, dried over anhydrous
 Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (11 g, 96% yield)
 as yellow solid. MS: 120.3 [M+H]⁺. ¹H NMR (400 MHz, CHCl₃-d₁): δ 11.15 (br, 1H), 8.65-
 8.63 (m, 1H), 8.37 (s, 1H), 7.90 (d, J = 11.6 Hz, 1H), 7.36-7.32 (m, 1H).

Intermediate F-2**6-Fluoro-1*H*-pyrazolo[4,3-*b*]pyridine**5 **[A1] 3,5-Difluoropicolinaldehyde**

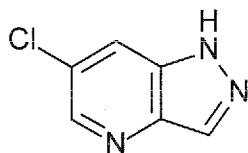
To a stirred solution of 3, 5-difluoropicolinaldehyde (30 g, 214 mmol) in THF (300 mL) was added DIBAL (235.7 mL, 235.7 mmol) and stirred at - 20 °C for 2 h. After TLC (petroleum ether :EtOAc = 5:1, R_f =0.4) showed the starting material was consumed, the reaction was quenched with 1 N HCl to pH = 5. The reaction mixture was extracted with EtOAc (500 mL three times) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound difluoropicolinaldehyde (25 g, 81.7% yield) as a yellow solid. This crude product was used directly in the next step without further purification.

15

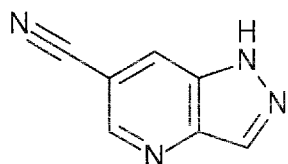
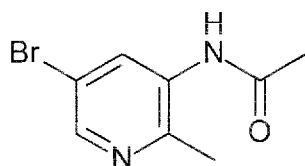
[B] 6-Fluoro-1*H*-pyrazolo[4,3-*b*]pyridine

A mixture solution of 3,5-difluoropicolinaldehyde (25 g, 175 mmol) and hydrazine (87.5 g, 1.75 mol) in n-BuOH (500 mL) was stirred at 130 °C for 20 h. After TLC (petroleum ether: EtOAc = 5:1) showed the starting material was consumed, the solvent was removed under reduced pressure. The residue was re-dissolved in EtOAc (1 L) and washed with citric acid (200 mL x 5), water, and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (9.7 g, 41% yield) as a yellow solid. MS: 138.1 [M+Hf. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.94 (dd, J=9.29, 1.63 Hz, 1 H) 8.34 (s, 1 H) 8.54 (dd, J=2.26, 1.51 Hz, 1 H) 13.44 (brs, 1 H).

25

Intermediate F-3**6-Chloro-1H-pyrazolo[4,3-b]pyridine**

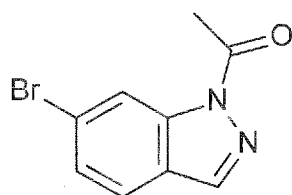
5

intermediate F-4**1H-Pyrazolo[4,3-b]pyridine-6-carbonitrile****[AT /V-(5-Bromo-2-methylpyridin-3-yl)acetamide**

10

To a solution of 5-bromo-2-methylpyridin-3-amine (20 g, 106 mmol) and Et₃N (11.7 g, 116 mmol) in DCM (200mL) was added Ac₂O (14.1 g, 139 mmol) and the resulting reaction mixture was stirred at 150 °C for 12 h. Afterwards, the mixture solution was concentrated under reduced pressure. The residue was diluted with water, basified with aq. NaHCO₃ solution (10 mL), and then extracted with EtOAc (10 mL three times). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (14 g, 66.3% yield) as a solid. MS: 231.7 [M+H]⁺

15

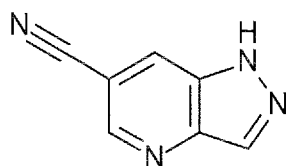
IB 11-(6-Bromo-1H-pyrazolo[4,3-b]pyridin-1-yl)ethanone

20

To a solution of A/(5-bromo-2-methylpyridin-3-yl)acetamide (14 g, 61.1 mmol) in toluene (200 mL) was added Ac₂O (21 mL, 183 mmol), AcOH (21 mL, 300 mmol) and KOAc (11.7 g, 120

mmol). The resulting reaction mixture was warmed up to 90 °C, added CHMe₂CH₂CH₂N₂ (110 mL) and stirred at 90 °C for 5 h. After cooling to room temperature, the mixture was poured into water, basified with aq. NaHCO₃ solution, and extracted with EtOAc (50 mL x 6). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give a crude title compound (6.5 g, 44.5% yield) as a solid. MS: 241.06 [M+H]⁺.

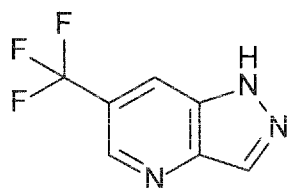
[C] 1-/-pyrazolo[4.3-b]pyridine-6-carbonitrile



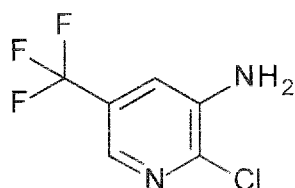
- 10 To a stirred solution of 1-(6-bromo-1H-pyrazolo[4,3-b]pyridin-1-yl)ethanone (6.5 g, 27.04 mmol) in DMA (60 mL) was added Zn (0.416 g, 6.5 mmol), DPPF (1.19 g, 2.08 mmol), Zn(CN)₂ (2.08 g, 17.55 mmol) and Pd₂(dba)₃ (0.97 g, 0.78 mmol). The reaction was warmed up to 90 °C before iPrN₂ (19.5 mL) was added, and the resulting mixture was stirred at 120 °C for 5 h. After cooling to room temperature, the mixture was diluted with EtOAc (60 mL) and satd. aq. NaHCO₃ solution (100 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give a crude title compound (0.95 g, 24.4 % yield) as a solid. MS: 145.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 8.84 (d, J=1.5 Hz, 1H), 8.74 (s, 1H), 8.51 (s, 1H).

20 Intermediate F-5

6-{Trifluoromethyl}-1H-pyrazolo[4,3-b]pyridine



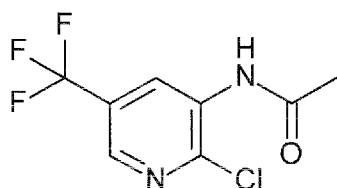
FA] 2-Chloro-5-(trifluoromethyl)pyridin-3-amine



- 25 A mixture solution of 2-chloro-3-nitro-5-(trifluoromethyl)pyridine (80 g, 352.8 mmol) and

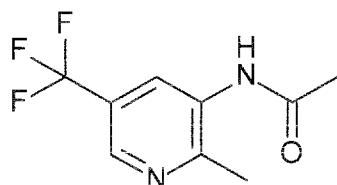
SnCl₂·2H₂O (320 g, 1.4 mol) in EtOAc (1 L) was stirred at 80 °C for 2 h. After TLC (petroleum ether: EtOAc = 5:1) showed that the reaction was completed, the reaction was quenched by pouring into ice cooled satd. aq. NaHCO₃ solution (200 mL). The mixture was extracted with EtOAc (1500 mL) and the organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give desired crude title compound (75 g, 100% yield) as yellow oil. MS: 197.0 [M+H]⁺. This crude product was used directly in the next step without further purification.

1B 1A/(2-Chloro-5-(trifluoromethyl)pyridin-3-yl)acetamide



A mixture solution of 2-chloro-5-(trifluoromethyl)pyridin-3-amine (75 g, 381.6 mmol) and Ac₂O (82.5 mg, 808.1 mmol) in pyridine (200 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, it was diluted with EtOAc (500 mL), washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was first purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) and then crystallization in petroleum ether (100 mL) to afford the title compound (65 g, mixture of mono- and bis-Ac protected product, 73% yield) as white solids. MS: 239.0 [M+H]⁺.

1C 1A/(2-Methyl-5-(trifluoromethyl)pyridin-3-yl)acetamide

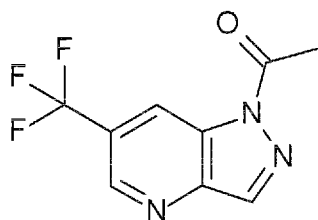


To a mixture of 1A/(2-chloro-5-(trifluoromethyl)pyridin-3-yl)acetamide and 1A-acetyl-N-(2-methyl-5-(trifluoromethyl)pyridin-3-yl)acetamide (35 g, 146.7 mmol), K₂CO₃ (62.2 g, 450 mmol), methyl boroxine (50% in ether, 70 g, 278.8 mmol) and X-phos (14.4 g, 43 mmol) in MeCN (250 mL) and water (150 mL) was added Pd(OAc)₂ (3.4 g, 15.1 mmol). And the resulting reaction mixture was stirred at 100 °C for 16 h. After cooling to room temperature, The reaction was diluted with EtOAc (300 mL), washed with water (300 mL) and brine (300 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in

vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) to afford the title compound (20 g, 57% yield) as a gray solid. MS: 219.0 [M+H]⁺. ¹H NMR (400MHz, CHCl₃-d₁): δ 8.62 (s, 1H), 8.54 (s, 1H), 7.1 1 (br, 1H), 2.60 (s, 3H), 2.28 (s, 3H).

5

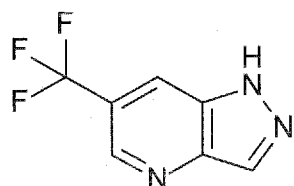
[DI 1-(6-(Trifluoromethyl)-1H-pyrazolo[4,3-b]pyridin-1-yl)ethanone



To a mixture solution of N-(2-methyl-5-(trifluoromethyl)pyridin-3-yl)acetamide (25 g, 105 mmol), KOAc (22 g, 225 mmol) in toluene (280 mL) was added AcOH (35 mL) and Ac₂O (35 mL). The reaction mixture was heated to reflux temperature followed by the addition of CHMe₂CH₂CH₂N₂O₂ (430 mg, 3.6 mmol). The mixture was stirred at 120 °C for additional 2 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (300 mL), washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was first purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) and then crystallization in petroleum ether (100 mL) to give the title compound (12.5 g, 54% yield) as a gray solid. MS: 230.1 [M+H]⁺.

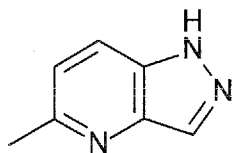
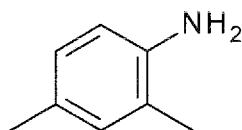
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[EI 6-(Trifluoromethyl)-1H-pyrazolo[4,3-b]pyridine

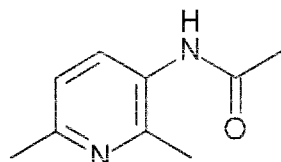


To a stirred solution of 1-(6-(trifluoromethyl)-1H-pyrazolo[4,3-b]pyridin-1-yl)ethanone (12.2 g, 53 mmol) in MeOH (100 mL) was added K₂CO₃ (8.8 g, 64 mmol) and the reaction mixture was heated to 90 °C for 5 min. After TLC (petroleum ether: EtOAc = 5:1) showed that the reaction was completed, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo and the residue was re-dissolved in EtOAc (100 mL), washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give product crude title compound (6.5 g, 65% yield) as a gray solid. MS: 188.1 [M+H]⁺. ¹H NMR (400MHz, CHCl₃-d₁): δ 11.2 (br, 1H), 8.89 (d, J = 1.6 Hz, 1H), 8.47 (s, 1H), 8.19 (s, 1H).

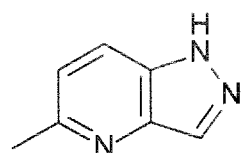
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Intermediate F-6**5-Methyl-1H-pyrazolo[4,3-b]pyridine**5 **IA1 2,6-Dimethylpyridin-3-amine**

To a solution of 2,6-dimethyl-3-nitropyridine (20g, 130 mmol) in MeOH (100 mL) was added Pd/C (2 g) and the reaction mixture was stirred at 150 °C under H₂ atmosphere (1 atm) for 3 h. Afterwards, the mixture was filtered and the filtrate was concentrated in vacuo to give a crude title compound (14.7 g, 91.8% yield) as an oil. This crude product was used directly in the next step without further purification.

IB1 N-(2,6-Dimethylpyridin-3-yl)acetamide

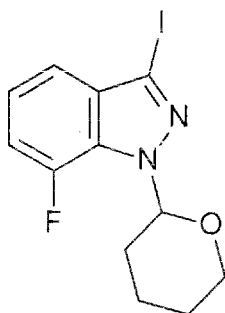
To a solution of 2,6-dimethylpyridin-3-amine (14.7 g, 0.12mol), Et₃N (13.3 g, 0.13 mol) in DCM (140 mL) was added Ac₂O (36.8 g, 0.36mol) and the resulting mixture solution was stirred at room temperature for 12 h. Afterwards, the reaction mixture was concentrated under reduced pressure, and the residue was diluted with water, basified with aq. NaHCO₃ solution (10 mL), and extracted with EtOAc (10 mL three times). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound acetamide (12 g, 60.9% yield) as a white solid. MS: 165.20 [M+H]⁺

[C] 5-Methyl-1H-pyrazolo[4,3-b]pyridine

To a solution of *N*-(2,6-dimethylpyridin-3-yl)acetamide (12 g, 72.9 mmol) in toluene (200 mL) was added Ac₂O (32 mL, 292.3 mmol), AcOH (32 mL, 485 mmol) and KOAc (19 g, 194 mmol). The mixture solution was warmed up to 90°C followed by the addition of *i*PrNO₂ (16 mL). The resulting reaction mixture was stirred at 90°C for 4 h. After TLC (MeOH:DCM=1:10) showed that the reaction was completed, the mixture was concentrated under reduced pressure and the residue was re-dissolved in MeOH (200 mL) and added K₂CO₃ (93.7 g, 679 mmol). The mixture was stirred at 90°C for another 1 h before it was cooled back to room temperature. The reaction mixture was filtered and filtrate was concentrated in vacuo to give a crude title compound (2 g, 20.5% yield) as a solid. MS: 134.1 [M+H]⁺. ¹H NMR (400 MHz, CHCl₃-d₁): δ 13.16 (br. s., 1H), 8.14 (s, 1H), 7.89 (d, J=8.5 Hz, 1H), 7.23 (d, J=8.5 Hz, 1H), 2.57 (s, 3H).

Intermediate G-1a

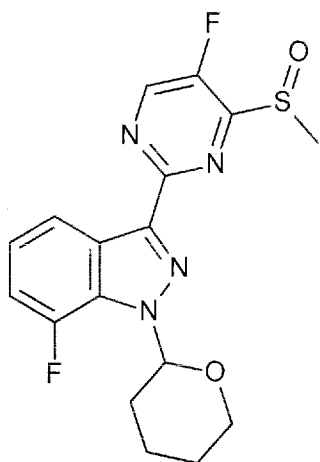
7-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



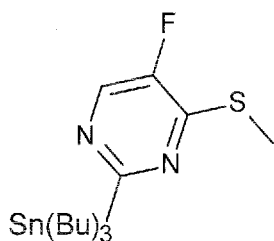
To a stirred mixture solution of 7-fluoro-3-iodo-1*H*-indazole (5 g, 19.1 mmol) and DHP (12.8 g, 153 mmol) in toluene (20 mL) was added 2,2,2-trifluoroacetic acid (435 mg, 3.82 mmol) and the resulting reaction mixture solution was stirred at 100°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (5.3 g, 80.2% yield) as a white solid. MS: 347.1 [M+H]⁺.

Intermediate G-1b

7-Fluoro-3-(5-fluoro-2-ethylsulfinyl-pyrimidin-2-yl)-1-tetrahydropyran-2-yl-indazole

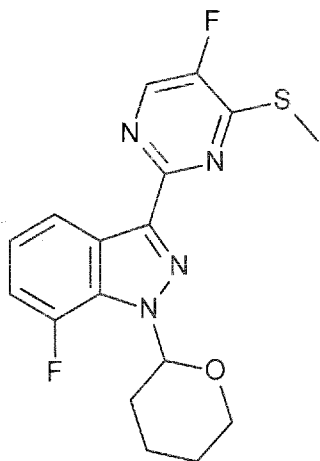


[AT 5-Fluoro-4-(methylthio)-2-(tributylstannyl)pyrimidine]



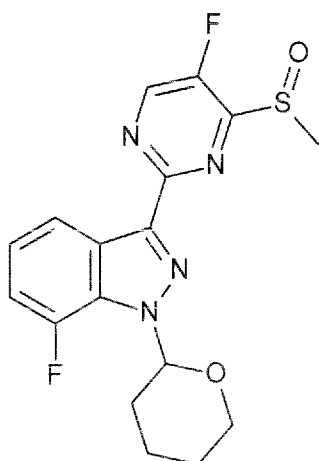
A mixture solution of 2-chloro-5-fluoro-4-(methylthio)pyrimidine (619 mg, 3.46 mmol),
 5 Sn₂Bu₆ (2.21 g, 3.82 mmol), Pd₂(dba)₃ (380 mg, 0.52 mmol) and X-Phos (250 mg, 0.52 mmol)
 in methyl-THF (10 mL) was stirred at 100 °C for 2 h. After TLC (petroleum ether: EtOAc =
 40:1) showed that the reaction was completed, the reaction mixture was used directly in the
 next step without further purification. MS: 435.1 [M+H]⁺.

10 [B] 7-Fluoro-3-(5-fluoro-4-(methylthio)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



A mixture solution of 7-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-1a, 900 mg, 2.6 mmol), 5-fluoro-4-(methylthio)-2-(tributylstannyl)pyrimidine (3.46 mmol), $\text{Pd}_2(\text{dba})_3$ (480 mg, 0.42 mmol), X-Phos (200 mg, 0.42 mmol), and CuI (80 mg, 0.42 mmol) in methyl-THF (5 mL) was stirred at 92°C for 24 h. After TLC (petroleum ether:EtOAc = 40:1) showed that half of the start material was consumed, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 20:1 to 6:1) to afford the title compound (0.37 g, 39% yield) as a solid. MS: 279.0 $[\text{M}+\text{H}]^+$.

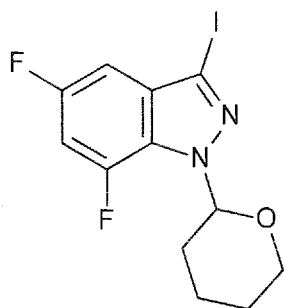
10 [C] 7-Fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



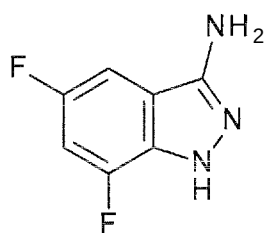
To a stirred solution of 7-fluoro-3-(5-fluoro-4-(methylthio)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.5 g, 4.44 mmol) in DCM (30 mL) was added m-CPBA (0.92 g, 4.55 mmol) with ice-water bath cooling. Afterwards, the reaction was stirred at 5°C for 1 h and quenched by the addition of satd. Na_2SO_3 solution after TLC (petroleum ether:EtOAc = 10:1) showed the start material was consumed. The mixture solution was then extracted with DCM (30 mL twice) and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 2:1 to DCM:EtOAc = 1:1) to afford the title compound (0.5 g, 13.6% yield) as a solid. MS: 379.0 $[\text{M}+\text{H}]^+$.

Intermediate G-2

5,7-Difluoro-3-iodo-1-tetrahydropyran-2-yl-indazole

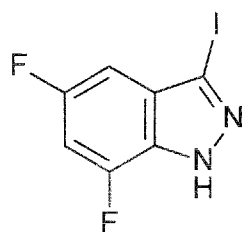


FAT 5,7-Difluoro-1 H-indazol-3-amine



- 5 A stirred solution of 2,3,5-trifluorobenzonitrile (15.7 g, 100 mmol) and hydrazine hydrate (30 mL) in EtOH (150 mL) was heated at SOX for 12 h. After TLC showed the completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 2:1) to afford the title compound (8 g, 47% yield) a white solid. MS: 170.1 [M+H]⁺. ¹H NMR (400MHz DMSO-d₆) ppm 5.49 (s, 2 H) 7.08 - 7.23 (m, 1 H) 7.36 (dd, J=8.78, 2.01 Hz, 1 H) 11.96 (s, 1 H).
- 10

[B] 5,7-Difluoro-3-Iodo-1H-indazole

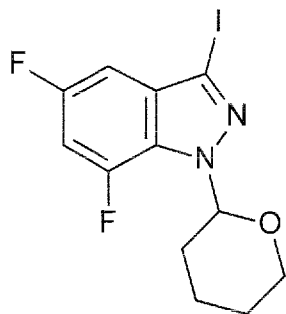


- To a stirred solution of 5,7-difluoro-1H-indazole-3-amine (7.5 g, 44.3 mmol) in 6 M H₂SO₄ (100 mL) was added sodium nitrite (3.97 g, 57.6 mmol) at 0°C. After stirred for 30 min, the above mixture was added slowly to another flask that contains potassium iodine (73.5 g, 443 mmol) and CuI (8.4 g, 44.3 mmol) in H₂O (100 mL) and the resulting mixture was stirred at 50°C for 2 h. After TLC showed that the reaction was completed, the reaction was quenched with aq. Na₂SO₃ solution (200 mL) and extracted with EtOAc (200 mL twice).
- 15
- 20 The organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and

concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum: EtOAc = 20:1 to 10:1) to afford the title compound (5.1 g, 41.2% yield) as a yellow solid. MS: 280.9 [M+H]⁺ ¹H NMR (300 MHz CHCl₃-d₁) δ 7.01-7.04 (m, 2 H) 10.47 (brs. 1H).

5

[Cl 5,7-Difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole]

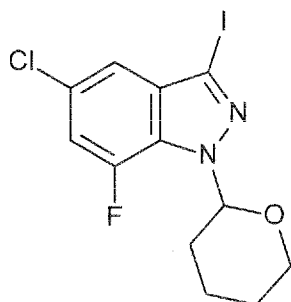


To a stirred mixture solution of 5,7-difluoro-3-iodo-1H-indazole (2.2 g, 7.86 mmol) and DHP (5.29 g, 62.9 mmol) in toluene (20 mL) was added 2,2,2-trifluoroacetic acid (179 mg, 1.57 mmol) and the reaction mixture solution was stirred at 100°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (700 mg, 24.5% yield) as a white solid. MS: 365.1 [M+H]⁺.

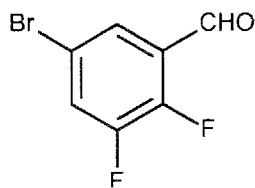
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Intermediate G-3

5-Chloro-7-fluoro-3-iodo-1-tetrahydropyran-2-yl-indazole

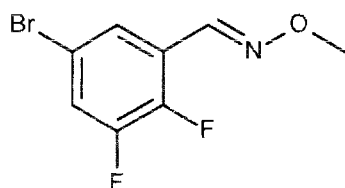


20 [A] 5-Bromo-2,3-difluorobenzaldehyde



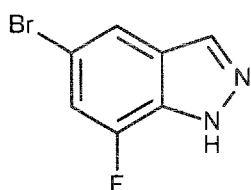
To a stirring solution of 2,3-difluorobenzaldehyde (35 g, 246 mmol) in H_2SO_4 (100 mL) was added NBS (60 g, 337 mmol) in portions at 50°C . After the addition, the reaction mixture was stirred at 60°C for 12 h. After cooling to room temperature, the reaction was quenched with ice-water (800 mL) and extracted with EtOAc (800 mL three times). The combined organic layers were then washed with satd. aq. NaHCO_3 solution (200 mL twice), and the organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether : EtOAc = 100:1-10:1) to afford the title compound (30 g, 55.2% yield) as yellow oil.

[B] (E)-5-Bromo-2,3-difluorobenzaldehyde O-methyl oxime



To a solution of 5-bromo-2,3-difluorobenzaldehyde (30 g, 135 mmol) in DME (100 mL) was added $\text{NH}_2\text{OME} \cdot \text{HCl}$ (12.7 g, 152 mmol) and K_2CO_3 (22.2 g, 160 mmol) and the resulting mixture was stirred at 60°C for 12 h. After TLC (petroleum ether:EtOAc = 5:1) showed the consumption of the starting material, the solvent was removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 500:1~20:1) to afford the title compound (15 g, 44.5% yield) as a white solid. MS: 250.1, 252.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CHCl_3 - d_1) δ 8.21 (s, 1H), 7.76-7.75 (m, 1H), 7.35-7.30 (m, 1H), 4.02 (s, 1H).

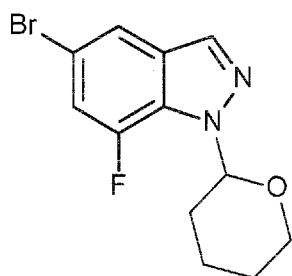
[C] 5-Bromo-7-fluoro-1H-indazole



To a solution of (E)-5-bromo-2,3-difluorobenzaldehyde O-methyl oxime (15 g, 60 mmol) in THF (60 mL) was added NH_2NH_2 (60 mL, 1170 mmol) and the reaction mixture was stirred

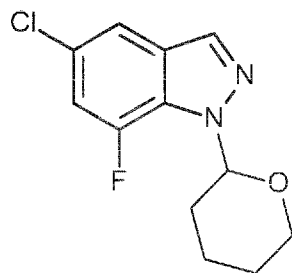
at 90 °C for 48 h. After TLC (petroleum ether:EtOAc = 3:1) showed the complete consumption of starting material, the solvent was removed under reduced pressure. The residue was re-dissolved in EtOAc (100 mL) and washed with water (50 mL twice). The organic layer was then dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was recrystallized from EtOAc to afford the title compound (6 g, 46.5 % yield) as a white solid. MS: 213.1 & 215.1 [M+H]⁺

[P] 5-Bromo-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



To a stirred solution of 5-bromo-7-fluoro-1H-indazole (6 g, 27.9 mmol) and 3,4-dihydro-2H-pyran (2.82 g, 33.5 mmol) in DCM (100 mL) was added TsOH (2 g, 11.2 mmol) at room temperature and stirred for 2 h. The reaction mixture was neutralized with satd. aq. NaHCO_3 solution (100 mL) and extracted with EtOAc (200 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 20:1-5:1) to afford the title compound (8 g, 76.9 % yield) as a white solid. ¹H NMR(400MHz, CHCl_3 -d1) δ 8.00-7.99 (m, 1H), 7.65 (s, 1H), 7.24-7.22 (m, 1H), 5.87-5.84 (m, 1H), 4.07-4.04 (m, 1H), 3.78-3.73 (m, 1H), 2.60-2.57 (m, 1H), 2.17-2.09 (m, 2H), 1.79-1.74 (m, 2H), 1.63-1.55 (m, 1H).

[E] 5-Chloro-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

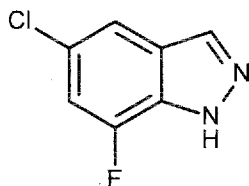


To a mixture solution of 5-bromo-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (3 g, 10 mmol), Cu_2O (0.29 g, 2 mmol) and s-proline (0.46 g, 4 mmol) in n-BuOH (10 mL) was added Me_4NCl (2.2 g, 20 mmol). The resulting reaction mixture was stirred at 150 °C for 2 h under

microwave heating. After cooling to room temperature, the solution was diluted with EtOAc (150 mL) and washed with brine (50 mL twice). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (1g, 39.7% yield) as a white solid.

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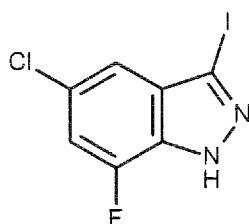
F T5-Chloro-7-fluoro-1 H-indazole



To a stirred solution of 5-chloro-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazole (3.56 g, 14 mmol) in DCM (100 mL) was added TFA (31.9 g, 280 mmol) in portions. After the addition, the reaction mixture was stirred at room temperature for 12 h. After TLC showed the complete consumption of starting material, the reaction mixture was concentrated in vacuo. The residue was re-dissolved in EtOAc (200 mL) and washed with satd. aq. NaHCO_3 solution (100 mL) and water. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 20:1-1:1) to afford the title compound (2.1 g, 88.2% yield) as a white solid.

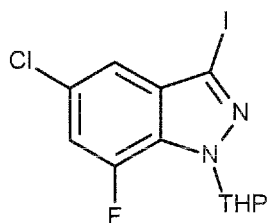
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[G] 5-Chloro-7-fluoro-3-Iodo-1 H-indazole

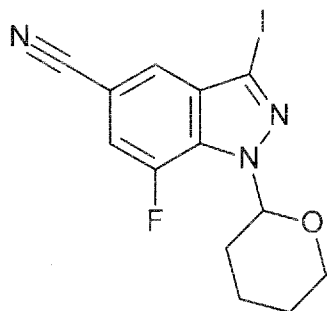
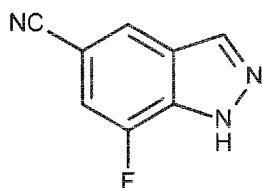


To a stirred solution of 5-chloro-7-fluoro-1 H-indazole (2.1 g, 12.3 mmol) and KOH (2.76 g, 49.2 mmol) in DMF (70 mL) was added I_2 (6.24 g, 24.6 mmol) in portions and after the addition, the mixture was stirred at room temperature for 12 h. The reaction was quenched with aq. Na_2SO_3 solution (100 mL), acidified with 1 N HCl to pH = 7 and extracted with EtOAc (500 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 10:1-1:1) to afford the title compound (3.1 g, 85.1% yield) as a white solid. MS: 297.0 $[\text{M}+\text{H}]^+$. ^1H NMR(400MHz, CHCl_3 -d1) δ 7.525-7.520 (m, 1H), 7.49 (s, 1H), 7.36 (s, 1H).

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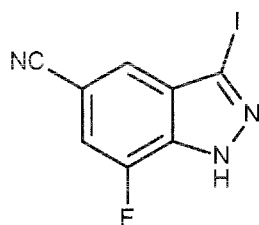
[H] 5-Chloro-7-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

To a solution of 5-chloro-7-fluoro-3-iodo-1H-indazole (9g, 30 mmol) and 3,4-dihydro-2H-pyran (3 g, 36 mmol) in DCM (80 mL) was added TsOH (2.06 g, 12 mmol) in portions, and the resulting mixture solution was stirred at room temperature for 12 h. After TLC showed the complete consumption of starting material, the solution was neutralized with satd. aq. NaHCO₃ solution (100 mL) and extracted with EtOAc (200 mL three times). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 20:1-5:1) to afford the title compound (9.8 g, 85.9% yield) as a white solid. ¹H NMR(400MHz, CHCl₃-d₁) δ 7.30-7.28 (m, 1H), 7.21-7.18 (m, 1H), 5.83 (t, 1H), 4.07-4.05 (m, 1H), 3.74 (t, 1H), 2.61-2.58 (m, 1H), 2.18-2.09 (m, 2H), 1.78-1.74 (m, 2H), 1.64-1.62 (m, 1H).

intermediate G-47-Fluoro-3-iodo-1-(tetrahydropyran-2-yl)-indazole-5-carbonitrile17-Fluoro-1H-indazole-5-carbonitrile

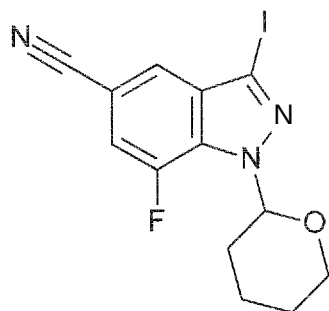
To a solution of 5-bromo-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (7.2 g, 24.0 mmol) and $\text{Pd(PPh}_3)_4$ (2.7 g, 2.4 mmol) in DMF (50 mL) was added Zn(CN)_2 (5.6 g, 48 mmol) in one portion and the reaction mixture was stirred at 120°C for 12 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was quenched with water (200 mL) and extracted with EtOAc (500 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1-1:1 then DCM:MeOH = 100:1-10:1) to afford the title compound (1.3 g, 34.2% yield) as a white solid. MS: 162.2 $[\text{M}+\text{H}]^+$.

[B] 7-Fluoro-3-iodo-1H-indazole-5-carbonitrile



To a stirred solution of 7-fluoro-1H-indazole-5-carbonitrile (1.28 g, 8 mmol) and KOH (1.8 g, 32 mmol) in DMF (20 mL) was added I_2 (4 g, 16.0 mmol) in portions, and after the addition, the reaction mixture was stirred at room temperature for 12 h. After TLC showed the complete consumption of starting material, the reaction was quenched with aq. Na_2SO_3 solution (200 mL), acidified with 1 N HCl to pH = 7, and extracted with EtOAc (300 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1-1:1) to afford the title compound (2 g, 89.3% yield) as a yellow solid. ^1H NMR (300MHz, CHCl_3 -d1) δ 14.63 (s, 1H), 7.98 (s, 1H), 7.85-7.82 (d, 1H, J=10.8Hz).

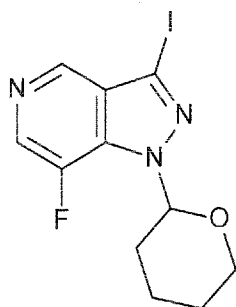
[C] 7-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-indazole-5-carbonitrile



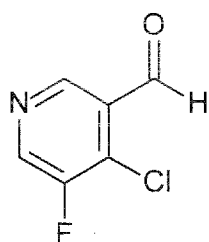
To a stirred mixture solution of 7-fluoro-3-iodo-1H-indazole-5-carbonitrile (2 g, 6.97 mmol) and DHP (4.69 g, 5.1 mL, 55.7 mmol) in toluene (150 mL) was added 2,2,2-trifluoroacetic acid (159 mg, 1.39 mmol) at room temperature and the resulting reaction mixture solution was heated at 100°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (1.6 g, 61.9% yield) as a white solid. MS: 372.1 [M+H]⁺.

Intermediate G-5

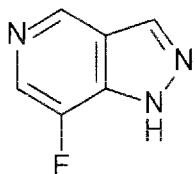
7-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridine



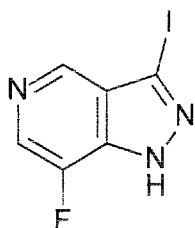
4-Chloro-5-fluoronicotinaldehyde



To a stirred solution of LDA (114.5 mL, 229 mmol) in THF (200 mL) was added 4-chloro-3-fluoropyridine (15 g, 114.5 mmol) dropwise in THF (50 mL) at -78°C. After the addition, the mixture was stirred at -73°C for 1 h before DMF (25 g, 343.5 mmol) was added dropwise and the resulting reaction mixture was stirred at -78°C for another 3 h. The reaction was quenched with satd. aq. NH₄Cl solution and extracted with EtOAc (200 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 20:1 to 5:1) to afford the title compound (8 g, 44.0% yield) as a yellow solid. ¹H NMR (300 MHz, CHCl₃-d₁) δ 8.71 (s, 1 H), 8.89 (s, 1 H), 10.47 (s, 1 H).

[B] 7-Fluoro-1 H-pyrazolo[4,3-c]pyridine

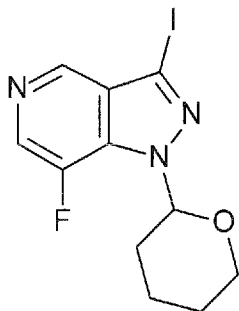
5 A mixture solution of 4-chloro-5-fluoronicotinaldehyde (12.5 g, 78.6 mmol) and hydrazine (19.6 g, 392.5 mmol) in n-BuOH (200 mL) was stirred at 130°C for 20 h. After TLC (petroleum ether:EtOAc = 5:1) showed the starting material was consumed, the solvent was removed under reduced pressure. The residual was re-dissolved in EtOAc (500 mL), and washed with water, brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (7 g, 65% yield) as a yellow solid. MS: 10 138.0 [M+H]⁺

[C] 7-Fluoro-3-iodo-1 H-pyrazolo[4,3-c]pyridine

15 To a stirred solution of 7-fluoro-1H-pyrazolo[4,3-c]pyridine (7.0 g, 51.1 mmol) and potassium carbonate (11.5 g, 204.4 mmol) in DMF (100 mL) was added iodine (26.2 g, 102.2 mmol) in portions in ice-water bath. After the addition, the reaction mixture was stirred at room temperature for 3 h before it was quenched with satd. aq. NH₄Cl solution and extracted with EtOAc (200 mL twice). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to a crude title compound (5.28 g, 40% yield) as a yellow solid. MS: 263.9 [M+H]⁺. ¹H NMR (300 MHz, MeOH-*d*₄) δ ppm 8.34 (d, J=3.20 Hz, 1 H). 8.65 (d, J=1.88 Hz, 1 H).

20

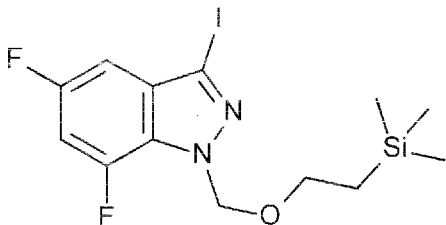
[D] 7-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridine



To a stirred mixture solution of 7-fluoro-3-iodo-1H-pyrazolo[4,3-c]pyridine (5 g, 19 mmol) and DHP (12.8 g, 152 mmol) in toluene (20 mL) was added 2,2,2-trifluoroacetic acid (434 mg, 3.8 mmol) and the resulting reaction mixture solution was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (3 g, 45.5% yield) as a white solid. MS: 348.1 [M+H]⁺.

intermediate G-6

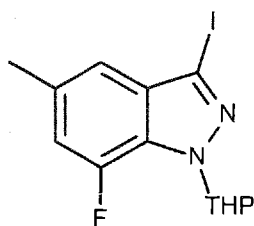
2-[(5,7-Difluoro-3-iodo-indazol-1-yl)methoxy]ethyl-trimethyl-silane



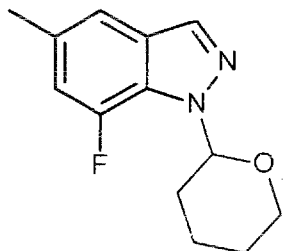
To a stirred mixture solution of 5,7-difluoro-3-iodo-1H-indazole (Intermediate G-2/Step B, 2.2 g, 7.86 mmol) and NaH (943 mg, 23.58 mmol) in DMF (20 mL) was added (2-(chloromethoxy)ethyl)trimethylsilane (1.31g, 23.58 mmol) dropwise at 0°C and stirred for 0.5 h. Afterwards, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL twice). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (2.4 g, 75% yield) as a solid. MS: 411.1 [M+H]⁺.

Intermediate G-7

7-Fluoro-3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

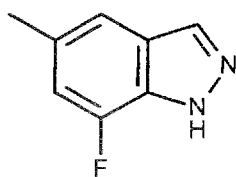


IA 1 7-Fluoro-5-methyl-1-(tetrahydro-2/-7-pyran-2-yl)-1 H-indazole



To a solution of 5-bromo-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (10 g, 33.3 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (5 g, 40 mmol) in DMF (30 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (1.92 g, 1.67 mmol) and K_2CO_3 (13.8 g, 100 mmol) in one portion and the resulting reaction mixture was stirred at 120 °C for 4 h. After cooling to room temperature, the mixture solution was diluted with EtOAc (300 mL) and washed with brine (100 mL three times). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 20:1~5:1) to afford the title compound (4.5 g, 57.7% yield) as a white solid. MS: 151.3 $[\text{M}+\text{H}]^+$.

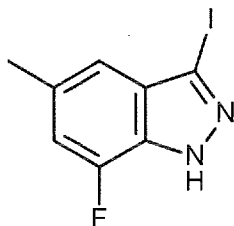
FBI 7-Fluoro-5-methyl-1 H-indazole



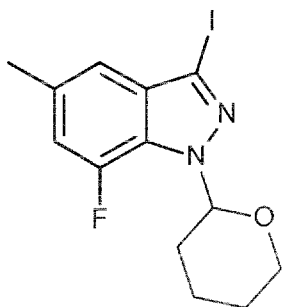
15

To a stirred solution of 7-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazole (5.8 g, 24.7 mmol) in DCM (50 mL) was added TFA (28 g, 247 mmol) and the reaction mixture was stirred at room temperature for 12 h. After TLC showed the complete consumption of starting material, the reaction mixture was concentrated in vacuo and the residue was re-dissolved in EtOAc (200 mL). The organic phase was washed with satd. aq. NaHCO_3 solution (100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (4.5 g) as a white solid. MS: 151.3 $[\text{M}+\text{H}]^+$

20

fCl 7-Fluoro-3-iodo-5-methyl-1 H-indazole

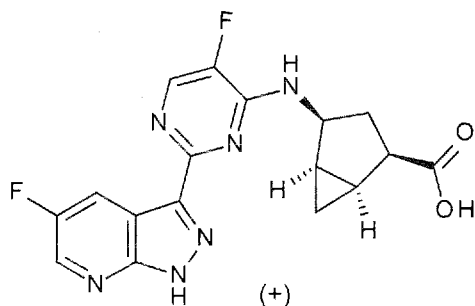
To a stirred solution of 7-fluoro-5-methyl-1 H-indazole (4.5 g 24.7 mmol) and KOH (5.5 g, 98.8 mmol) in DMF (50 mL) was added I_2 (12.5 g, 49.4 mmol) in portions at room temperature and stirred for 12 h. After TLC showed the complete consumption of the starting material, the reaction was quenched with aq. Na_2SO_3 solution (200 mL), acidified with 1 N HCl to pH = 7, and extracted with EtOAc (500 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (5.2 g) as a white solid. MS: 276.1 [M+H]⁺.

IDI 7-Fluoro-3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazole

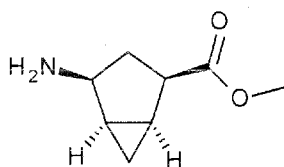
To a stirred solution of 7-fluoro-3-iodo-5-methyl-1 H-indazole (5.2 g 15.0 mmol) and 3,4-dihydro-2H-pyran (1.51 g, 18 mmol) in DCM (60 mL) was added TsOH (1.03 g, 6 mmol) at room temperature and stirred for 3 h. After TLC showed the complete consumption of the starting material, the mixture was neutralized with satd. aq. $NaHCO_3$ solution (100 mL) and extracted with EtOAc (300 mL three times). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified first by silica gel flash chromatography (petroleum ether:EtOAc = 20:1-5:1) and then Prep-HPLC to give title compound (3.2 g, 59.2% yield) as a white solid. MS: 383.0, 277.0 [M+Na]⁺ and [M+H-84]⁺. ¹H NMR (400 MHz, $CHCl_3-d_1$) δ ppm 7.04-7.00 (m, 2H), 5.84-5.81 (m, 1H), 4.09-4.06 (m, 1H), 3.77-3.72 (m, 1H), 2.63-2.59 (m, 1H), 2.47 (s, 3H), 2.19-2.11 (m, 2H), 1.79-1.76 (m, 2H), 1.74-1.62 (m, 1H).

Example 1

(+)-(1R,2S,4R,5S)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid



1A1 (+)-Methyl (1R,2S,4R,5S)-2-aminobicyclo[3.1.0]hexane-4-carboxylate

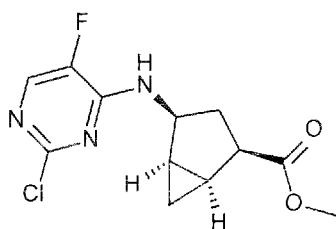


5 (+)

A solution of (+)-methyl (1R,2S,4R,5S)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-1, 400 mg, 1.6 mmol) in TFA/DCM (8 mL, 1:1) was stirred at room temperature for 3 h. Afterwards, the solvent was evaporated to dryness to give a crude title compound (500 mg) as yellow gum. MS: 156.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

10

1B1 (+)-methyl (1R,2S,4R,5S)-2-(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate

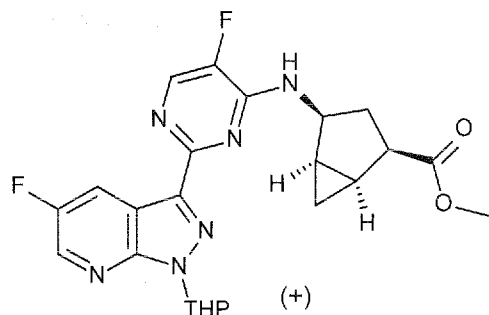


(+)

15 A stirred mixture solution of (+)-methyl (1R,2S,4R,5S)-2-aminobicyclo[3.1.0]hexane-4-carboxylate (500 mg, 1.6 mmol), 2,4-dichloro-5-fluoropyrimidine (334 mg, 2 mmol) and DIPEA (1.3 g, 10 mmol) in THF (20 mL) was heated at 60°C for 16 h. Afterwards, the solvent was evaporated to dryness to give a crude product, which was purified by silica gel flash chromatography (EtOAc/petroleum ether, 0-20% gradient) to afford the title compound (400 mg, 89% yield) as a yellow solid. MS: 286.2 [M+H]⁺

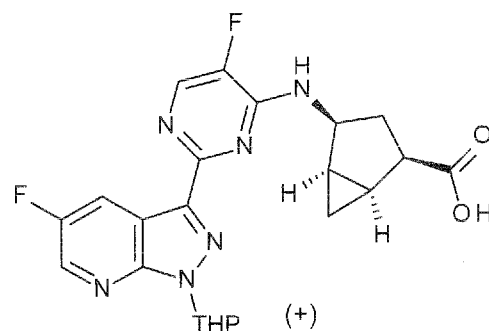
20

(+)-Methyl (1R,2S,4R,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate



- 5 A stirred mixture solution of 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 348 mg, 1 mmol), bis(pinacolato)diboron (348 mg, 1.37 mmol), KOAc (245 mg, 2.5 mmol) and Pd(dppf)Cl₂ (70 mg) in dioxane (12 mL) was heated at 100°C under microwave heating for 30 min. After cooling to room temperature, (+)-methyl (1R,2S,4R,5S)-2-[[2-chloro-5-fluoro-pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate (400 mg, 1.30 mmol), Cs₂CO₃ (650 mg, 2 mmol) and water (2 mL) were added to the above mixture and re-heated at 130°C under microwave heating for additional 1 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the title compound (30 mg, 6% yield) as a yellow solid. MS: 471.2 [M+H]⁺.

(+)-Methyl (1R,2S,4R,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid

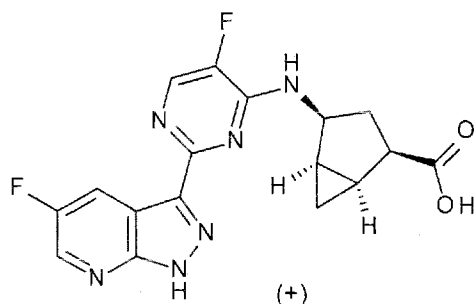


20

A solution of (+)-methyl (1R,2S,4R,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate (30 mg, 0.06 mmol) and LiOH monohydrate (200 mg, 4.7 mmol) in THF/water (10 mL, 1:1) was

stirred at room temperature for 2 h. Afterwards, the mixture was concentrated under vacuum to give a crude title compound (300 mg) as yellow gum. MS: 457.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

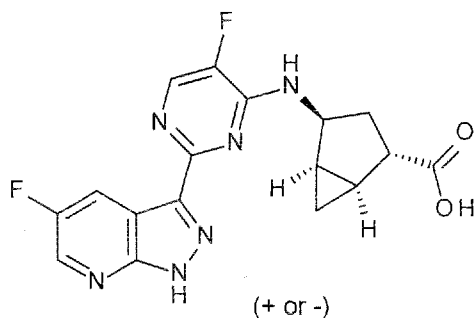
5 IE 1 (+)-(1R,2S,4R,5S)-2-ri5-Fluoro-2-(5-fluoro-1 H-pyrazoloi3.4-b1pvridin-3-vl)pvrimidin-4-vnamino1bicyclof3.1 .Olhexane-4-carboxylic acid



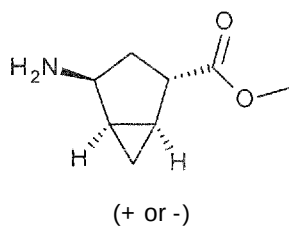
A solution of (+)-(1R,2S,4R,5S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (300 mg, 0.06 mmol) in TFA/DCM (5 mL/2 mL) was stirred at room temperature for 5 h. Afterwards, the solvent was evaporated to dryness and the residue was purified by Prep-HPLC to afford the title compound (3 mg, 16% yield) as a white solid. MS: 373.2 [M+H]⁺.

Example 2

15 **(+ or -)-(1R,2S,4S,5S)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid**

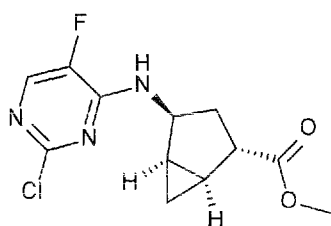


[A] (+ or -)-Methyl (1R,2S,4S,5S)-2-aminobicyclo[3.1.0]hexane-4-carboxylate



A solution of (+ or -)-methyl (1R,2S,4S,5S)-2-(feri-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-3, 900 mg, 3.5 mmol) in TFA/DCM (20 mL, 1:1) was stirred at room temperature for 3 h. Afterwards, the solvent was evaporated to dryness under reduced pressure and afforded a crude title compound (900 mg) as yellow gum. MS: 156.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

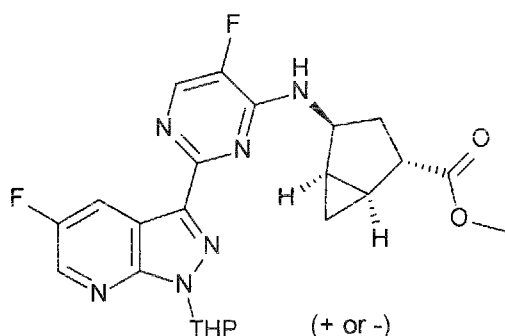
IB] (+ or -VMethyl (1R,2S,4S,5S)-2-[2-chloro-5-fluoro-pyrimidin-4-yl]amino1bicvclor3.1 .01 - hexane-4-carboxyiate



10 (+ or -)

A stirred mixture solution of (+ or -)-methyl (1R,2S,4S,5S)-2-aminobicyclo[3.1.0]hexane-4-carboxylate (900 mg, 3.5 mmol), 2,4-dichloro-5-fluoro-pyrimidine (1.5 g, 8.9 mmol) and DIPEA (10 g, 77.5 mmol) in THF (20 mL) was heated at 60°C for 16 h. Afterwards, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the title compound (500 mg, 50% yield) as a yellow solid. MS: 286.2 [M+H]⁺.

[c i (+ or -VMethyl (1R,2S,4S,5S)-2-ri5-fluoro-2-(5-fluoro-1-tetrahdropyran-2-yl)-Pyrazolo[3,4-b]pvridin-3-yl]pvrimidin-4-vllamino1bicvclor3.1 .Qlhexane-4-carboxylate

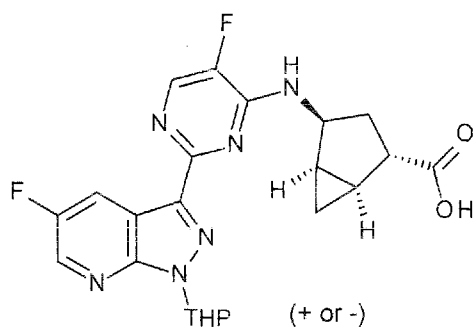


20

A stirred mixture solution of 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 348 mg, 1 mmol), bis(pinacolato)diboron (348 mg, 1.37 mmol), KOAc (245 mg, 2.5 mmol) and Pd(dppf)Cl₂ (70 mg) in dioxane (12 mL) was heated at 100°C under microwave heating for 30 min. After cooling to room temperature, (+ or -)-methyl

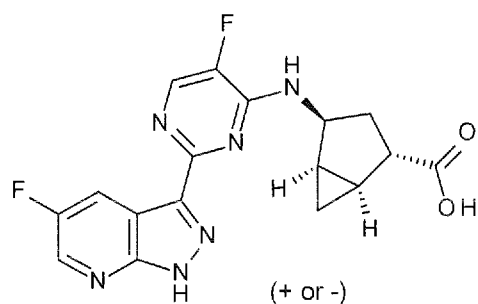
(1R,2S,4S,5S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate (400 mg, 1.39 mmol), Cs_2CO_3 (650 mg, 2 mmol) and water (2 mL) were added to the above reaction mixture and re-heated at 130°C under microwave heating for an additional 1 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0~60% gradient) to afford the title compound (25 mg, 5% yield) as a yellow solid. MS: 471.2 $[\text{M}+\text{H}]^+$.

10 [D1] (+ or -)-(1R,2S,4S,5S)-2-rr5-Fluoro-2-(5-fluoro-1-tetrahdropyran-2-yl-Dyra2olor3,4-b1pyridin-3-yl)pyrimidin-4-yllaminolbicvclof3. 1.01hexane-4-carboxylic acid



A mixture solution (+ or -)-methyl (1R,2S,4S,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydro-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate (25 mg, 0.05 mmol) and LiOH monohydrate (50 mg, 1.2 mmol) in THF/water (20 mL, 1:1) was stirred at room temperature for 2 h. Afterwards, the reaction mixture was acidified with 1N HCl to pH = 5 and extracted with EtOAc. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (50 mg) as yellow gum. MS: 457.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

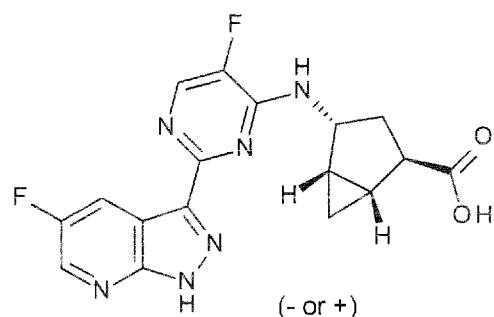
20 [EE] (+ or -)-(1R,2S,4S,5S)-2-rr5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-pyrimidin-4-ylamino]bicyclo[3.1.0]hexane-4-carboxylic acid



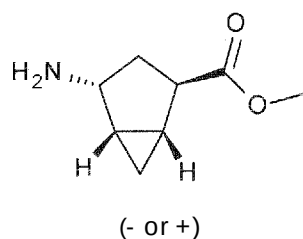
A solution of (+ or -)-(1R,2R,4R,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (50 mg, 0.05 mmol) in TFA/DCM (6 mL/ 3 mL) was stirred at room temperature for 16 h. Afterwards, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (2 mg, 11% yield) as a white solid. MS: 373.2 [M+H]⁺

Example 3

(- or +)-(1S,2R,4R,5R)-2-[[5-Fluoro-2-{5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl}pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid

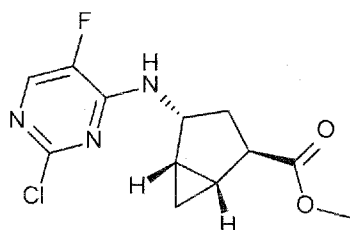


(- or +)-Methyl (1S,2R,4R,5R)-2-aminobicyclo[3.1.0]hexane-4-carboxylate



A solution of (- or +)-methyl (1S,2R,4R,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-4, 900 mg, 3.5 mmol) in TFA/DCM (15 mL, 2:1) was stirred at room temperature for 3 h. Afterwards, the solvent was evaporated to dryness under reduced pressure and afforded a crude title compound (1 g) as yellow gum. MS: 156.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

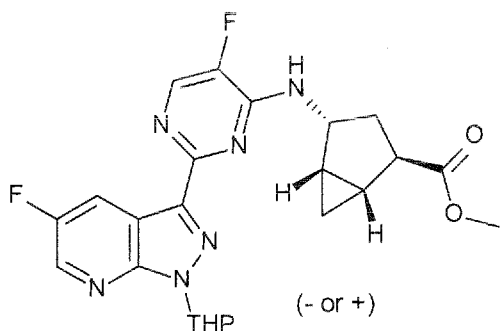
IB1 (- or +)-Methyl (1S,2R,4R,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate



(- or +)

- 5 A stirred mixture solution of (- or +)-methyl (1S,2R,4R,5R)-2-aminobicyclo[3.1.0]hexane-4-carboxylate (1 g, 3.5 mmol), 2,4-dichloro-5-fluoro-pyrimidine (2 g, 11.9 mmol) and DIPEA (10 g, 77.5 mmol) in THF (20 ml) was heated at 60°C for 16 h. After cooling to room temperature, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the title compound (600 mg, 60% yield) as a yellow solid.
 10 MS: 286.2 [M+H]⁺

[C] (- or +)-Methyl (1S,2R,4R,5R)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate



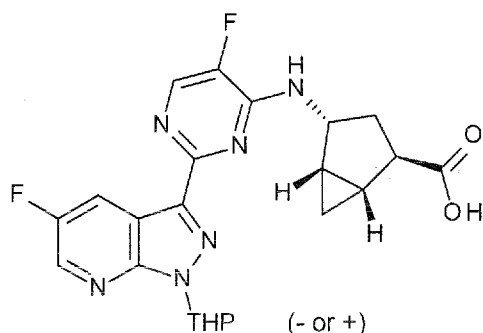
(- or +)

- 15 A stirred mixture solution of 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 348 mg, 1 mmol), bis(pinacolato)diboron (348 mg, 1.37 mmol), KOAc (245 mg, 2.5 mmol) and Pd(dppf)Cl₂ (70 mg) in dioxane (12 mL) was heated at 100°C under microwave heating for 30 min. After cooling to room temperature, (- or +)-Methyl (1S,2R,4R,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate (400 mg, 1.39 mmol). Cs₂CO₃ (650 mg, 2 mmol) and water (2 mL) were then added to the above mixture and the resulting reaction mixture was re-heated at 130°C under microwave heating for another 1 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed
 20

with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the title compound (40 mg, 6% yield) as a yellow solid. MS; 471.2 $[\text{M}+\text{H}]^+$.

5

[D] (- or +)-(1S,2R,4R,5R)-2-rr5-Fluoro-2-(5-fluoro-1-tetrahdropyran-2-yl-pyrazolof3.4-bipyridin-3-yl)pyrimidin-4-vnamino1bicvcloi3.1.0hexane-4-carboxylic acid

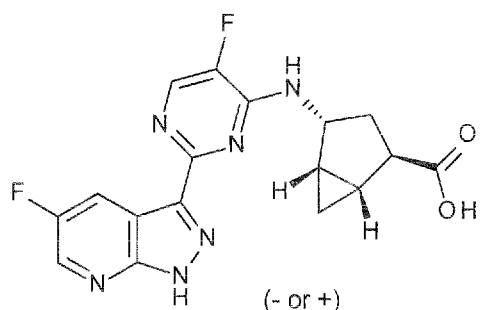


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A mixture solution of (- or +)-methyl (1S,2R,4R,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate (80 mg, 0.17 mmol) and LiOH monohydrate (200 mg, 4.7 mmol) in THF/water (20 mL, 1:1) was stirred at room temperature for 2 h. Afterwards, the mixture was acidified with 1N HCl to pH = 5 and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (50 mg) as yellow gum. MS: 457.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

15

[E] (- or +)-(1S,2R,4R,5R)-2-rr5-Huoro-2-(5-fluoro-1 /-pyrazoloi3.4-b1pyridin-3-yl)- pyrimidin-4-vllamino1bicyclof3.1.0hexane-4-carboxylic acid



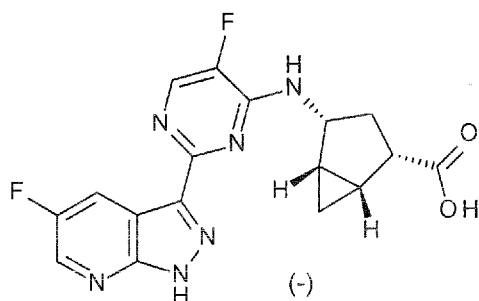
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A solution of (- or +)-(1S,2R,4R,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3.4-b]pyridin-3-yl)pyhmidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (120 mg, 0.26 mmol) in TFA (5 mL) was stirred at room temperature for 5 h. Afterwards, the

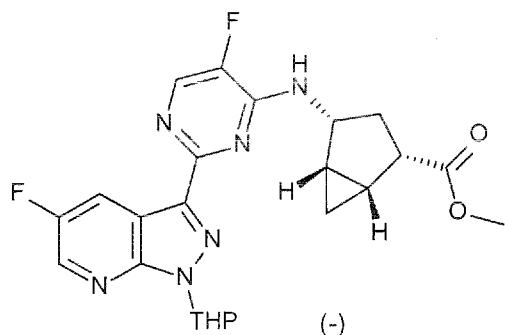
solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (5 mg, 12% yield) as a white solid. MS: 373.2 [M+Hf. ¹H NMR (400 MHz, MeOH-*d*₄) δ 0.63 (td, *J*=7.78, 5.77 Hz, 1 H) 0.71 - 0.82 (m, 1 H) 1.49 (ddd, *J*=13.61, 9.85, 8.16 Hz, 1 H) 1.69 - 1.79 (m, 1 H) 1.88 (dq, *J*=9.76, 4.11 Hz, 1 H) 2.43 (dd, *J*=13.68, 7.91 Hz, 1 H) 2.97 - 3.06 (m, 1 H) 5.20 - 5.34 (m, 1 H) 8.16 (d, *J*=3.51 Hz, 1 H) 8.53 (s, 1H) 8.62 (dd, *J*=8.16, 2.64 Hz, 1 H).

Example 4

(-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid



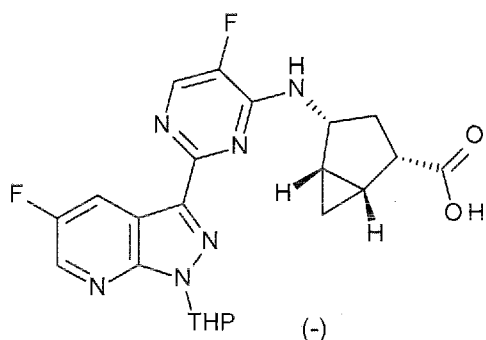
[A] (-)-Methyl (1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]aminobicyclo[3.1.0]hexane-4-carboxylate



- 15 A mixture solution of (-)-methyl (1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-7/step B, 300 mg, 1.1 mmol), hexa-n-butyltin (1 mL, 1.98 mmol) and Pd(PPh₃)₄ (200 mg) in dioxane (16 mL) was heated at 125°C under microwave heating for 1 h. After cooling down, 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1 a, 400 mg, 1.1 mmol) and
- 20 Pd(PPh₃)₄ (200 mg) were added to the above mixture and the resulting mixture was re-heated at 145°C for additional 1 h. After cooling to room temperature, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the

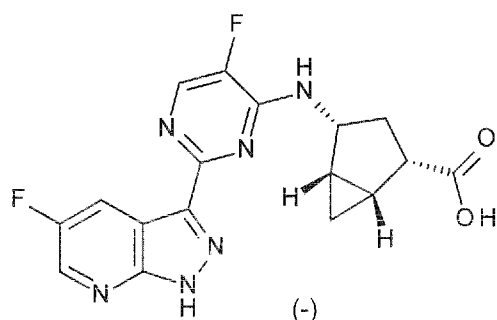
title compound (150 mg, 31% yield) as a yellow solid. MS: 471.2 [M+H]⁺.

[B] (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid



A mixture solution of (-)-methyl (1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate (150 mg, 0.32 mmol) and LiOH monohydrate (200 mg, 4.7 mmol) in THF/water (20 mL, 1:1) was stirred at room temperature for 2 h before the reaction mixture was acidified with 1N HCl to pH = 5 and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (120 mg) as yellow gum. MS: 457.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

[C] (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid

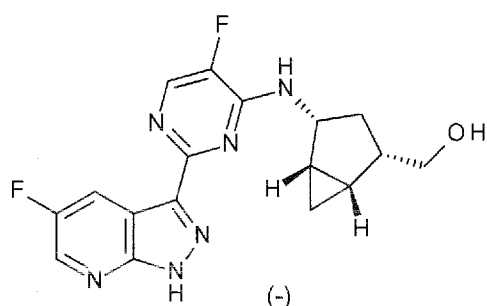


A solution of (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (120 mg, 0.26 mmol) in TFA (5 mL) was stirred at room temperature for 5 h. Afterwards, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (15 mg, 15% yield) as a white solid. MS: 373.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.28 - 0.45 (m, 1 H) 0.77 - 0.90 (m, 1 H) 1.57 -

1.81 (m, 3 H) 2.02 (dt, $J=13.18, 7.97$ Hz, 1 H) 3.00 - 3.15 (m, 1 H) 4.95 (br. s., 1 H) 8.10 (d, $J=4.52$ Hz, 1 H) 8.35 (d, $J=4.02$ Hz, 1 H) 8.45 (dd, $J=8.66, 2.38$ Hz, 1 H) 8.68 (dd, $J=2.51, 1.51$ Hz, 1 H) 11.69 - 12.73 (m, 1 H) 14.39 (br. s., 1 H).

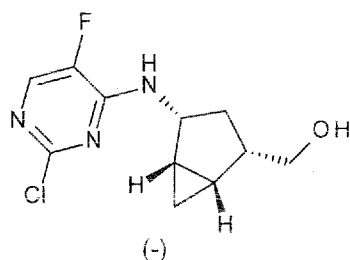
5 Example 5

(-)-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]methanol



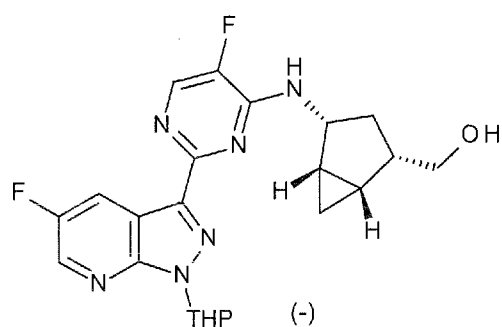
(-)-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]methanol

10 methanol



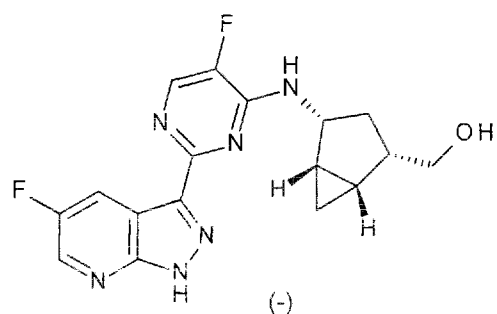
To a stirred solution of (-)-methyl (1S,2R,4S,5R)-2-[(2-chloro-5-fluorG-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-7/step B, 400 mg, 1.39 mmol) in THF (5 mL) was added LiBH_4 portion-wise at 40°C and the resulting mixture was stirred at 40°C for 2 h. The reaction was quenched with aq. KOH solution at -20°C and then extracted with DCM. The organic layer was washed with **brine**, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to give the title compound (280 mg, 78% yield) as a white solid. MS: 258.1 $[\text{M}+\text{H}]^+$

(-)-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropryan-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]methanol



in analogy to the synthesis of example 4/step A, (-)-[(1S, 2R, 4S, 5R)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]methanol (258 mg, 1 mmol) was used to give a crude product, which was then purified by silica gel flash chromatography (EtOAc/petroleum, 0-100% gradient) to afford the title compound (80 mg, 18% yield) as a yellow solid. MS: 443.2 [M+H]⁺.

[C] (-)-[(1S, 2R, 4S, 5R)-2-[(5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]methanol



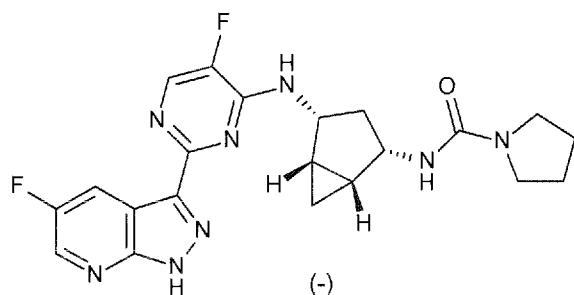
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In analogy to the synthesis of example 4/step C, (-)-[(1S, 2R, 4S, 5R)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]methanol (80 mg, 0.18 mmol) was used to give a crude product, which was then purified by Prep-HPLC to afford the title compound (10 mg, 15% yield) as a white solid. MS: 359.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.16 - 0.29 (m, 1 H) 0.70 (q, J=3.93 Hz, 1 H) 0.94 - 1.10 (m, 1 H) 1.35 - 1.46 (m, 1 H) 1.65 - 1.77 (m, 1 H) 1.90 (dt, J=13.05, 7.65 Hz, 1 H) 2.29 - 2.42 (m, 1 H) 4.54 (t, J=5.02 Hz, 1 H) 4.85 (br. s., 1 H) 7.63 (d, J=7.28 Hz, 1 H) 8.29 (d, J=3.76 Hz, 1 H) 8.48 (d, J=7.03 Hz, 1 H) 8.64 (br. s., 1 H) 14.15 (s, 1 H).

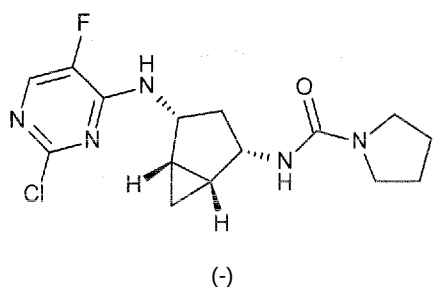
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Example 6

(-)-W-[(1R, 2S, 4R, 5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide

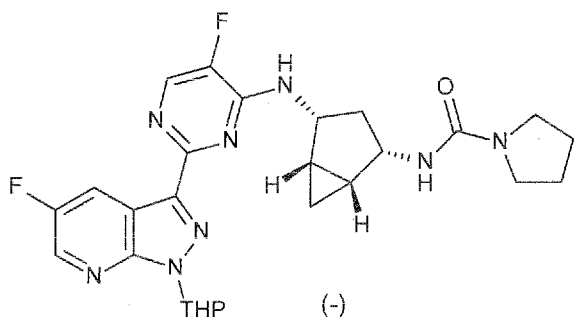


[A] (-)-N-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexan-5-yl]pyrrolidine-1-carboxamide



- 5 A stirred mixture solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino] bicyclo[3.1.0]hexane-4-carboxylic acid (Intermediate B-7/step C, 500 mg, 1.84 mmol), DPPA (800 mg, 2.9 mmol) and TEA (808 mg, 8 mmol) in toluene (10 mL) was heated at 100°C for 1 h. After cooling to room temperature, pyrrolidine (500 mg, 6.76 mmol) was added and the resulting reaction mixture was stirred at room temperature for 30 min. The mixture was then concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-80% gradient) to afford the title compound (420 mg, 67% yield) as a white solid. MS: 340.2 [M+Hf].

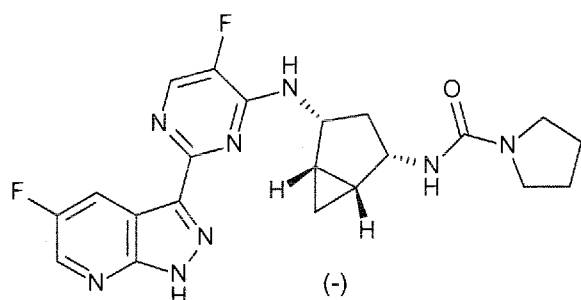
15 [B] (-)-N-[(1R,2S,4R,5S)-4-[(5-fluoro-2-(5-fluoro-1H-pyridin-2-yl)pyrazolo[3,4-b]pyridin-3-yl)amino]-2-bicyclo[3.1.0]hexan-5-yl]pyrrolidine-1-carboxamide



In analogy to the synthesis of example 4/step A, (-)-N-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexan-5-yl]pyrrolidine-1-carboxamide (300 mg, 0.88 mmol) was used to give a crude product, which was then purified by silica gel flash

chromatography (MeOH/ DCM, 0-10% gradient) to afford the title compound (140 mg, 30% yield) as a yellow solid. MS: 525.1 [M+H]⁺

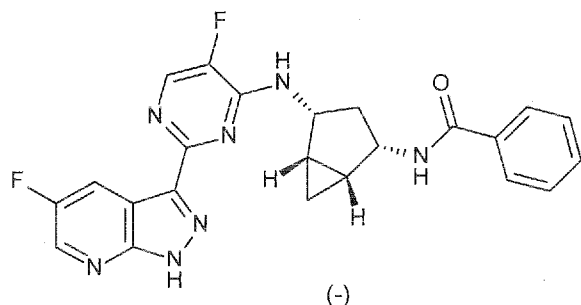
(-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide



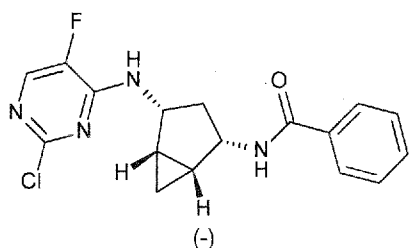
In analogy to the synthesis of example 4/step C, (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide (140 mg, 0.27 mmol) was used to give a crude product, which was then purified by Prep-HPLC to afford the title compound (20 mg, 15% yield) as a white solid. MS: 441.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.26 - 0.43 (m, 1 H) 0.99 (q, J=4.02 Hz, 1 H) 1.25 - 1.39 (m, 1 H) 1.54 - 1.63 (m, 1 H) 1.68 - 1.86 (m, 5 H) 2.12 (dt, J=12.80, 7.53 Hz, 1 H) 3.23 (t, J=6.65 Hz, 4 H) 4.35 (br. s., 1 H) 4.80 (dd, J=1.76, 0.75 Hz, 1 H) 5.79 (d, J=6.27 Hz, 1 H) 8.15 (br. s., 1 H) 8.16 (br. s., 1 H) 8.36 (d, J=4.02 Hz, 1 H) 8.46 (dd, J=8.53, 2.51 Hz, 1 H) **8.68** (dd, J=2.51, 1.51 Hz, 1 H) 13.92 - 14.69 (m, 1 H).

Example 7

(-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide

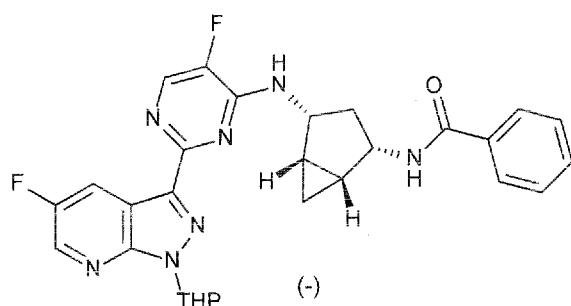


(-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide



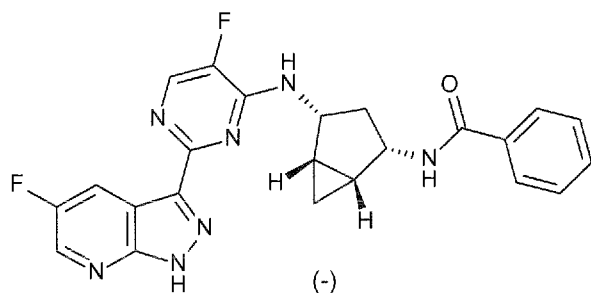
To a stirred solution of (-)-(1S,2R,4S,5R)-A/2-(2-chloro-5-fluoropyrimidin-4-yl)bicyclo[3.1.0]hexane-2,4-diamine (Intermediate B-7, 300 mg, 0.76 mmol) and TEA (500 mg, 5.0 mmol) in DCM (10 mL) was added benzoyl chloride (214 mg, 1.52 mmol) dropwise at 0°C. After the addition, the resulting mixture was allowed to warm up to room temperature and stirred for 2 h. The mixture was then evaporated to dryness under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the title compound (132 mg, 50% yield) as a solid. MS: 347.2 [M+H]⁺.

[B] (-)-N-[(1R,2S,4R,5S)-4-(2-fluoro-5-fluoro-1-tetrahydro-2-yl-pyrazolo[3,4-b]pyrimidin-3-yl)pyrimidin-2-aminol-2-bicyclo[3.1.0]hexanyl]benzamide



In analogy to the synthesis of example 4/step A, (-)-N-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]benzamide (100 mg, 0.38 mmol) was used to give a crude product, which was then purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-100% gradient) to afford the title compound (100 mg, 49% yield) as a yellow solid. MS: 532.1 [M+H]⁺.

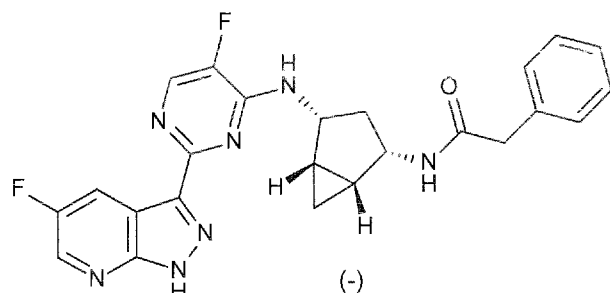
[C] (-)-N-[(1R,2S,4R,5S)-4-(2-fluoro-5-fluoro-1-H-pyrazolo[3,4-b]pyrimidin-3-yl)pyrimidin-2-aminol-2-bicyclo[3.1.0]hexanyl]benzamide



In analogy to the synthesis of example 4/step C, (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide (100 mg, 0.19 mmol) was used to give a crude product, which was then purified by Prep-HPLC to afford the title compound (15 mg, 17% yield) as a white solid. MS: 448.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.35 - 0.45 (m, 1 H) 1.03 - 1.12 (m, 1 H) 1.39 - 1.52 (m, 1 H) 1.64 - 1.72 (m, 1 H) 1.76 - 1.86 (m, 1 H) 2.23 (dt, J=12.67, 7.59 Hz, 1 H) 4.60 - 4.71 (m, 1 H) 4.88 (br. s., 1 H) 7.41 - 7.57 (m, 3 H) 7.85 - 7.91 (m, 2 H) 8.07 (br. s., 1 H) 8.35 (d, J=3.76 Hz, 1 H) 8.43 (d, J=7.28 Hz, 1 H) 8.49 (dd, J=8.53, 2.76 Hz, 1 H) 8.68 (dd, J=2.64, 1.63 Hz, 1 H) 13.93 - 14.64 (m, 1 H).

Example 8

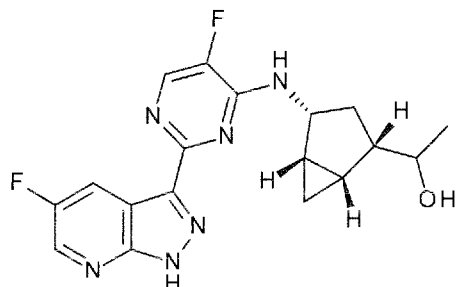
(-)-yV-[(1R,2S,4R,5S)-4-[[5-fluoro-2-{5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl}pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]-2-phenyl-acetamide



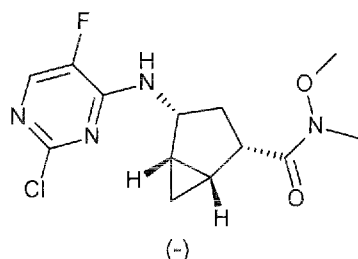
In analogy to the synthesis of example 7, 2-phenylacetyl chloride was used in step A. Following subsequent Stille coupling (step B) and de-protection of THP (step C), the title compound (12 mg, 32% yield) was obtained after Prep-HPLC purification as a white solid. MS: 462.1 [M+Hf]. ¹H NMR (400 MHz, MeOH-d₄) δ 0.56 - 0.68 (m, 1 H) 0.99 - 1.12 (m, 1 H) 1.34 (dt, J=12.96, 10.15 Hz, 1 H) 1.75 - 1.86 (m, 1 H) 1.89 - 1.98 (m, 1 H) 2.49 (dt, J=13.08, 7.76 Hz, 1 H) 2.68 (s, 1 H) 3.55 (s, 2 H) 4.62 (dd, J=7.59, 5.21 Hz, 1 H) 5.14 (br. s., 1 H) 7.22 - 7.30 (m, 1 H) 7.30 - 7.34 (m, 4 H) 8.33 (d, J=5.14 Hz, 1 H) 8.37 - 8.44 (m, 1 H) 8.62 - 8.67 (m, 1 H).

Example 9

1-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-{5-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]ethanol

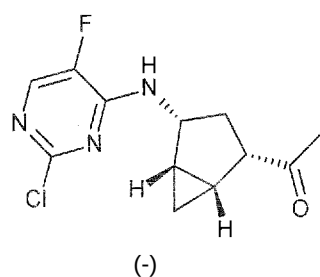


5 **1-[(1S,2R,4S,5R)-2-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]-*N*-methoxy-*N*-methyl-bicyclo[3.1.0]hexane-4-carboxamide**



To a stirred solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylic acid (Intermediate B-7/step C, 240 mg, 0.89 mmol) in DCM (15 mL) was added the Weinreb amine (262 mg, 2.67 mmol), HATU (1.32 g, 4.0 mmol) and DIEPA (1.29 g, 10 mmol) and the resulting reaction mixture was stirred at room temperature overnight. Brine was added and the mixture was extracted with DCM twice. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 30-70% gradient) to afford the title compound (210 mg, 75% yield) as light yellow oil. MS: 315.1 [M+H]⁺.

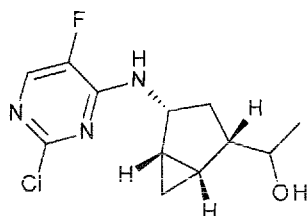
1-[(1S,2R,4S,5R)-2-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]ethanone



To a stirred solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-4-methoxy-1-methyl-bicyclo[3.1.0]hexane-4-carboxamide (170 mg, 0.54 mmol) in THF (10 mL) was added MeMgBr (3.0 M in ether, 200 μ L, 0.60 mmol) at -78°C under N₂ protection. The resulting mixture was stirred at -78°C for 1 h before it was allowed to warm up to -40°C.

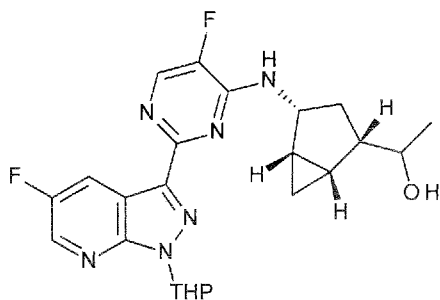
5 The reaction was quenched with satd. aq. NH₄Cl solution and the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (160 mg) as light yellow oil. MS: 270.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

10 ICJ 1-[(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]ethanol



To a stirred solution of crude (-)-1-[(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]ethanol (160 mg, 0.59 mmol) in MeOH (15 mL) was added NaBH₄ (82 mg, 2.16 mmol) at room temperature and stirred for 4 h. The mixture was evaporated to dryness under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 20-70% gradient) to afford the title compound (113 mg, 77% yield over 2 steps) as light yellow oil. MS: 272.1 [M+H]⁺.

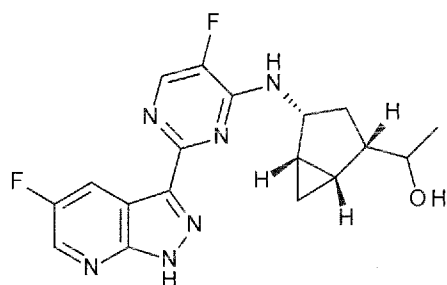
20 IP1 1-[(1S,2R,4S,5R)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)amino]-4-bicyclo[3.1.0]hexanyl]ethanol



To a stirred solution of 1-[(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]ethanol (113 mg, 0.42 mmol) in dioxane (10 mL) was added Pd(PPh₃)₄ (50 mg, 0.043 mmol) and Bu₆Sn₂ (500 mg, 0.86 mmol) and the resulting mixture

was heated to reflux for 1 h. After cooling down, 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 170 mg, 0.50 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (50 mg, 0.043 mmol) were added to the above solution and the resulting solution was re-heated to 140°C under microwave heating for 1 h. The reaction was allowed to cool back to room temperature, and volatiles were removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 20~70% gradient) to afford the title compound (34 mg, 15% yield) as light yellow oil. MS: 457.1 $[\text{M}+\text{H}]^+$.

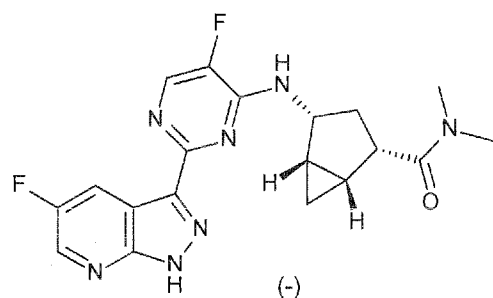
[E] 14(1S,2R,4S,5R)-2-ir5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ylaminol-4-bicyclo[3.1.0]hexan-1-ol



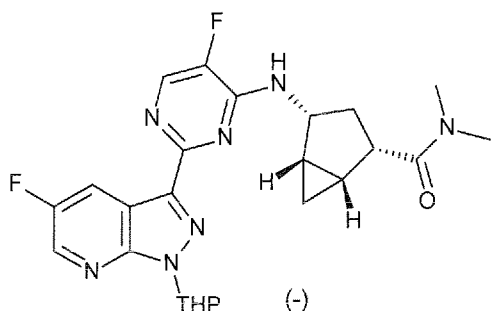
A solution of 1-[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexan-1-ol] (34 mg, 0.074 mmol) in 30% TFA in DCM (5 mL) was stirred at room temperature for 2 h. After the mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC to afford the title compound (2.3 mg, 8% yield) as white powder. MS: 373.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.55 (s, 2 H), 8.14 (d, $J = 4$ Hz, 1 H), 5.00 - 5.18 (m, 1 H), 3.52 - 3.69 (m, 1 H), 2.20 - 2.39 (m, 1 H), 2.04 (s, 1 H), 1.78 - 1.91 (m, 1 H), 1.58 - 1.73 (m, 1 H), 1.19 (d, $J = 6$ Hz, 3 H), 0.90 - 1.09 (m, 1 H), 0.78 (d, $J = 5$ Hz, 1 H), 0.41 (d, $J = 5$ Hz, 1 H).

Example 10

(-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N,N-dimethyl-bicyclo[3.1.0]hexan-4-carboxamide

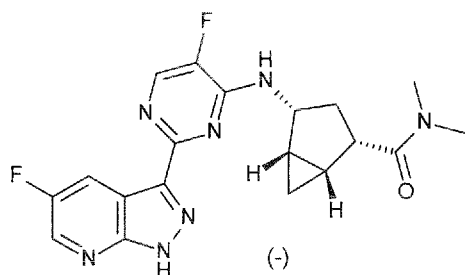


1A 1 (-)-(1S,2R,4S,5R)-2-rr5-Fluoro-2-(5-fluoro-1-tetrahdropyran-2-yl-pyrazolof3.4-blpyndin-3-yl)pynmidin-4-vnaminol-A/,A/-dimethyl-bicvcloi3.1 .01hexane-4-carboxamide



To a solution of (-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (example 4/step B, 28 mg, 0.061 mmol) in DCM (15 mL) was added dimethylamine HCl salt (20 mg, 0.25 mmol), HATU (114 mg, 0.30 mmol) and DIPEA (300 mg, 2.33 mmol) and the resulting mixture solution was stirred at room temperature overnight. Aqueous HCl solution was added to adjust pH to 3 - 4 and the mixture was extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford a crude title compound (35 mg) as yellow oil. MS: 484.1 [M+H]⁺. This crude product was used directly in the next step without further purifications.

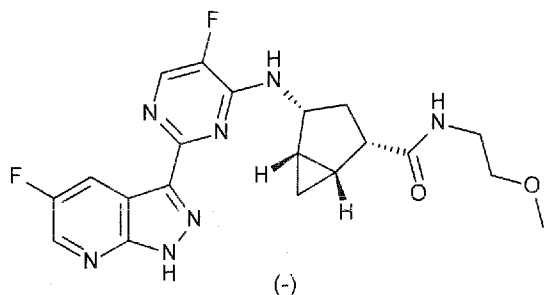
15 fB] (-)-(1S,2R,4S,5R)-2-rr5-Fluoro-2-(5-fluorch1H-Pyrazolo [3,4-b]pyridin-3-yl)pyrimidin-4-ylamino]-N,N-dimethyl-bicyclo[3.1.0]hexane-4-carboxamide



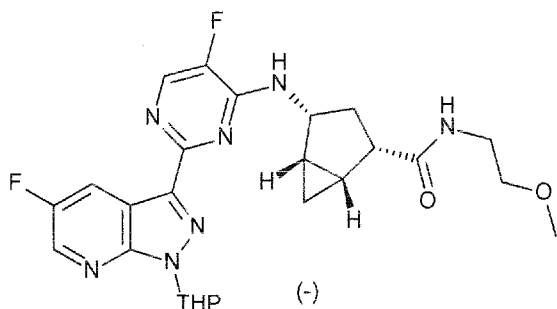
The crude (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N,N-dimethyl-bicyclo[3.1.0]hexane-4-carboxamide (35 mg, 0.072 mmol) was treated with 30% TFA in DCM (5 mL) for 2 h at room temperature. After the mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC to afford the title compound (10.6 mg, 43% yield over 3 steps) as white powder. MS: 400.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.47 - 8.64 (m, 2 H), 8.16 (d, J=4 Hz, 1 H), 5.03 - 5.18 (m, 1 H), 3.51 - 3.61 (m, 1 H), 3.24 (s, 3 H), 3.00 (s, 3 H), 2.07 - 2.23 (m, 1 H), 1.65 - 1.90 (m, 3 H), 0.90 - 1.07 (m, 1 H), 0.37 - 0.51 (m, 1 H).

Example 11

(-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-(2-methoxyethyl)bicyclo[3.1.0]hexane-4-carboxamide

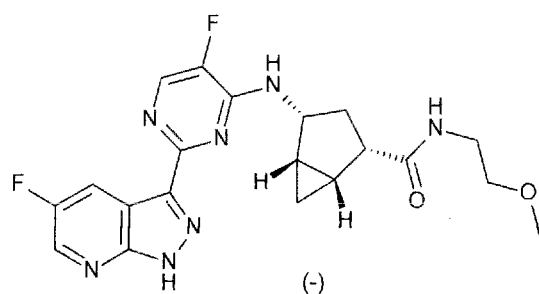


[A] (-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino-1-A-(2-methoxyethyl)bicyclo[3.1.0]hexane-4-carboxamide



To a stirred solution of (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino)bicyclo[3.1.0]hexane-4-carboxylic acid (example 4/step B, 28 mg, 0.061 mmol) in DCM (15 mL) was added 2-methoxyethanamine (20 mg, 0.25 mmol), HATU (114 mg, 0.30 mmol) and DIPEA (300 mg, 2.33 mmol) and the resulting mixture solution was stirred at room temperature overnight. Aqueous HCl solution was added to adjust pH to 3 - 4 and the mixture was extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to afford a crude title compound (48 mg) as yellow oil. MS: 514.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

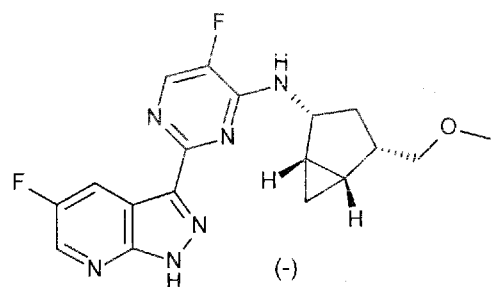
[B] (-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino-1-A-(2-methoxyethyl)bicyclo[3.1.0]hexane-4-carboxamide



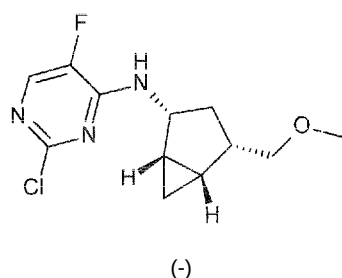
The crude (1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-N-(2-methoxyethyl)bicyclo[3.1.0]hexane-4-carboxamide (48 mg) was treated with 30% TFA in DCM (5 mL) for 2 h at room temperature. After the mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC to afford the title compound (6.7 mg, 26% yield over 2 steps) as white powder. MS: 430.3 [M+H]⁺. ¹H NMR (400 MHz, MeOH-c/4) δ 8.51 - 8.60 (m, 2 H) 8.16 (d, J = 4 Hz, 1 H) 5.10 (t, J = 11 Hz, 1 H) 3.50 (d, J = 5 Hz, 2 H) 3.39 - 3.45 (m, 2 H) 3.39 (s, 3 H) 3.14 (td, J = 8, 4 Hz, 1 H) 2.22 (dt, J = 13, 8 Hz, 1 H), 1.81 - 1.92 (m, 1 H). 1.54 - 1.74 (m, 2 H), 0.96 - 1.04 (m, 1 H), 0.43 - 0.55 (m, 1 H).

Example 12

(-)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-[(1S,2R,4S,5R)-4-(methoxymethyl)-2-bicyclo[3.1.0]hexanyl]pyrimidin-4-amine



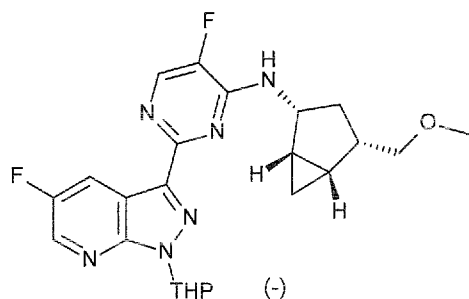
[A] (-)-2-Chloro-5-fluoro-N-[(1S,2R,4S,5R)-4-(methoxymethyl)bicyclo[3.1.0]hexan-2-yl]pyrimidin-4-amine



To a stirred solution of (-)-[(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]methanol (example 5A, 150 mg, 582 μmol) in THF (20 mL) was

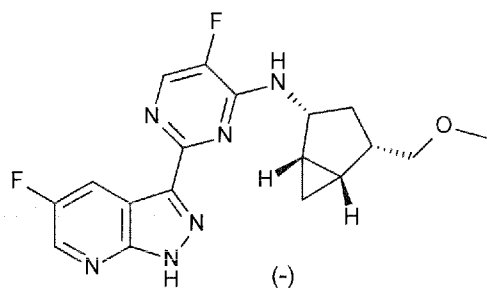
added sodium hydride (34.9 mg, 1.46 mmol) and iodomethane (124 mg, 873 μmol) at room temperature and the resulting reaction mixture was stirred for 3 h. The reaction was quenched with satd. aq. NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 20-70% gradient) to afford the title compound (50 mg, 25% yield) as light yellow oil. MS: 272.1 $[\text{M}+\text{H}]^+$

[B] (-)-5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4S,5R)-4-(methoxymethyl)-2-bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine



To a stirred solution of (-)-2-chloro-5-fluoro-N-((1S,2R,4S,5R)-4-(methoxymethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine (50 mg, 184 μmol) in dioxane (10 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (42.5 mg, 36.8 μmol) and Bu_6Sn_2 (213 mg, 368 μmol) and the resulting mixture was heated to reflux for 2 h. After cooling down, 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 77 mg, 221 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (42.5 mg, 36.8 μmol) were added to the above mixture and the resulting mixture was re-heated to 140°C under microwave heating for 1 h. After cooling down and removal of the volatiles, the residue was purified by silica gel flash chromatography (hexane/EtOAc, 20-80% gradient) to afford the title compound (45 mg, 54 % yield) as light yellow oil. MS: 457.1 $[\text{M}+\text{H}]^+$.

[C] (-)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4S,5R)-4-(methoxymethyl)-2-bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine

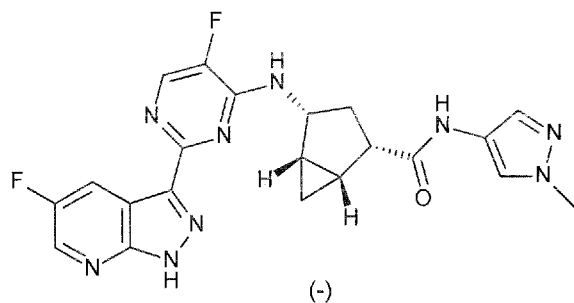


(-)-5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)-N-

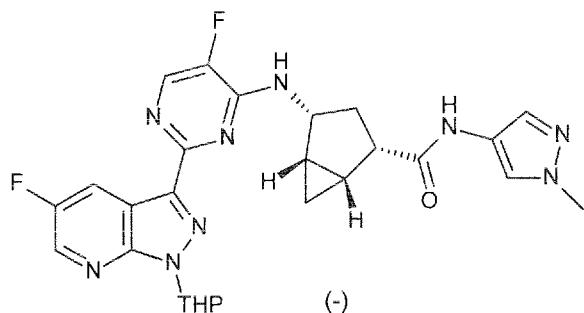
[(1S,2R,4S,5R)-4-(methoxymethyl)-2-bicyclo[3.1.0]hexanyl]pyrimidin-4-amine (48 mg, 0.1 mmol) was treated with 30% TFA in DCM (5 mL) for 30 min at room temperature. After the mixture was concentrated under reduced pressure, the residue was purified by Prep-HPLC to afford the title compound (3.3 mg, 9% yield) as white powder. MS: 373.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.39 - 8.66 (m, 2 H), 8.22 (d, J = 7 Hz, 1 H), 5.26 - 5.45 (m, 1 H), 3.60 (d, J = 7 Hz, 2 H), 3.39 (d, J = 3 Hz, 3 H), 2.40 - 2.60 (m, 1 H), 2.05 (d, J = 6 Hz, 1 H), 1.85 - 2.00 (m, 1 H), 1.63 (brs, 1 H), 1.54 (brs, 1 H), 1.00 - 1.16 (m, 1 H), 0.56 - 0.75 (m, 1 H).

Example 13

(-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-(1-methylpyrazol-4-yl)bicyclo[3.1.0]hexane-4-carboxamide

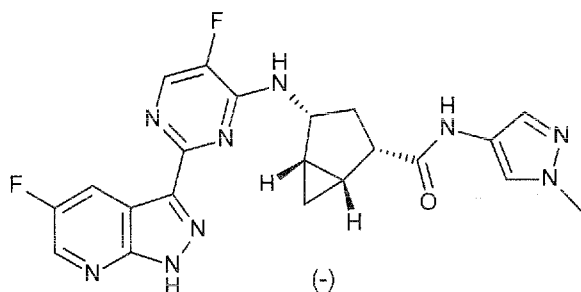


IA 1 (-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-(1-methylpyrazol-4-yl)bicyclo[3.1.0]hexane-4-carboxamide



To a stirred mixture solution of EDC (56 mg, 292 μmol), DMAP (75 mg, 613 μmol), and 1-methyl-1H-pyrazol-4-amine (18 mg, 184 μmol) in DCM (15 mL) was added (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (example 4/step B, 56 mg, 123 μmol) and the resulting mixture was stirred at room temperature overnight. After the mixture was concentrated under reduced pressure, the crude product (132 mg) was used directly in the next step without further purification. MS: 536.1 [M+H]⁺

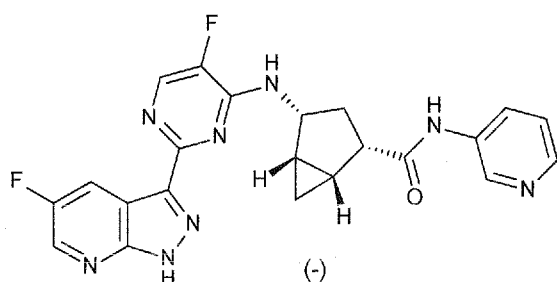
Example 13 (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-(1-methylpyrazol-4-yl)bicyclo[3.1.0]hexane-4-carboxamide



To the crude (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-(1-methylpyrazol-4-yl)bicyclo[3.1.0]hexane-4-carboxamide (132 mg, 0.25 mmol) in DCM (10 mL) was added TFA (5 g, 3.38 mL, 43.9 mmol). The resulting mixture was stirred at room temperature for 1 h. After the mixture solution was concentrated under reduced pressure, the crude product was subjected to Prep-HPLC purification to afford the title compound (7 mg, 13% yield over 2 steps) as white powder. MS: 452.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH) δ 8.47 - 8.69 (m, 2 H), 8.17 (d, J = 4 Hz, 1 H), 7.90 (s, 1 H), 7.53 (s, 1 H), 5.10 - 5.18 (m, 1 H), 3.88 (s, 3 H), 3.20 - 3.28 (m, 1 H), 2.19 - 2.33 (m, 1 H), 1.87 - 1.98 (m, 1 H), 1.63 - 1.81 (m, 2 H), 1.00 - 1.13 (m, 1 H), 0.43 - 0.58 (m, 1 H).

Example 14

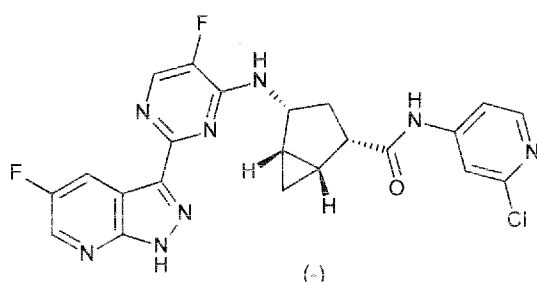
Example 14 (-)-(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-(3-pyridyl)bicyclo[3.1.0]hexane-4-carboxamide



In analogy to the synthesis of example 13, pyridin-3-amine was used in step A. After de-protection of THP (step B), Prep-HPLC purification then afforded the title compound (11.1 mg, 19% yield over 2 steps) as white powder. MS: 449.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 8.80 (d, J = 2 Hz, 1 H), 8.56 (brs, 2 H), 8.28 (brs, 2 H), 8.18 (d, J = 4 Hz, 1 H), 7.31 - 7.52 (m, 1 H), 5.09 - 5.26 (m, 1 H), 2.20 - 2.34 (m, 2 H), 1.83 (brs, 3 H), 1.10 (brs, 1 H), 0.54 (d, J = 6 Hz, 1 H).

Example 15

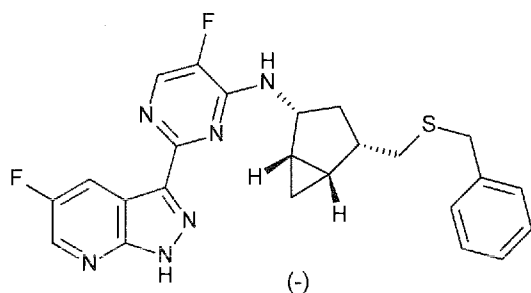
10 **(-)-(1S,2R,4S,5R)-4-(2-Chloro-4-pyridyl)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxamide**



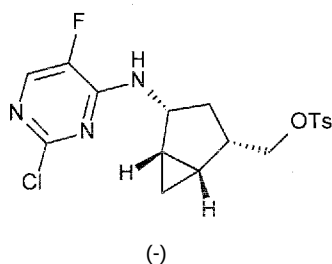
In analogy to the synthesis of example 13, 2-chloropyridin-4-amine was used in step A. After de-protection of THP (step B). Prep-HPLC purification then afforded the title compound (6.2 mg, 10% yield over 2 steps) as white powder. MS: 483.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH) δ 8.47 - 8.71 (m, 2 H), 8.15 - 8.29 (m, 2 H), 7.87 (d, J = 2 Hz, 1 H), 7.56 (dd, J = 6, 2 Hz, 1 H), 5.18 (brs, 1 H), 2.19 - 2.32 (m, 2 H), 1.75 - 1.97 (m, 3 H), 1.06 (d, J = 5 Hz, 1 H), 0.53 (d, J = 7 Hz, 1 H).

20 Example 18

(-)-4-[(1S,2R,4S,5R)-4-(Benzylsulfanylmethyl)-2-bicyclo[3.1.0]hexanyl]-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine

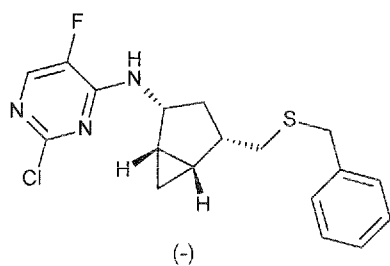


[A] (-)-r(1S,2R,4S,5R)-2-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]-4-methylbenzenesulfonate



- 5 To a stirred solution of (-)-[(1S,2R,4S,5R)-2-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]methanol (example 5/step A, 500 mg, 1.94 mmol) in DCM (40 mL) was added TsCl (1.11 g, 5.82 mmol) and Et₃N (295 mg, 406 μL, 2.91 mmol) and the resulting mixture was stirred at room temperature overnight. After the mixture was concentrated under reduced pressure, the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30-70% gradient) to afford the title compound (642 mg, 80% yield) as light yellow oil. MS: 412.4 [M+H]⁺.
- 10

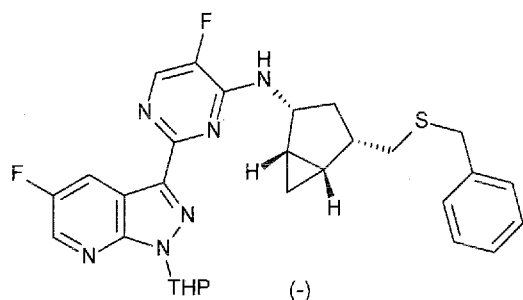
[B] (-)-N-[(1S,2R,4S,5R)-4-(benzylsulfanyl)methyl]-2-bicyclo[3.1.0]hexan-2-chloro-5-fluoro-pyrimidin-4-amine



- 15 To a stirred solution of (-)-[(1S,2R,4S,5R)-2-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]methyl 4-methylbenzenesulfonate (320 mg, 777 μmol) in THF (10 mL) was added NaH (74.6 mg, 3.11 mmol) and phenylmethanethiol (145 mg, 1.17 mmol) and the resulting mixture was stirred at room temperature overnight. The mixture was treated with aqueous HCl solution and extracted with EtOAc. The organic layer was washed with
- 20 brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude

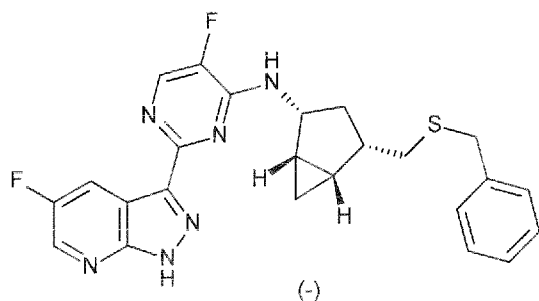
product, which was then purified by silica gel flash chromatography (hexane/EtOAc, 30-70% gradient) to afford the title compound (100 mg, 35% yield) as light yellow oil. MS: 364.4 [M+H]⁺

- 5 [C] (-)-N-[(1S,2R,4S,5R)-4-(benzylsulfanylmethyl)-2-bicyclo[3.1.0]hexanyl]-2-chloro-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-4-amine



- To a stirred solution of (-)-N-[(1S,2R,4S,5R)-4-(benzylsulfanylmethyl)-2-bicyclo[3.1.0]hexanyl]-2-chloro-5-fluoro-pyrimidin-4-amine (100 mg, 275 μmol) in dioxane (10 mL) was added Pd(PPh₃)₄ (63.5 mg, 55 μmol) and Bu₄Sn₂ (319 mg, 550 μmol) and the resulting mixture was heated to 125°C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 124 mg, 357 μmol) and second batch of Pd(PPh₃)₄ (63.5 mg, 55 μmol) were added into the above mixture. The resulting reaction mixture was re-heated to 145°C under microwave heating for additional 1 h. After the mixture was concentrated in vacuo, the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30-80% gradient) to afford the title compound (33 mg, 22% yield) as light yellow oil. MS: 549.1 [M+H]⁺

- 20 [D] (-)-N-[(1S,2R,4S,5R)-4-(benzylsulfanylmethyl)-2-bicyclo[3.1.0]hexanyl]-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-4-amine

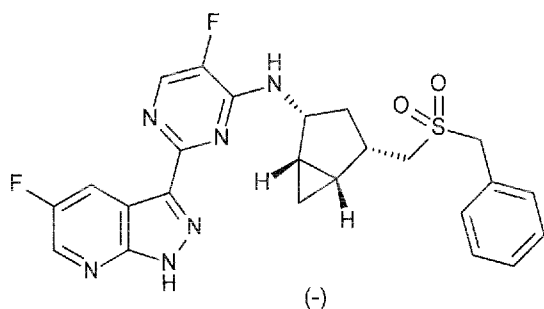


To a stirred solution of (-)-N-[(1S,2R,4S,5R)-4-(benzylsulfanylmethyl)-2-bicyclo[3.1.0]hexanyl]-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-4-amine (60 mg, 109 μmol) in DCM (5 mL) was added TFA (3 g, 26.3 mmol) and the

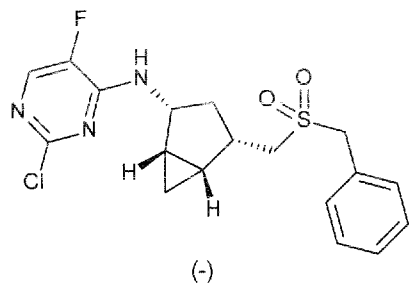
resulting mixture was stirred at room temperature for 1 h. After the mixture was concentrated in vacuo, the crude product was subject to Prep-HPLC purification to afford the title compound (2.6 mg, 5% yield) as white powder. MS: 465.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.59 (brs, 1 H), 8.46 - 8.54 (m, 1 H), 8.09 - 8.29 (m, 1 H), 7.16 - 7.39 (m, 5 H), 4.95 - 5.08 (m, 1 H), 3.80 (s, 2 H), 2.43 - 2.66 (m, 3 H), 2.15 - 2.30 (m, 1 H), 1.78 - 1.91 (m, 1 H), 1.54 - 1.70 (m, 1 H), 1.00 (d, J = 13 Hz, 1 H), 0.73 (d, J = 6 Hz, 1 H), 0.39 (d, J = 6 Hz, 1 H).

Example 17

(-)-W-[(1S,2R,4S,5R)-4-(benzylsulfonylmethyl)-2-bicyclo[3.1.0]hexanyl]-5-fluoro-2-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine

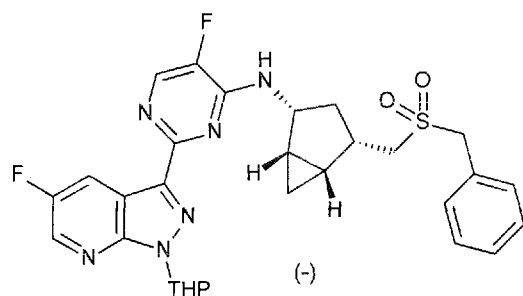


17.1 (-)-W-[(1S,2R,4S,5R)-4-(benzylsulfonylmethyl)-2-bicyclo[3.1.0]hexan-2-yl]-5-fluoro-2-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine



To a stirred solution of (-)-W-[(1S,2R,4S,5R)-4-(benzylthiomethyl)bicyclo[3.1.0]hexan-2-yl]-2-chloro-5-fluoropyrimidin-4-amine (example 16/step B, 70 mg, 192 μmol) in DCM (5 mL) was added 3-chlorobenzoperoxoic acid (133 mg, 769 μmol) and the resulting mixture was stirred at room temperature for 2 h. The mixture solution was then washed sequentially with satd. aq. NaHCO₃, Na₂SO₃ solution and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 30-70% gradient) to afford the title compound (65 mg, 86% yield) as white foam. MS: 396.1 [M+H]⁺.

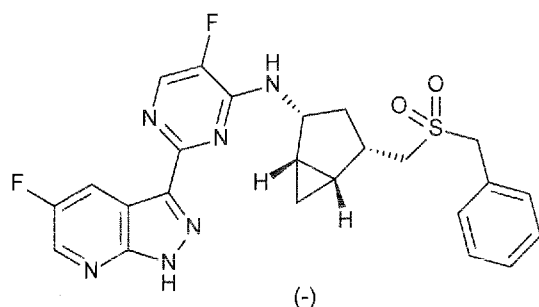
[B] (-)-N-((1S,2R,4S,5R)-4-(benzylsulfonylmethyl)-2-bicyclo[3.1.0]hexan-5-yl)-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine



To a stirred mixture solution of *N*-((1*S*,2*R*,4*S*,5*R*)-4-(benzylsulfonylmethyl)-2-

- 5 bicyclo[3.1.0]hexanyl]-2-chloro-5-fluoro-pyrimidin-4-amine (65 mg, 164 μmol) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (37.9 mg, 32.8 μmol) in dioxane (10 mL) was added Bu_6Sn_2 (190 mg, 328 μmol) and the resulting mixture was heated to 125°C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (Intermediate A-1a, 68.4 mg, 197 μmol) and second batch of $\text{Pd}(\text{Ph}_3\text{P})_4$ (37.9 mg, 32.8 μmol) were added into the above mixture and the reaction mixture was re-heated to 145°C under microwave heating for additional 1 h. After the mixture was concentrated under reduced pressure, the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30-80% gradient) to afford the title compound (30 mg, 32% yield) as light yellow oil. MS: 580.1 $[\text{M}+\text{H}]^+$

15 [C] (-)-N-((1S,2R,4S,5R)-4-(benzylsulfonylmethyl)-2-bicyclo[3.1.0]hexanyl]-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine



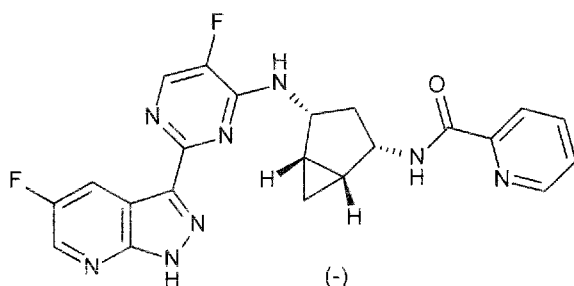
To a stirred solution of (-)-*N*-((1*S*,2*R*,4*S*,5*R*)-4-(benzylsulfonylmethyl)-2-bicyclo[3.1.0]hexanyl]-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-*b*]pyridin-

- 20 yl)pyrimidin-4-amine (30 mg, 51.7 μmol) in DCM (2 mL) was added TFA (58.9 mg, 39.8 μmol , 517 μmol) and the resulting mixture was stirred at room temperature for 3 h. After the mixture was concentrated under reduced pressure, the crude product was purified by Prep-HPLC to afford the title compound (4 mg, 15% yield) as white powder. MS: 497.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, MeOH-*d*/4) δ 8.44 - 8.71 (m, 2 H), 8.08 - 8.29 (m, 1 H), 7.25 - 7.57 (m, 5

H), 5.04 - 5.14 (m, 1 H), 4.39 - 4.55 (m, 2 H), 3.25 (dd, $J = 14, 7$ Hz, 1 H), 3.05 - 3.15 (m, 1 H), 2.89 - 3.03 (m, 1 H), 2.30 - 2.49 (m, 1 H), 1.79 - 1.94 (m, 1 H), 1.67 - 1.78 (m, 1 H), 1.06 - 1.20 (m, 1 H), 0.68 - 0.77 (m, 1 H), 0.40 - 0.52 (m, 1 H).

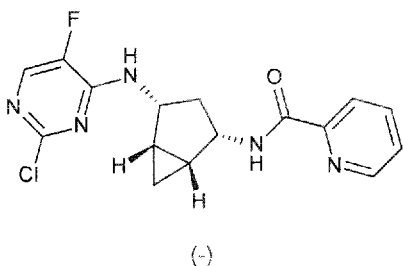
5 **Example 18**

(-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropran-2-yl)pyridin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanylpyridine-2-carboxamide



[A] (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropran-2-yl)pyridin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanylpyridine-2-carboxamide

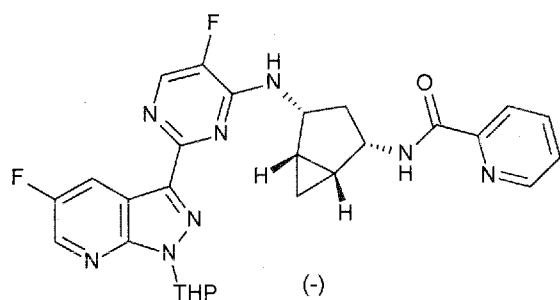
10



To a stirred solution of (-)-(1S,2R,4S,5R)-N-[(2-chloro-5-fluoro-pyrimidin-4-yl)bicyclo[3.1.0]hexane-2,4-diamine (Intermediate B-7, 48.5 mg, 200 μ mol) in DCM (10 mL) was added picolinic acid (98.5 mg, 800 μ mol), HATU (304 mg, 800 μ mol) and DIPEA (258 mg, 349 μ mol, 2 mmol). The resulting mixture was stirred at room temperature overnight before it was concentrated in vacuo. The crude product was then purified by silica gel flash chromatography (hexane/EtOAc, 30-80% gradient) to afford the title compound (43 mg, 62% yield) as light yellow oil. MS: 348.1 [M+Hf].

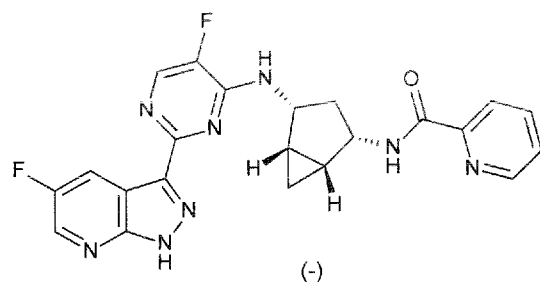
15

20 fB] N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropran-2-yl)pyridin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanylpyridine-2-carboxamide



To a stirred mixture solution of (-)-A-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]pyridine-2-carboxamide (43 mg, 124 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (28.6 mg, 24.7 μmol) in dioxane (10 mL) was added Bu_6Sn_2 (143 mg, 247 μmol). The resulting reaction mixture was heated to 125°C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 55.8 mg, 161 μmol) and second batch of $\text{Pd}(\text{PPh}_3)_4$ (28.6 mg, 24.7 μmol) were added to the above solution and the reaction mixture was re-heated to 145°C under microwave heating for additional 1 h. The mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 30-80% gradient) to afford the title compound (40 mg, 61% yield) as light yellow oil. MS: 533.1 $[\text{M}+\text{H}]^+$.

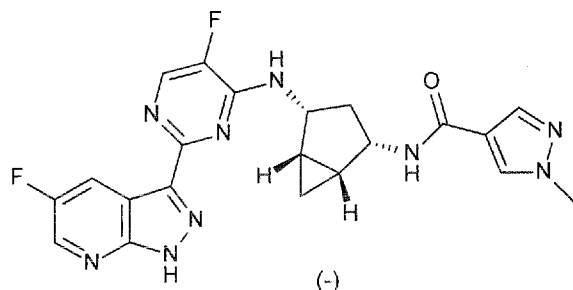
Cl (-)-A-[(1R,2S,4R,5S)-4-[(5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]pyridine-2-carboxamide



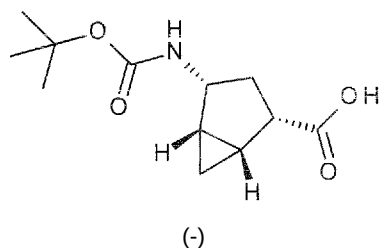
To a stirred solution of A-[(1R,2S,4R,5S)-4-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyridine-2-carboxamide (40 mg, 75.1 μmol) in DCM (4 mL) was added TFA (85.6 mg, 57.9 μmol , 751 μmol) and the resulting mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and the crude product was purified by Prep-HPLC to afford the title compound (4.3 mg, 12% yield) as white powder. MS: 449.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.67 (d, J = 5 Hz, 1 H), 8.60 (brs, 2 H), 8.20 - 8.32 (m, 1 H), 8.13 (s, 1 H), 8.00 (d, J = 2 Hz, 1 H), 7.54 - 7.66 (m, 1 H), 5.11 - 5.27 (m, 1 H), 2.46 - 2.62 (m, 1 H), 1.77 - 2.12 (m, 3 H), 1.63 (brs, 1 H), 1.11 (d, J = 6 Hz, 1 H), 0.62 (d, J = 6 Hz, 1 H).

Example 19

(-)-W4(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4 -b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]-1-methyl-pyrazole-4-carboxamide



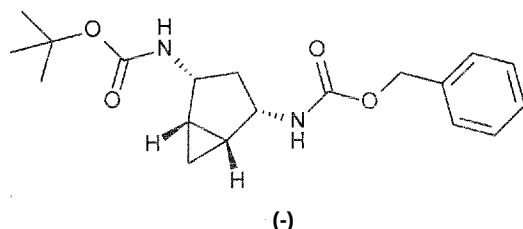
5 1A1 (-)-(1S,2R,4S,5R)-2-(tert-Butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylic acid



To a stirred solution of (-)-methyl (1S,2R,4S,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-2, 11.8 g, 46.2 mmol) in THF/water (25/25 mL, 1:1) was added LiOH·H₂O (2.21 g, 92.4 mmol). The resulting mixture was stirred at room temperature for 2 h before aqueous HCl was added to adjust pH = 4, and extracted with EtOAc. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford a crude title compound (11.2 g) as a light yellow solid. MS. 242.1 [M+H⁺]. This crude product was used directly in the next step without further purification.

15

1B1 H-tert-Butyl N-((1S,2R,4S,5R)-4-(benzyloxycarbonylamino)-2-bicyclo[3.1.0]hexanyl)-carbamate

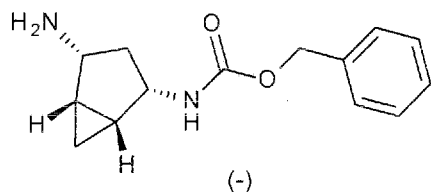


To a stirred solution of (-)-(1S,2R,4S,5R)-2-(tert-butoxycarbonylamino)bicyclo[3.1.0]hexane-4-carboxylic acid (5 g, 20.7 mmol) in toluene (20 mL) was added diphenyl phosphorazidate (8.55 g, 31.1 mmol) and TEA (6.29 g, 62.2 mmol) and the resulting mixture was heated to reflux for 2 h. After cooling down, phenylmethanol (3.36 g, 31.1 mmol) was added and the

resulting mixture solution was refluxed overnight. After the mixture was concentrated under reduced pressure, the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30-80% gradient) to afford the title compound (5.6 g, 78% yield) as light yellow oil. MS: 347.1 [M+Hf.

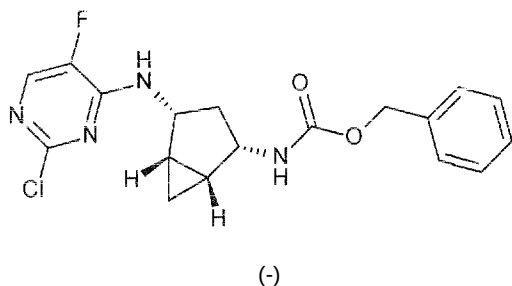
5

[C] (-)-Benzyl *N*-[(1*R*,2*S*,4*R*,5*S*)-4-amino-2-bicyclo[3.1.0]hexanyl]carbamate



To a stirred solution of (-)-tert-butyl *N*-[(1*S*,2*R*,4*S*,5*R*)-4-(benzyloxycarbonylamino)-2-bicyclo[3.1.0]hexanyl]carbamate (1.2 g, 3.46 mmol) in DCM (5 ml) was added TFA (3.95 g, 2.67 ml, 34.6 mmol). The mixture solution was stirred at room temperature for 3 h before it was concentrated under reduced pressure to give a crude title compound (900 mg, 100% yield) as light yellow oil. This crude product was used directly in the next step without further purification. MS: 247.1 [M+H]⁺.

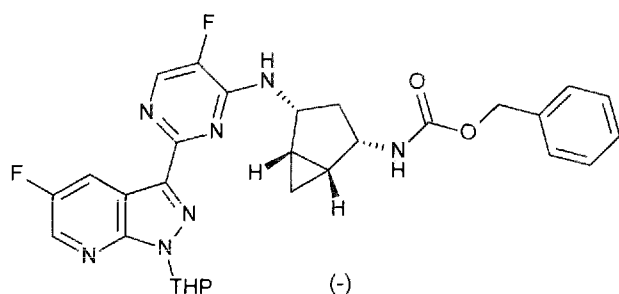
15 [D] (-)-Benzyl *N*-[(1*R*,2*S*,4*R*,5*S*)-4-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]carbamate



To a stirred solution of (-)-benzyl *N*-[(1*R*,2*S*,4*R*,5*S*)-4-amino-2-bicyclo[3.1.0]hexanyl]carbamate (852 mg, 3.46 mmol) in THF (10 ml) was added 2,4-dichloro-5-fluoropyrimidine (867 mg, 5.19 mmol) and DIPEA (1.79 g, 2.42 ml, 13.8 mmol). The resulting mixture was heated to reflux temperature overnight. After cooling down, the solvent was removed under reduced pressure, and the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30-70% gradient) to afford the title compound (450 mg, 35% yield) as light yellow oil. MS: 377.3 [M+H]⁺.

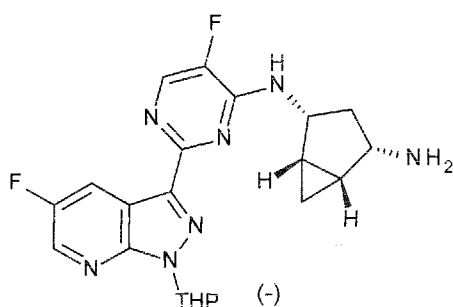
25

[E] Benzyl *N*-[(1*R*,2*S*,4*R*,5*S*)-4-[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ylaminol-2-bicyclo[3.1.0]hexanyl]carbamate



To a stirred mixture solution of (-)-benzyl *N*-[(1*R*,2*S*,4*R*,5*S*)-4-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]carbamate (225 mg, 597 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (138 mg, 119 μmol) in dioxane (10 mL) was added Bu_6Sn_2 (693 mg, 1.19 mmol) and the resulting
 5 reaction mixture was heated to 125°C for 2 h. After cooling down, 5-fluoro-2-(5-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3.4-*b*]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]carbamate (Intermediate A-1a, 311 mg, 896 μmol) and second batch of $\text{Pd}(\text{PPh}_3)_4$ (138 mg, 119 μmol) were added into the above mixture and the reaction mixture was re-heated to 145°C under microwave heating for additional 1 h. The reaction mixture was then concentrated under reduced pressure, and
 10 the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30-80% gradient) to afford the title compound (164 mg, 49% yield) as light yellow oil. MS: 562.3 $[\text{M}+\text{H}]^+$.

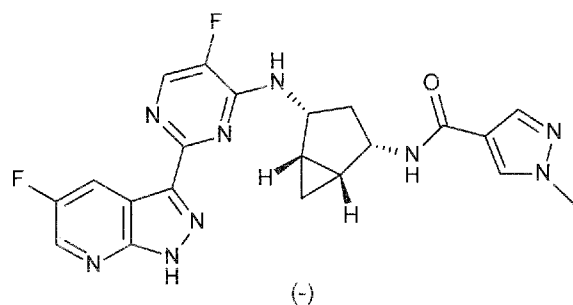
f1] (-)-(1*S*,2*R*,4*S*,5*R*)-*N*-(2-(5-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-pyrazolo[3.4-*b*]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexane-2,4-diamine
 15



Under N_2 protection, to a solution of benzyl *N*-[(1*R*,2*S*,4*R*,5*S*)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydro-2-yl)-pyrazolo[3.4-*b*]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]carbamate (164 mg, 292 μmol) in THF/MeOH (5 mL/5 mL, 1:1) was
 20 added catalytic Pd/C . the resulting reaction mixture was then stirred at room temperature under an atmosphere of H_2 (1 atm) for 3 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford a crude title compound as light yellow oil. MS: 428.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

CN1C=CC(=C1)C(=O)N[C@H]2C[C@@H](C[C@H]3C[C@H](C2)N3)c4nc5c(ncn4C5)c6cc(F)cc6

1H1 (-)-N-r(1R,2S,4R,5S)-4-fluoro-2-(5-fluoro-1H-pyrazolof3,4-blpyridin-3-yl)pvrin!din-4-
yllaminol-2-bicyclo[3.1.0]hexanyl]-1-methyl-pyrazole-4-carboxamide

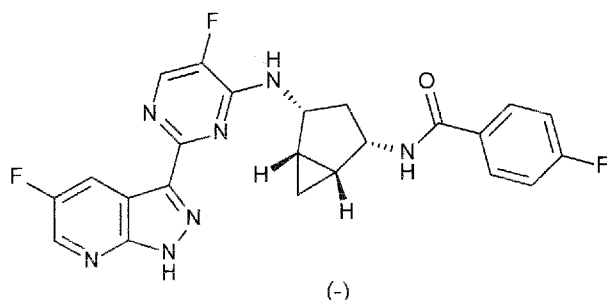


229

(m, 1 H), 1.87 - 1.98 (m, 1 H), 1.63 - 1.81 (m, 2 H), 1.00 - 1.13 (m, 1 H), 0.43 - 0.58 (m, 1 H).

Example 20

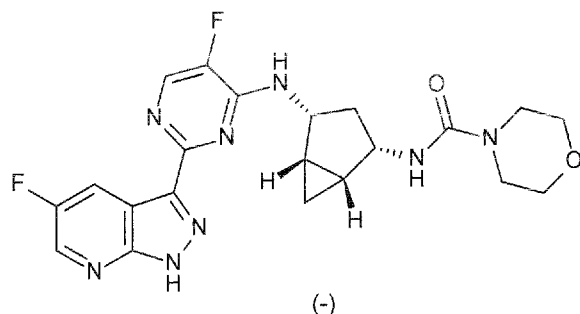
- 5 **(-)-4-Fluoro-W-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide**



In analogy to the synthesis of example 19, 4-fluorobenzoic acid was used in step G. After de-protection of THP protecting group (step H), the title compound (1.4 mg, 3% yield over
10 2 steps) was obtained by Prep-HPLC purification as white powder. MS; 464.4 [M+H]⁺.

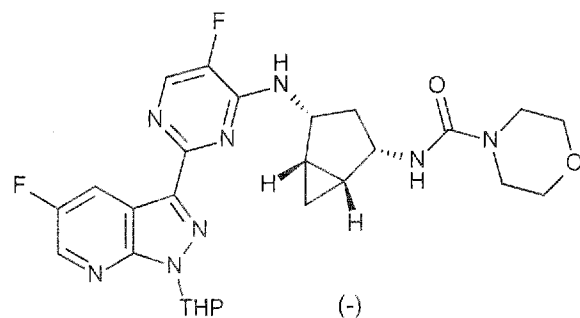
Example 21

- (-)-W-[(1R,2S,4R,5S)-4-[[5-Fluoro-2-{5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl}pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]morpholine-4-carboxamide**



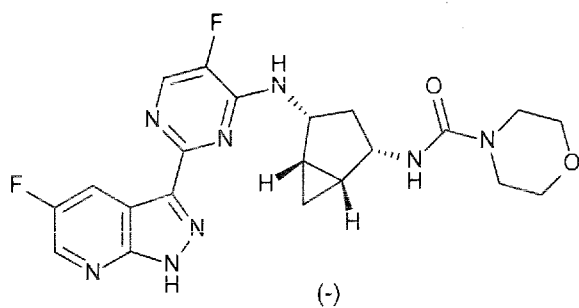
15

Table 1 A/(1R,2S,4R,5S)-4-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexan-2-ylmorpholine-4-carboxamide



To a stirred solution of (-)-(1S,2R,4S,5R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]bicyclo[3.1.0]hexane-2,4-diamine (example 19/step F, 42 mg, 98.3 μ mol) in DCM (1 mL) was added morpholine-4-carbonyl chloride (58.8 mg, 393 μ mol) and DIPEA (127 mg, 172 μ L, 983 μ mol). The resulting mixture solution was stirred at room temperature overnight before it was washed with aq. HCl solution and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to afford a crude title compound (53 mg, 100% yield) as light yellow oil. MS: 540.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

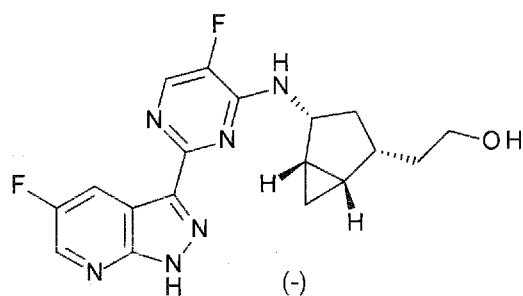
10 IB 1 (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]morpholine-4-carboxamide



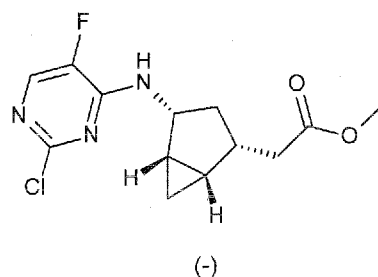
To a stirred solution of N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]morpholine-4-carboxamide (53.1 mg, 98.3 μ mol) in DCM (1 mL) was added TFA (112 mg, 983 μ mol) and the resulting mixture was stirred at room temperature for 1 h. After solvent was removed under reduced pressure, the crude product was purified by Prep-HPLC to afford the title compound (0.6 mg, 1% yield over 2 steps) as colorless oil. MS: 457.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-*d*₄) δ 0.47 - 0.58 (m, 1 H) 0.84 - 0.95 (m, 1 H) 0.97 - 1.05 (m, 1 H) 1.20 - 1.38 (m, 2 H) 1.74 - 1.85 (m, 1 H) 1.85 - 1.93 (m, 1 H) 2.44 (dt, J=13.11, 7.62 Hz, 1 H) 3.35 - 3.46 (m, 4 H) 3.62 - 3.72 (m, 4 H) 4.49 - 4.59 (m, 1 H) 5.07 (br. s., 1 H) 8.27 (br. s., 1 H) 8.48 (d, J=5.27 Hz, 1 H) 8.61 (br. s., 1 H).

Example 22

25 (-)-2-[(1S,2R,4R,5S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]ethanol

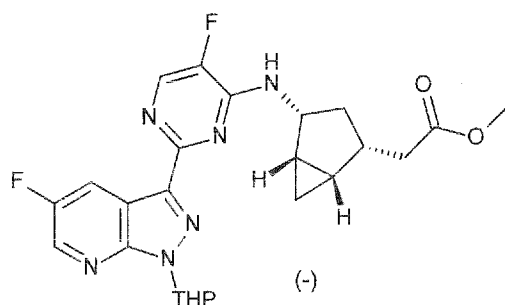


[A] (-)-Methyl 2-[(1S,2R,4R,5S)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]acetate



5 A stirred mixture solution of (-)-methyl 2-[(1S,2R,4R,5S)-2-amino-4-bicyclo[3.1.0]hexanyl]acetate (intermediate B-14, 0.1 g, 0.48 mmol), 2,4-dichloro-5-fluoropyrimidine (0.09 g, 0.54 mmol) and DIPEA (0.18 g, 1.44 mmol) in THF (5 mL) was heated at 60°C for 2 h. After cooling to room temperature, the mixture was poured into ice water and extracted with EtOAc (10 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) to afford the title compound (80 mg, 56% yield) as a white solid. MS: 299.1 [M+H]⁺.

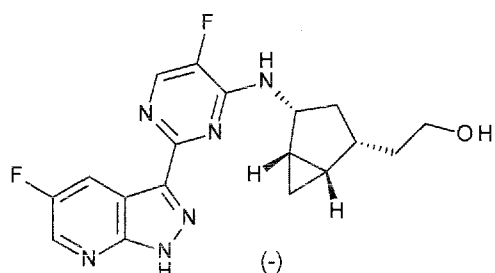
15 [B1] (-)-Methyl 2-[(1S,2R,4R,5S)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)amino]-4-bicyclo[3.1.0]hexanyl]acetate



A stirred mixture solution of (-)-methyl 2-[(1S,2R,4R,5S)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]acetate (125.6 mg, 0.42 mmol), tributyl-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)stannane (Intermediate A-1b, 165 mg, 0.42

mmol), Pd₂(dba)₃ (30.6 mg, 0.042 mmol) and X-phos (39.9 mg, 0.084 mmol) in dioxane (4 mL) was heated at 145°C under microwave heating for 4 h. After TLC showed the completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the title compound (50 mg, 24% yield) as a solid. MS: 485.2 [M+H]⁺.

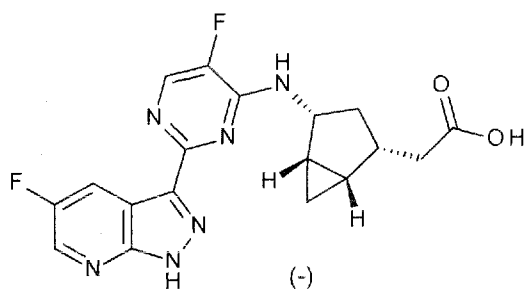
(-)-2-[(1S,2R,4R,5S)-2-[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)]pyrimidin-4-yl]amino-1,4-bicyclo[3.1.0]hexan-1-ol



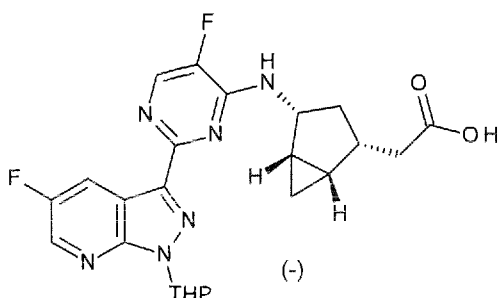
To a stirred solution of (-)-methyl 2-[(1S,2R,4R,5S)-2-[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)]pyrimidin-4-yl]amino-1,4-bicyclo[3.1.0]hexan-1-yl acetate (50 mg, 0.103 mmol) in THF (1 mL) was added DIBALH (1 mL, 1 mmol) slowly at 10°C. After the reaction mixture was stirred at 15°C for 4 h, the mixture was concentrated in vacuo. The residue was re-dissolved in HCl/dioxane (5 mL) and stirred at 15°C for additional 4 h. The volatiles were removed under reduced pressure, and the crude product was subject to Prep-HPLC separation to afford the title compound (2 mg, 5% yield) as a white solid. MS: 373.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ ppm 0.39 - 0.49 (m, 1 H) 0.71 - 0.80 (m, 1 H) 1.02 - 1.17 (m, 1 H) 1.54 - 1.63 (m, 1 H) 1.65 - 1.76 (m, 2 H) 1.78 - 1.88 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.52 (ddd, J=1.01, 7.12, 4.33 Hz, 1 H) 2.61 - 2.64 (m, 1 H) 2.66 (s, 3 H) 3.51 (t, J=6.71 Hz, 2 H) 5.05 - 5.15 (m, 1 H) 8.33 (br. s., 1 H) 8.39 (dd, J=7.97, 2.45 Hz, 1 H) 8.66 (s, 1 H).

Example 23

(-)-2-[(1S,2R,4R,5S)-2-[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)]pyrimidin-4-yl]amino-1,4-bicyclo[3.1.0]hexan-1-ol

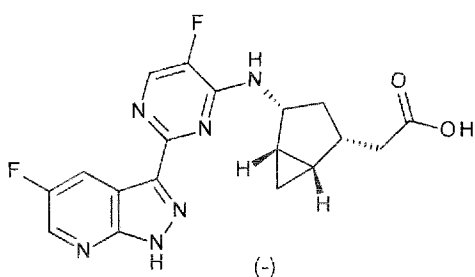


[A] (-)-2-((1S,2R,4R,5S)-2-(5-fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino-1,4-bicyclo[3.1.0]hexan-2-yl)acetic acid



- 5 To a stirred mixture solution of (-)-methyl 2-((1S,2R,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)acetate (example 22/step B, 100 mg, 206 μmol) in THF (6 mL) and MeOH (2 mL) was added LiOH (24.7 mg, 1.03 mmol) pre-dissolved in 2 mL of H_2O . The resulting reaction mixture was stirred at room temperature for 16 h before being diluted with water
- 10 (10 mL) and extracted with diethyl ether (20 mL). The organic layer was separated and discarded. The aqueous layer was acidified with concentrated hydrochloric acid to pH = 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (95 mg, 98% yield) as yellow oil. MS: 470.2 $[\text{M}+\text{H}]^+$. It was used directly in the next step without
- 15 more purification.

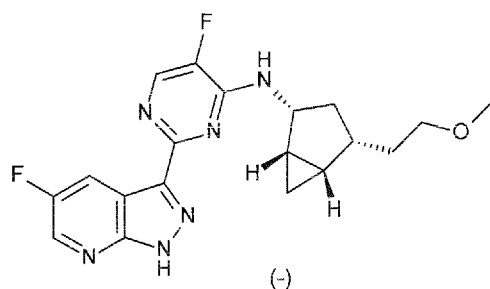
iB] (-)-2-((1S,2R,4R,5S)-2-(5-fluoro-2-(5-fluoro-1-H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino-1,4-bicyclo[3.1.0]hexan-2-yl)acetic acid



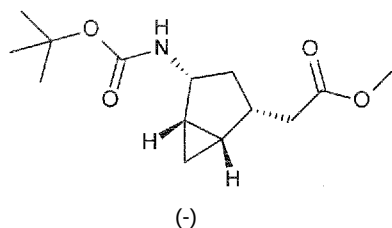
To a stirred solution of (-)-2-((1S,2R,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)acetic acid (95 mg, 202 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol). The resulting reaction mixture was stirred at room temperature for 12 h before it was concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (13 mg, 17% yield) as white foam. MS: 387.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-*d*(4)) δ 8.53 - 8.61 (m, 2 H) 8.12 - 8.16 (m, 1 H) 5.01 - 5.09 (m, 1 H) 2.73 - 2.82 (m, 1 H) 2.36 - 2.46 (m, 2 H) 1.81 - 1.88 (m, 1 H) 1.56 - 1.65 (m, 2 H) 0.94 - 1.06 (m, 1 H) 0.71 - 0.77 (m, 1 H) 0.33 - 0.45 (m, 1 H).

Example 24

(-)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-yl-[(1S,2R,4R,5S)-4-(2-methoxyethyl)-2-bicyclo[3.1.0]hexanyl]pyrimidin-4-amine

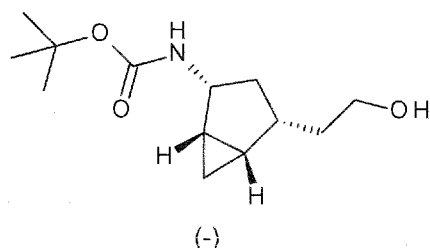


[A] (-)-Methyl 2-((1S,2R,4R,5S)-2-(tert-butoxycarbonylamino)-4-bicyclo[3.1.0]hexanyl)acetate



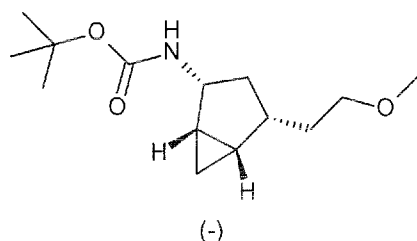
To a stirred solution of (-)-methyl 2-((1S,2R,4R,5S)-4-aminobicyclo[3.1.0]hexan-2-yl)acetate (Intermediate B-14, 0.5 g, 2.4 mmol) and TEA (0.48 g, 3.6 mmol) in DCM (10 mL) was added Boc_2O (0.79 g, 3.6 mmol) slowly and the resulting mixture was stirred at room temperature for 2 h. Afterwards, the mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 5:1) to afford the title compound (0.4 g, 63% yield) as an oil. MS: 270.2 $[M+H]^+$.

[B] (-)-tert-butyl 1-((1S,2R,4R,5S)-4-(2-hydroxyethyl)-2-bicyclo[3.1.0]hexanyl)carbamate



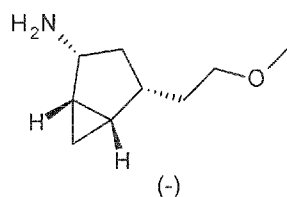
To a stirred solution of (-)-methyl 2-[(1S,2R,4R,5S)-2-(tert-butoxycarbonylamino)-4-bicyclo[3.1.0]hexanyl]acetate (0.4 g, 1.5 mmol) in THF (20 mL) was added DIBAL (4.5 mL, 4.5 mmol) slowly and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of satd. aq. NH_4Cl solution (10 mL) and then extracted with EtOAc (20 mL twice). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to afford a crude title compound (0.35 g, 96% yield) as an oil. MS: 242.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

[(-)-tert-Butyl N-[(1S,2R,4R,5S)-4-(2-methoxyethyl)-2-bicyclo[3.1.0]hexanyl]carbamate



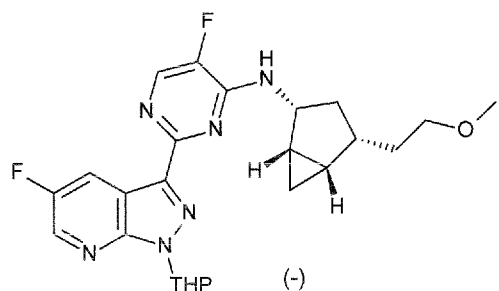
To a stirred mixture solution of (-)-tert-butyl N-[(1S,2R,4R,5S)-4-(2-hydroxyethyl)-2-bicyclo[3.1.0]hexanyl]carbamate (0.3 g, 1.2 mmol) and Ag_2O (0.55 g, 2.4 mmol) in toluene (10 mL) was added MeI (0.26 g, 1.8 mmol) and the resulting mixture solution was heated to 70°C for 12 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo to afford a crude title compound (0.2 g, 65% yield) as an oil. MS: 256.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

[(-)-(1S,2R,4R,5S)-4-(2-Methoxyethyl)bicyclo[3.1.0]hexan-2-amine



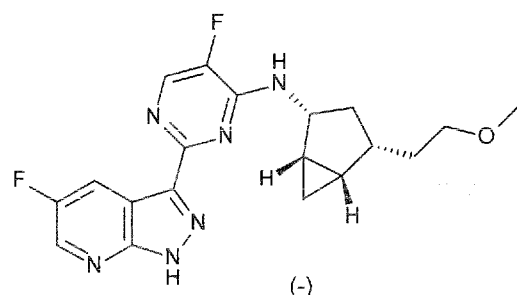
A solution of tert-butyl A-[(1S,2R,4R,5S)-4-(2-methoxyethyl)-2-bicyclo[3.1.0]hexanyl]carbamate (0.2 g, 0.78 mmol) in HCl/MeOH (5 mL/5 mL) was stirred at room temperature for 6 h. Afterwards, the mixture was concentrated in vacuo to give a crude title compound (0.2 g) as a white solid. MS: 156.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

[E] (-)-5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)-A-[(1S,2R,4R,5S)-4-(2-methoxyethyl)-2-bicyclo[3.1.0]hexanyl]pyrimidin-4-amine



A stirred mixture solution of 5-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-9, 56 mg, 0.15 mmol), (-)-(1S,2R,4R,5S)-4-(2-methoxyethyl)bicyclo[3.1.0]hexan-2-amine (45.8 mg, 0.3 mmol) and DIPEA (58 mg, 0.45 mmol) in i-PrOH (10 mL) was stirred at 80°C for 12 h. After cooling to room temperature, the mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the title compound (30 mg, 15% yield) as a solid. MS: 471.2 [M+H]⁺.

[F] (-)-5-Fluoro-2-(5-fluoro-1-(2-methoxyethyl)-2-bicyclo[3.1.0]hexanyl]pyrimidin-4-amine



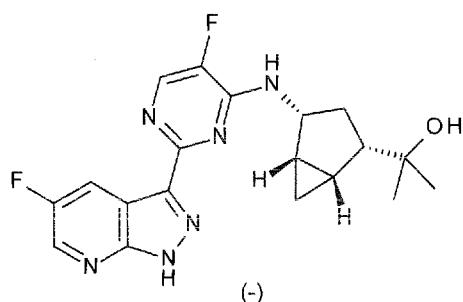
A solution of (-)-5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)-A-[(1S,2R,4R,5S)-4-(2-methoxyethyl)-2-bicyclo[3.1.0]hexanyl]pyrimidin-4-amine (34 mg, 0.07 mmol) in TFA (1 mL) was stirred at room temperature for 12 h. Afterwards, the mixture was concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (9 mg, 33% yield) as a solid. MS: 487.0 [M+H]⁺. ¹H NMR (400 MHz,

MeOH-c/4) δ 0.39 - 0.49 (m, 1 H) 0.71 - 0.80 (m, 1 H) 1.02 - 1.17 (m, 1 H) 1.54 - 1.63 (m, 1 H) 1.65 - 1.76 (m, 2 H) 1.78 - 1.88 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.52 (ddd, $J=1.01, 7.12, 4.33$ Hz, 1 H) 2.61 - 2.64 (m, 1 H) 2.66 (s, 3 H) 3.35 (s, 3 H) 3.51 (t, $J=6.71$ Hz, 2 H) 5.05 - 5.15 (m, 1 H) 8.33 (br. s., 1 H) 8.39 (dd, $J=7.97, 2.45$ Hz, 1 H) 8.66 (s, 1 H).

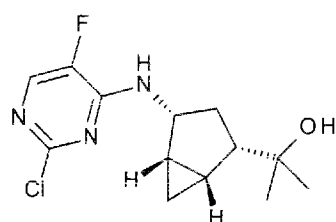
5

Example 25

2-[(1S,2R,4S,5R)-2-[[5-fluoro-2-{5-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]propan-2-ol

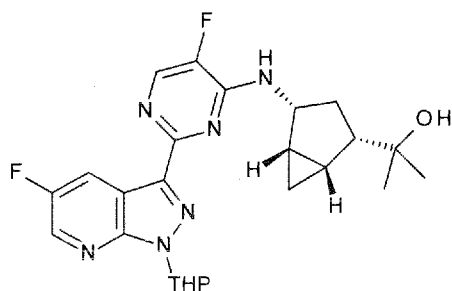


10 [A] (-)-2-[(1S,2R,4S,5R)-2-[[5-fluoro-2-{5-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]propan-2-ol



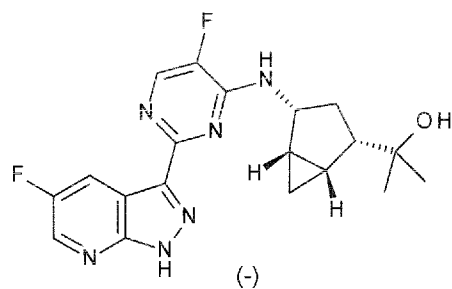
To a stirred solution of methyl (1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylate (Intermediate B-7/step B, 200 mg, 0.70 mmol) in THF (20 mL) was added MeMgBr (3.0 M in ether, 1.54 mmol) at -78°C under N₂. The resulting mixture was stirred -78°C for 1 h before it was allowed to warm up to -40°C. The reaction was then quenched with satd. aq. NH₄Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 30-70% gradient) to afford the title compound (170 mg, 85% yield) as yellow oil. MS: 286.1 [M+H]⁺

1B1 (-)-2-[(1S,2R,4S,5R)-2-[[5-fluoro-2-{5-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]propan-2-ol



To a stirred solution of (-)-2-[(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-4-bicyclo[3.1.0]hexanyl]propan-2-ol (170 mg, 0.45 mmol) in dioxane (10 mL) was added Pd(PPh₃)₄ (50 mg, 0.043 mmol) and Bu₆Sn₂ (500 mg, 0.86 mmol) and the resulting mixture solution was heated to reflux for 1 h. After cooling down, 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 170 mg, 0.50 mmol) and Pd(PPh₃)₄ (50 mg, 0.043 mmol) were added to the above solution and the resulting solution was re-heated to 140°C under microwave heating for 1 h. After cooling to room temperature, volatiles were removed under reduce pressure to give a crude product, which was purified by silica gel flash chromatography (hexane/EtOAc, 20-70% gradient) to afford the title compound (43 mg, 18% yield) as light yellow oil. MS: 471.1 [M+H]⁺

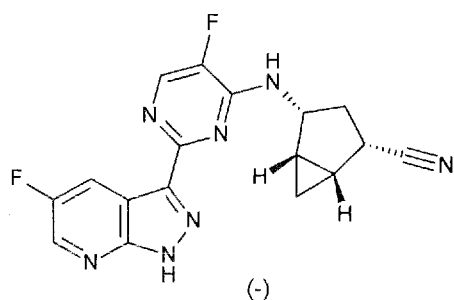
(-)-2-[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]propan-2-ol



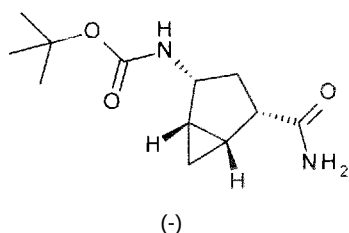
A solution of (-)-2-[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-4-bicyclo[3.1.0]hexanyl]propan-2-ol (43 mg, 0.091 mmol) in 30% TFA in DCM (5 mL) was stirred at room temperature for 2 h. Afterwards, the mixture was concentrated under reduced pressure, and the residue was subject to Prep-HPLC purification to afford the title compound (8.3 mg, 24% yield) as white powder. MS: 387.1 [M+H]⁺

Example 26

(-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonitrile

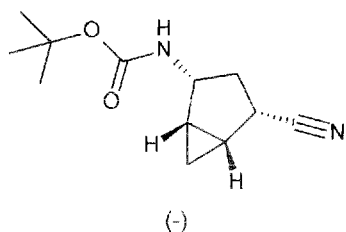


[A] (-)-tert-Butyl N-[(1S,2R,4S,5R)-4-carbamoyl-2-bicyclo[3.1.0]hexan-2-yl]-1H-pyrazolo[4,3-b]pyridine-6-carboxylate



To a stirred solution of (-)-tert-butyl N-[(1S,2R,4S,5R)-4-carbamoyl-2-bicyclo[3.1.0]hexan-2-yl]-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (example 19/step A, 1.42 g, 5.88 mmol) in DCM (50 mL) was added DCC (1.58 g, 7.64 mmol) and 1-hydroxypyrrolidine-2,5-dione (880 mg, 7.64 mmol). The resulting reaction mixture was stirred at room temperature overnight before filtration. The filtrate was concentrated under reduced pressure and the residue was re-dissolved into EtOAc (20 mL) and treated with ammonium hydroxide (2.29 mL, 58.8 mmol). The mixture was stirred at room temperature for additional 1 h. The organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound as a white solid (1.7 g). MS 241.1 $[\text{M} + \text{H}]^+$. This crude product was used directly in the next step without further purification.

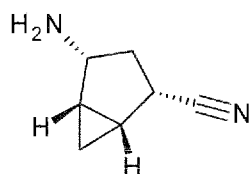
15 IB 1(-)-tert-butyl N-[(1S,2R,4S,5R)-4-cyano-2-bicyclo[3.1.0]hexan-2-yl]-1H-pyrazolo[4,3-b]pyridine-6-carboxylate



To a stirred solution of (-)-tert-butyl N-[(1S,2R,4S,5R)-4-carbamoyl-2-bicyclo[3.1.0]hexan-2-yl]-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (1.41 g, 5.87 mmol) and Et_3N (1.78 g, 17.6 mmol) in DCM (50 mL) was added Tf_2O (1.49 mL, 8.8 mmol) at 0°C under N_2 . The resulting reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was partitioned between with aq. NaHCO_3 solution and DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (2.1 g) as a light

brown solid. MS 223.1 $[M+H]^+$. This crude product was used directly in the next step without further purification.

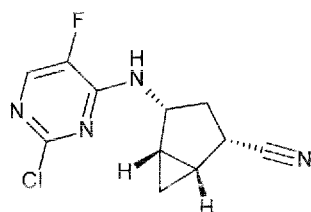
[DI] (-)-(1S,2R,4S,5R)-2-Aminobicyclo[3.1.0]hexane-4-carbonitrile



5 (-)

To a stirred solution of (-)-tert-butyl ((1S,2R,4S,5R)-4-cyanobicyclo[3.1.0]hexan-2-yl)carbamate (1.3 g, 5.87 mmol) in DCM (10 mL) was added TFA (6.69 g, 58.7 mmol) and the resulting mixture was stirred at room temperature for 2 h. After the mixture was concentrated under reduced pressure, the crude product was used directly in the next step without further purification. MS: 123.1 $[M+H]^+$.

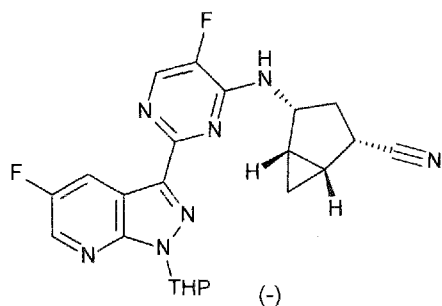
[EI] (-)-(1S,2R,4S,5R)-2-(2-Chloro-5-fluoro-pyrimidin-4-ylaminobicyclo[3.1.0]hexane-4-carbonitrile



(-)

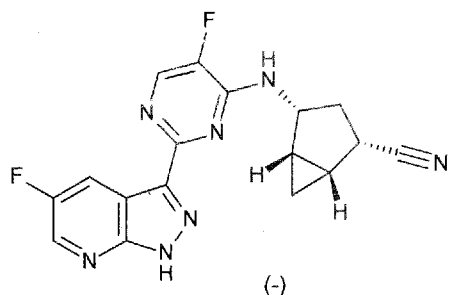
15 To a stirred solution of (-)-(1S,2R,4S,5R)-2-aminobicyclo[3.1.0]hexane-4-carbonitrile (717 mg, 5.87 mmol) in THF (20 mL) was added DIPEA (3.03 g, 4.1 mL, 23.5 mmol) and 2,4-dichloro-5-fluoropyrimidine (1.27 g, 7.63 mmol). The resulting mixture was heated to reflux temperature overnight. After the mixture was concentrated under reduced pressure, the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 30~80% gradient) to afford the title compound (900 mg, 61% yield over 4 steps) as a light yellow solid. MS: 253.1 $[M+H]^+$.

[F] (-)-(1S,2R,4S,5R)-2-H5-Fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-4-aminobicyclo[3.1.0]hexane-4-carbonitrile



To a stirred solution of (-)-(1R,2S,4R,5S)-4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carbonitrile (252 mg, 997 μmol) in dioxane (10 mL) was added $\text{Pd}(\text{Ph}_3\text{P})_4$ (230 mg, 199 μmol) and Bu_6Sn_2 (1.16 g, 1.99 mmol) and the mixture was heated to 125°C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 346 mg, 997 μmol) and another batch of $\text{Pd}(\text{Ph}_3\text{P})_4$ (230 mg, 199 μmol) were added. The reaction mixture was heated to 140°C for 1 h under microwave heating. After the mixture was concentrated under reduced pressure, the crude product was purified by silica gel flash chromatography (hexane/EtOAc, 20-90% gradient) to afford the title compound (250 mg, 58% yield) as light yellow oil. MS: 438.1 $[\text{M}+\text{H}]^+$.

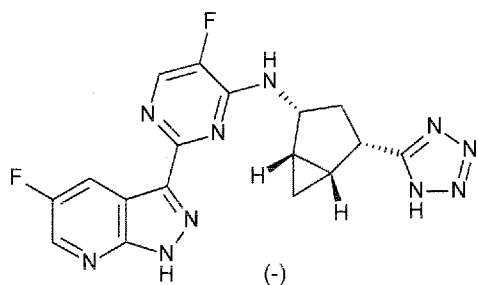
fGI (-)-(1S,2R,4S,5R)-2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-4-carbonitrile



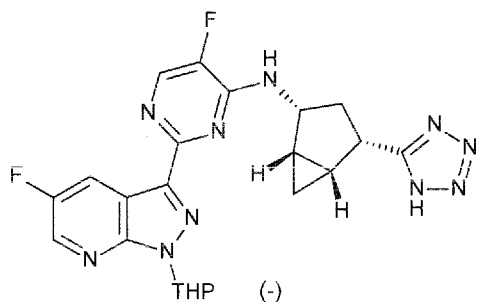
To a stirred solution of (-)-(1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carbonitrile (100 mg, 229 μmol) in DCM (10 mL) was added TFA (261 mg, 176 μmol , 2.29 mmol) and the reaction mixture was stirred at room temperature for 1 h. After the solvent was removed under reduced pressure, the crude product was purified by Prep-HPLC to afford the title compound (7 mg, 9% yield) as white powder. MS: 354.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) 8.47 - 8.74 (m, 2 H), 8.13 - 8.30 (m, 1 H), 5.07 - 5.20 (m, 1 H), 3.39 - 3.46 (m, 1 H), 2.37 - 2.61 (m, 1 H), 2.04 (s, 1 H), 1.83 - 1.92 (m, 1 H), 1.47 - 1.77 (m, 1 H), 0.97 - 1.07 (m, 1 H), 0.57 - 0.74 (m, 1 H).

Example 27

(-)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(1H-tetrazol-5-yl)-2-bicyclo[3.1.0]hexan-1-ylpyrimidin-4-amine

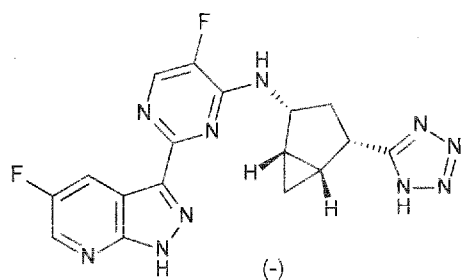


[A] (-)-5-Fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-4-(1H-tetrazol-5-yl)-2-bicyclo[3.1.0]hexan-1-ylpyrimidin-4-amine



To a stirred solution of (-)-1-(5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carbonitrile (example 26/step F, 150 mg, 343 μ mol) in DMF was added I_2 (52.2 mg, 206 μ mol) and sodium azide (66.9 mg, 1.03 mmol). The mixture was heated at 120°C under microwave heating for 2 h. After cooling to room temperature and removal of **DMF**, the crude product (165 mg) was used directly in the next step without further purification. MS: 438.1 (**M+H⁺**).

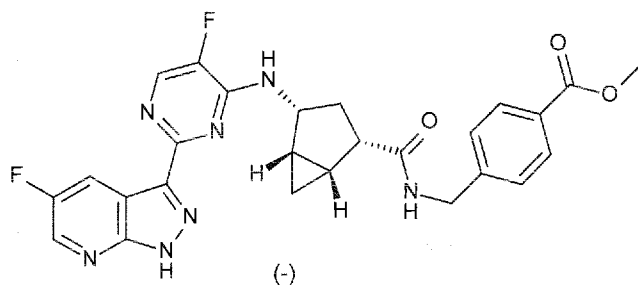
1B 1 (-)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(1H-tetrazol-5-yl)-2-bicyclo[3.1.0]hexan-1-ylpyrimidin-4-amine



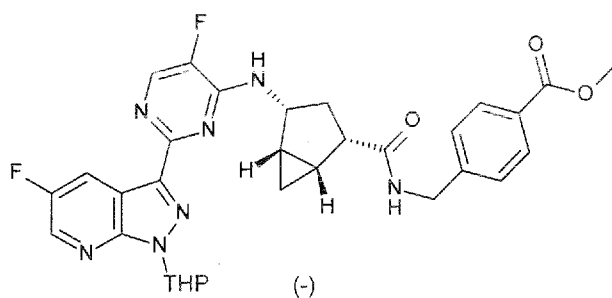
The crude material of (-)-N-((1S,2R,4S,5R)-4-(2H-tetrazol-5-yl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine (165 mg, 343 μmol) was treated with 50% TFA in DCM (10 mL) for 3 h. After the mixture was concentrated under reduced pressure, the crude product was subject to Prep-HPLC purification to afford the title compound (0.2 mg, 0.1% yield) as a white solid. MS: 397.2 [M+Hf. ^1H NMR (400 MHz, MeOH- d_4) δ 8.46 - 8.77 (m, 1 H), 8.05 - 8.29 (m, 1 H), 6.59 - 6.78 (m, 1 H), 5.09 - 5.32 (m, 1 H), 3.71 - 4.03 (m, 1 H), 2.67 - 2.88 (m, 2 H), 2.00 (s, 1 H), 1.81 - 1.93 (m, 1 H), 0.88 - 1.02 (m, 1 H), 0.33 - 0.57 (m, 1 H).

Example 28

(-)-Methyl 4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1- α -pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl]benzoate

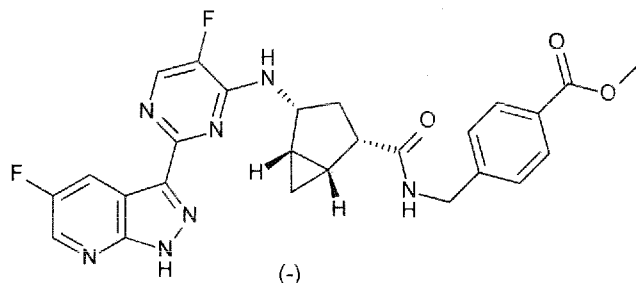


(-)-Methyl 4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1- α -pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl]benzoate



A stirred mixture solution of methyl 4-(aminomethyl)benzoate hydrochloride (26.5 mg, 131 μmol), triethylamine (26.6 mg, 263 μmol), HATU (50 mg, 131 μmol) and (-)-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid (30 mg, 65.7 μmol) (Example 4/Step B) in DCM (5 mL) was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with satd. aq. NaHCO_3 solution and extracted with DCM (5 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (60 mg, 100% yield) as yellow gum. MS: 604.2 [M+H] $^+$. This crude product was used directly in the next step without further purification.

IB 1 (-)-Methyl 4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-
yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl benzoate

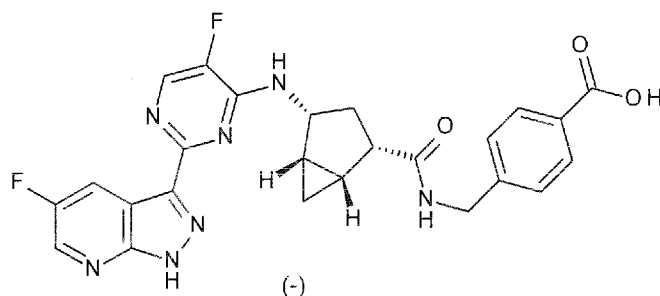


- 5 A solution of crude (-)-methyl 4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl]benzoate (30 mg crude, 65 μ mol) in TFA (4 mL) and DCM (4 mL) was stirred at room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford
- 10 the title compound (4 mg, 12% yield) as white foam. MS: 520.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-*d*₄) δ 0.53 - 0.60 (m, 1 H) 1.03 - 1.07 (m, 1 H) 1.75 - 1.83 (m, 2 H) 1.89 - 1.94 (m, 1 H) 2.25 - 2.30 (m, 1 H) 3.23 - 3.28 (m, 1 H) 3.91 (s, 3 H) 4.47 - 4.55 (m, 2 H) 5.17 (br. s., 1 H) 7.44 (d, J=8.53 Hz, 2 H) 8.00 (d, J=8.28 Hz, 2 H) 8.21 - 8.28 (m, 1 H) 8.52 (dd, J=8.28, 2.76 Hz, 1 H) 8.60 (br. s., 1 H).

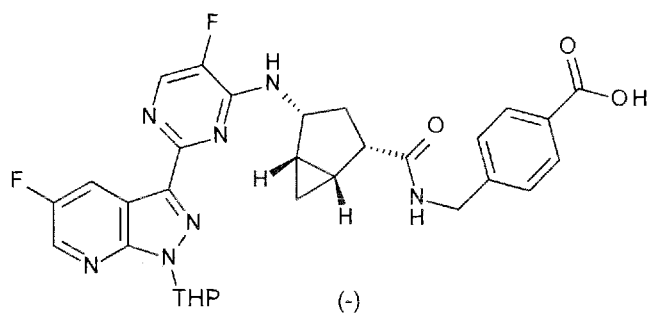
15

Example 29

(-)-4-[[[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1-*H*-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl] benzoic acid

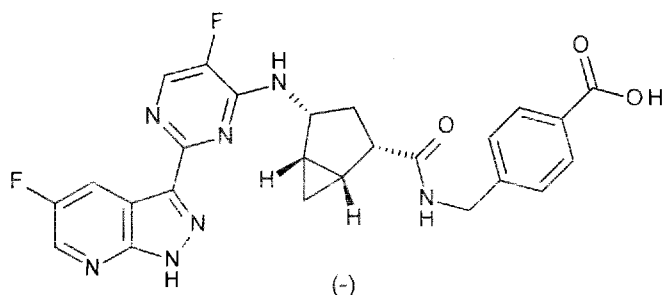


- 20 [A 1 (-)- 4-[[[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydroDvran-2-yl-Pvrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl] benzoic acid



(-)-Methyl 4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl]benzoate (Example 28/Step A) (39.7 mg, 65.7 μmol , Eq: 1) and LiOH monohydrate (40 mg) in tetrahydrofuran (4 mL) and water (4 mL) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to give a crude title compound (100 mg, 100% yield) as yellow gum. MS: 604.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

10 10 (-)-4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]methyl]benzoic acid

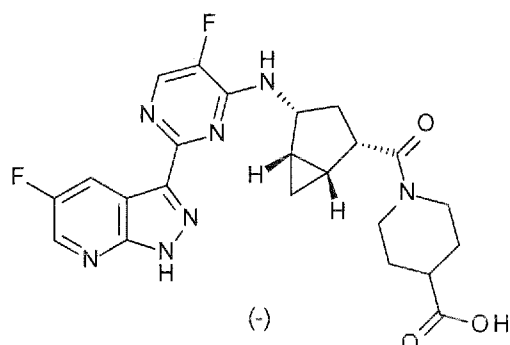


A solution of crude (-)-4-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-

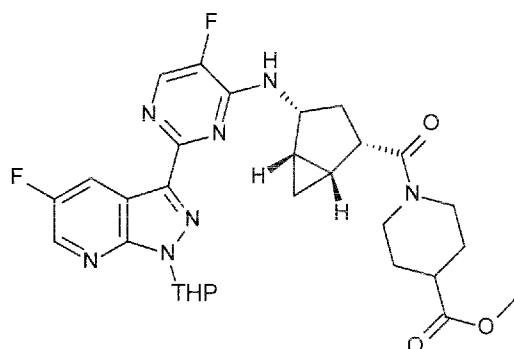
15 carbonyl]amino]methyl]benzoic acid (100 mg) in TFA (4 mL) and DCM (4 mL) was stirred at room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (4 mg, 12% yield) as a white foam. MS: 506.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 0.51 - 0.58 (m, 1 H) 1.01 - 1.06 (m, 1 H) 1.68 - 1.79 (m, 2 H) 1.90 (d, $J=7.53$ Hz, 1 H) 2.22 - 2.32 (m, 1 H) 2.90 - 3.20 (m, 2 H) 3.20 - 3.27 (m, 1 H) 4.43 - 4.60 (m, 2 H) 5.14 (br. s., 1 H) 7.44 (d, $J=8.28$ Hz, 2 H) 8.01 (d, $J=8.53$ Hz, 2 H) 8.20 (br. s., 1 H) 8.57 (br. s., 2 H).

Example 30

(-)-1-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]piperidine-4-carboxylic acid

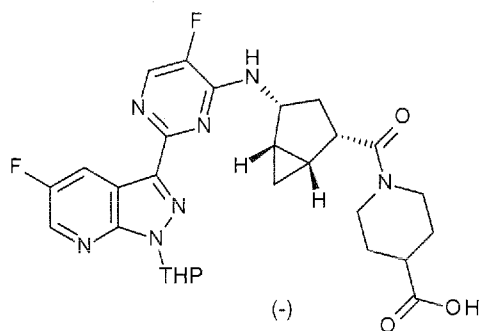


5 [A] (-)-Methyl 1-[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-5-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]piperidine-4-carboxylate



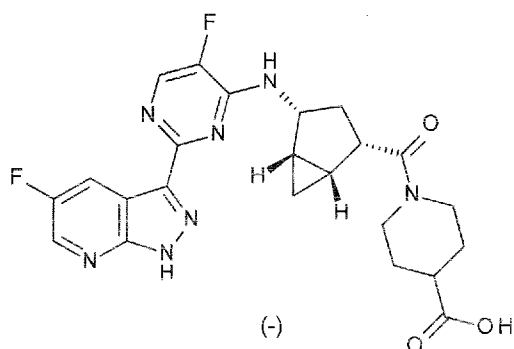
A stirred mixture solution of (1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid (Example 4/Step B, 30 mg, 65.7 μmol), HATU (50 mg, 131 μmol), methyl piperidine-4-carboxylate (18.8 mg, 131 μmol) and triethylamine (26.6 mg, 263 μmol) in DCM (5 mL) was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with satd. aq. NaHCO₃ solution and extracted with DCM (5 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (100 mg, 100%) as yellow gum. MS: 582.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

1B 1 (-)-1-[(1R,2S,4R,5S)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-5-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]piperidine-4-carboxylic acid



(-)-Methyl 1-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carbonyl)piperidine-4-carboxylate (100 mg, 65.7 μmol) in tetrahydrofuran (4 mL) and water (4 mL) was stirred at room temperature for 2 h. Afterwards, the mixture was concentrated in vacuo to give a crude title compound (100 mg, 100% yield) as yellow gum. This crude product was used directly in the next step without further purification.

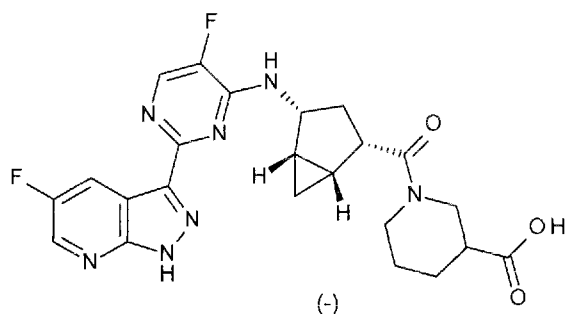
[C] (-)-1-((1S,2R,4S,5R)-2-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-4-carbonyl)piperidine-4-carboxylic acid



A solution of crude (-)-2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]piperidine-4-carboxylic acid (100 mg, 65.7 μmol) in TFA (4 mL) and DCM (4 mL) was stirred at room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (5 mg, 16% yield) as white foam. MS: 484.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 0.40 - 0.55 (m, 1 H) 0.95 (br. s., 1 H) 1.51 - 1.88 (m, 5 H) 1.89 - 2.20 (m, 3 H) 2.59 - 2.70 (m, 1 H) 2.83 - 2.99 (m, 1 H) 3.55 (br. s., 1 H) 4.12 - 4.25 (m, 1 H) 4.35 - 4.48 (m, 1 H) 5.02 - 5.14 (m, 1 H) 8.15 (d, $J=3.26$ Hz, 1 H) 8.53 (d, $J=3.26$ Hz, 2 H).

Example 31

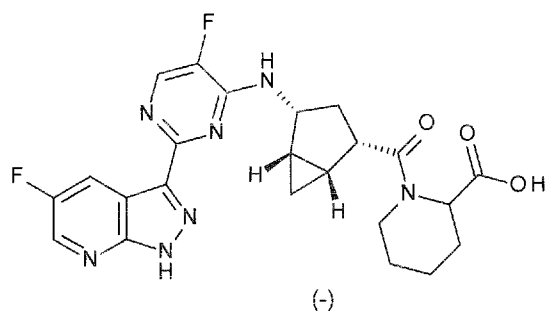
1-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]piperidine-3-carboxylic acid



In analogy to the synthesis of example 30, (-)-(1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino) bicyclo[3.1.0]hexane-2-carboxylic acid (30mg, 65.7 μ mol) was used in step A. After hydrolysis (Step B) and deprotection of THP (Step C), the title compound (5 mg, 16% yield) was obtained by Prep-HPLC purification as white foam. MS: 484.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 0.41 - 0.53 (m, 1 H) 0.96 (d, J=3.51 Hz, 1 H) 1.47 - 1.97 (m, 6 H) 2.04 - 2.21 (m, 2 H) 2.36 - 2.66 (m, 2 H) 2.93 - 3.08 (m, 1 H) 3.47 - 3.76 (m, 2 H) 3.87 - 4.21 (m, 2 H) 4.51 - 4.68 (m, 1 H) 5.10 (br. s., 1 H) 8.16 (d, J=3.76 Hz, 1 H) 8.45 - 8.62 (m, 2 H).

Example 32

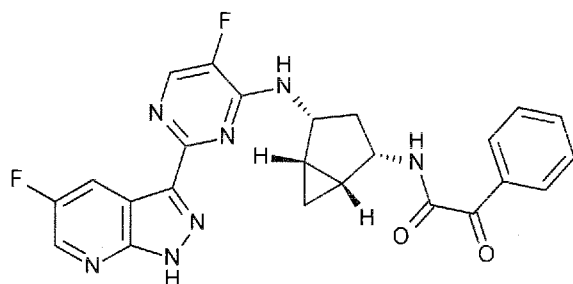
(-)-1-[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]piperidine-2-carboxylic acid



In analogy to the synthesis of example 30, (1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid (30mg, 65.7 μ mol) was used in Step A. After hydrolysis (Step B) and deprotection of THP (Step C), the title compound (10 mg, 37% yield) was obtained by Prep-HPLC purification as white foam. MS: 484.2 [M+H]⁺. ¹H NMR (400 MHz, METHANOL-d₄) δ 0.38 - 0.58 (m, 1 H) 0.89 - 1.02 (m, 1 H) 1.37 - 1.89 (m, 6 H) 2.07 - 2.25 (m, 1 H) 2.26 - 2.38 (m, 1 H) 3.50 - 3.67 (m, 1 H) 4.16 (d, J=13.55 Hz, 1 H) 4.99 - 5.14 (m, 1 H) 5.24 - 5.36 (m, 1 H) 8.16 (d, J=3.76 Hz, 1 H) 8.55 (br. s., 1 H) 8.56 - 8.62 (m, 1 H).

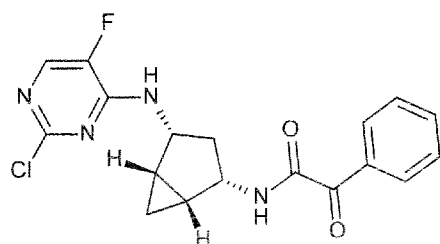
Example 33

(-)-N-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-2-oxo-2-phenylacetamide



5

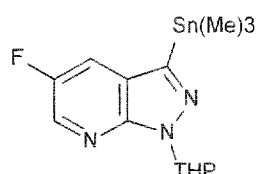
[A] (+ or -)-N-((1R,2S,4R,5S)-4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-2-oxo-2-phenylacetamide



To a stirred mixture solution of (1S,2R,4S,5R)-N-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2,4-diamine (Intermediate B-7, 0.34 g, 1.2 mmol) and Et₃N (0.48 g, 4.8 mmol) in DCM (8 mL) was added 2-oxo-2-phenylacetyl chloride (0.21 g, 1.2 mmol) dropwise and the resulting mixture solution was stirred at room temperature for 0.5 h. Afterwards, the mixture was concentrated in vacuo and the crude product was purified by column chromatography on silica gel (PE:EA=10:1) to afford the title compound (0.14 g, 31.8% yield) as a yellow solid. MS. 375.1 [M+H]⁺.

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[B] 5-Fluoro-1-(tetrahydro-2H-pyran-2-yl)-3-(trimethylstannyl)-1H-pyrazolo[3,4-b]pyridine



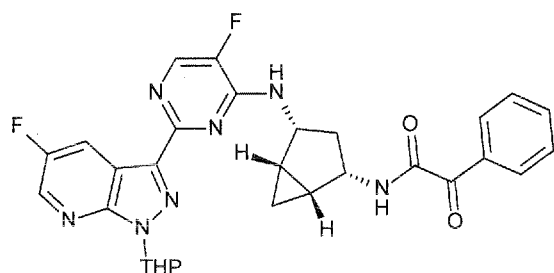
To a stirred solution of 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (2.3 g, 6.6 mmol) in dioxane (20 mL) was added Me₆Sn₂ (3.87 g, 11.7 mmol) and

20

Pd(PPh₃)₄ (0.76 g, 0.66 mmol) and the resulting mixture solution was stirred at 100°C for 1 h. After cooling to room temperature, the mixture was concentrated in vacuo and the crude product was purified by silica gel flash chromatography (petroleum ether:EtOAc = 30:1-10:1) to afford the title compound (2 g, 80% yield) as a yellow brown oil. MS: 386.1 [M+H]⁺.

5

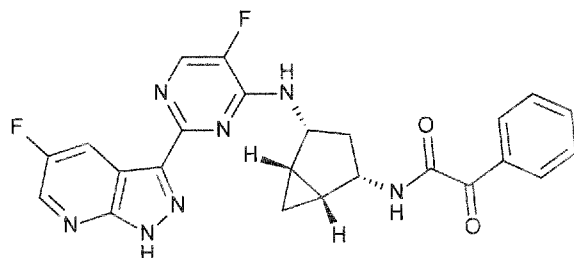
[C] (-)-N-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-2-oxo-2-phenylacetamide



- 10 A stirred mixture solution of (rac)-N-((1R,2S,4R,5S)-4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-2-oxo-2-phenylacetamide (0.13 g, 0.37 mmol), Pd₂(dppf)₃ (33.8 mg, 0.037 mmol), Xphos (35.3 mg, 0.074 mmol), and 5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-3-(trimethylstannyl)-1H-pyrazolo[3,4-b]pyridine (0.28 g, 0.74 mmol) in dioxane (5 mL) was heated at 140°C under microwave heating for 2 h. After cooling to room temperature,
- 15 the mixture solution was concentrated in vacuo and the crude product was purified by silica gel flash chromatography (petroleum ether:EtOAc = 5:1-1:1) to afford the title compound (12 mg, 5.5% yield) as yellow brown oil. MS: 560.2 [M+H]⁺.

- [D] (-)-N-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-2-oxo-2-phenylacetamide

20

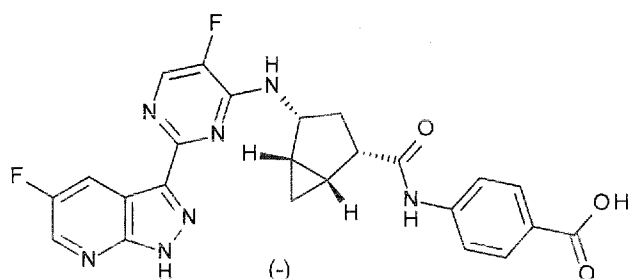


- A solution of (-)-N-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-2-oxo-2-phenylacetamide (12 mg, 0.021 mmol) in TFA (3 mL) was stirred at room temperature for
- 25 12 h. Afterwards, the reaction mixture was concentrated in vacuo and the crude product

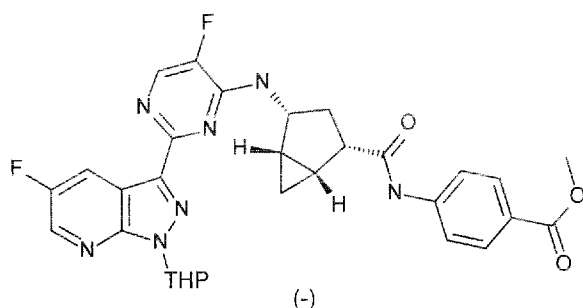
was purified by Prep-HPLC to afford the title compound (2 mg, 20% yield) as a white solid. MS: 476.2 [M+Hf. ¹H NMR (400MHz, MeOH-c/4) δ 8.54 (br. s., 2 H), 8.15 (br. s., 1 H), 8.08 (d, J=7.53 Hz, 2 H), 7.65-7.72 (m, 1 H), 7.55 (t, J=7.65 Hz, 2 H), 5.10 (br. s., 1 H), 4.75 (br. s., 1 H), 4.62 (br. s., 1 H), 4.37 (t, J=8.16 Hz, 1 H), 3.35 (br. s., 1 H), 2.67 (s, 1 H), 2.49-2.58 (m, 1 H), 1.83-1.98 (m, 2 H), 1.34-1.41 (m, 1 H), 1.01 (d, J=4.77 Hz, 1 H), 0.53-0.61 (m, 1 H).

Example 34

(-)-4-[[[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]benzoic acid

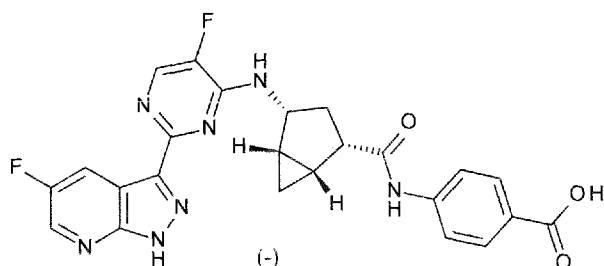


[AT (-)-Methyl 4-ff(1 S,2R,4S,5R)-2-ir5-fluoro-2-(5-fluoro-1-tetrahdropyran-2-yl-pyrazoior3.4-blpvridin-3-vl)pvrimid[n-4-vllaminolbicvclo[3 .1.0]hexane-4-carbonyllaminolbenzoate



A mixture solution of (-)-(1 R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2/-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3. 1.0]hexane-2-carboxylic acid (Example 4/Step B, 30 mg, 65.7 μmol), HATU (50 mg, 131 μmol), methyl 4-aminobenzoate (19.9 mg, 131 μmol) and triethylamine (26.6 mg, 263 μmol) in DCM (5 mL) was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with satd. aq. NaHCO₃ solution and extracted with DCM (5 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (100 mg, 100% yield) as yellow gum. MS: 604.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

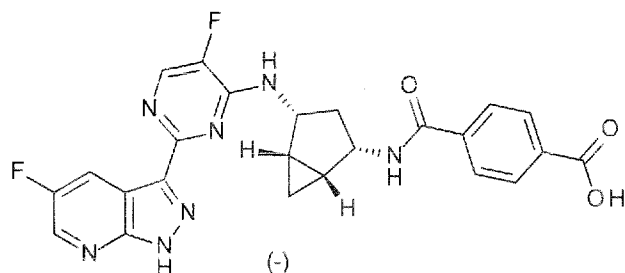
1B] (-)-4-rr(1S,2R,4S,5R)-2-[5-Fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]Pyridin-3 -yl)pyrimidin-4-
vnamino]bicyclo[3. 1.0]hexane-4-carbonvnamino]benzoic acid



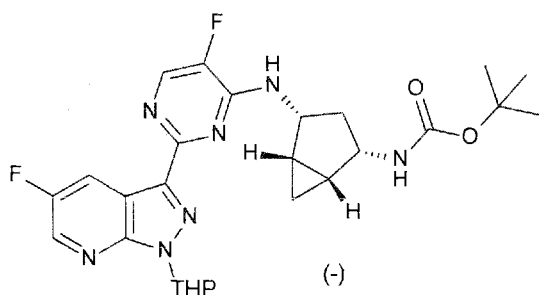
A solution of (-)-Methyl 4-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro- 1-(tetrahydro-2H -pyran-2-
5 yl)-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3. 1.0]hexane-2-
carboxamido)benzoate (38.7 mg, 65.7 μ mol) in tetrahydrofuran (4 mL) and water (4 mL)
was stirred at room temperature for 2 h. Afterwards, the mixture was concentrated in vacuo
to give a crude title compound (100 mg, 100% yield) as yellow gum. This material was then
re-dissolved in TFA (4 mL) and DCM (4 mL) and the resulting mixture solution was stirred at
10 room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under
reduced pressure and the crude product was purified by Prep-HPLC to afford the title
compound (10 mg, 31% yield) as a white foam. MS: 492.2 $[M+H]^+$. ^1H NMR (400 MHz,
MeOH-*d*(4) δ 0.49 - 0.54 (m, 1 H) 1.10 (dd, $J=9.41$, 3.89 Hz, 1 H) 1.28 - 1.33 (m, 1 H) 1.78 -
1.86 (m, 2 H) 1.91 (d, $J=3.51$ Hz, 1 H) 2.26 (dd, $J=13.18$, 7.40 Hz, 1 H) 5.17 (br. s., 1 H)
15 7.71 (d, $J=8.78$ Hz, 2 H) 7.98 (d, $J=8.78$ Hz, 2 H) 8.18 (d, $J=3.76$ Hz, 1 H) 8.56 (br. s., 1 H)
8.60 (d, $J=8.53$ Hz, 1 H).

Example 35

(-)-4-[[[1 R,2S,4R,5S)-4-[[5-Fiuoro-2-{5-fluoro-1 H-pyrazoio[3,4-b]pyridin-3-yl)pyrimidin-
20 4-yl]amino]-2-bicyclo[3. 1.0] hexanyl]carbamoyl]benzoic acid

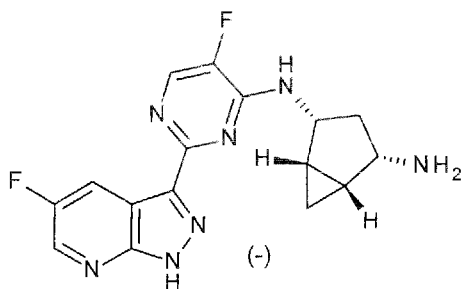


1A 1 (-)-4-rt-butyl A-1-(1R,2S,4R,5S)-4-fi5-fiuoro-2-(5-fluoro-1 -tetrahydropyran-2-vl-
PVrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-vilaminol-2-bicyclo[3. 1.0]hexanyl1carbamate



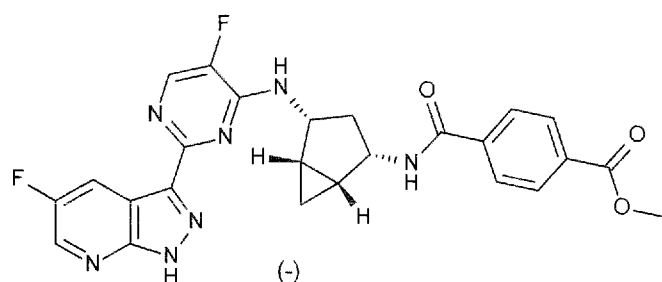
A mixture solution of (-)-tert-butyl ((1S,2S,4R,5R)-4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)carbamate (Intermediate B-7/Step D) (250 mg, 729 μ mol), 1,1,1,2,2,2-hexabutyldistannane (846 mg, 1.46 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μ mol) in dioxane (15 mL) was heated at 125°C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (380 mg, 1.09 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μ mol) was added and the resulting mixture solution was heated at 145°C under microwave heating for 50 min. After cooling to room temperature, the was evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography (EtOAc/petroleum ether = 0 to 100% gradient) to afford the title compound (125 mg, 32% yield) as a yellow solid. MS: 528.3 [M+H].

[B] (-)-((1S,2R,4S,5R)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)amine



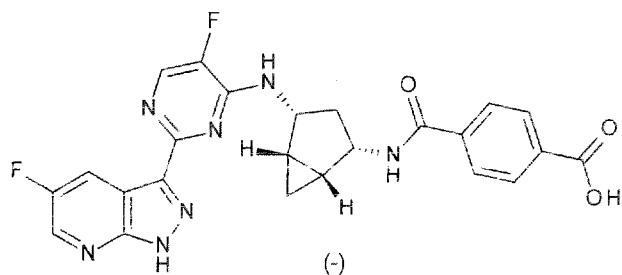
A solution of (-)-tert-butyl ((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)carbamate (45 mg, 85.3 μ mol) in TFA (20 mL) was stirred at room temperature for 2 h. Afterwards, the solvent was evaporated under reduced pressure to afford a crude title compound (50 mg, 100% yield). MS: 344.2 [M+H]. This crude product was used directly in the next step without further purification.

fClMethyl 4-(((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)carbamoyl)benzoate



A mixture solution of (-)-(1S,2R,4S,5R)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]bicyclo[3.1.0]hexan-2-yl]carbamoyl]benzoic acid (29.3 mg, 85 μ mol), HATU (64.9 mg, 171 μ mol), 4-(methoxycarbonyl)benzoic acid (30.7 mg, 171 μ mol) and triethylamine (34.5 mg, 341 μ mol) in DCM (5 mL) was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with satd. aq. NaHCO_3 solution and extracted with DCM (5 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (100 mg, 100% yield) as yellow gum. MS: 506.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

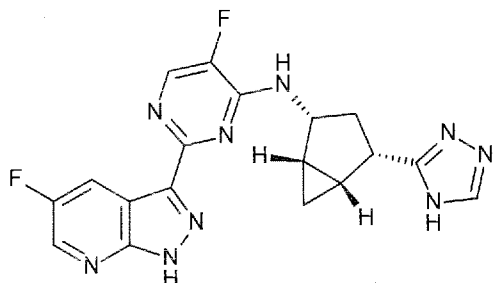
[D] (-)-4-[[[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexan-2-yl]carbamoyl]benzoic acid



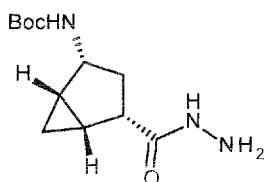
A mixture solution of LiOH monohydrate (35.8 mg, 853 μ mol) and (-)-methyl 4-(((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)carbamoyl]benzoate (43.1 mg, 85.3 μ mol) in tetrahydrofuran (4 mL) and water (4 mL) was stirred at room temperature for 3 h. Afterwards, the mixture was neutralized with 1 N HCl and then concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (9 mg, 22% yield) as a white solid. MS: 492.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 0.59 - 0.67 (m, 1 H) 0.86 - 0.95 (m, 1 H) 1.09 - 1.15 (m, 1 H) 1.40 - 1.50 (m, 1 H) 1.87 - 2.01 (m, 2 H) 2.53 - 2.63 (m, 1 H) 4.84 (br. s., 1 H) 5.16 (d, $J=10.92$ Hz, 1 H) 7.94 (d, $J=8.53$ Hz, 2 H) 8.13 (d, $J=8.66$ Hz, 2 H) 8.28 (d, $J=4.52$ Hz, 1 H) 8.54 (dd, $J=8.16, 2.64$ Hz, 1 H) 8.63 (br. s., 1 H).

Example 36

(+ or -)-IV-((1S,2R,4S,5R)-4-(4A-1,2,4-tiazol-3-yl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine

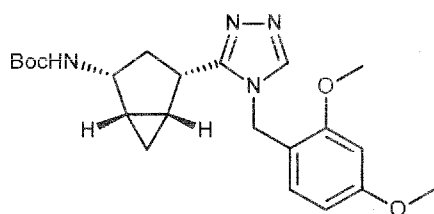


5 IA1 (+ or -)-te/t-Butyl((1S,2R,4S,5R)-4-(hydrazinecarbonyl)bicyclo[3.1.0]hexan-2-yl)carbamate



A stirred solution of (+ or -)-(1R,2S,4R,5S)-methyl 4-((tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexan-2-carboxylate (Intermediate B-2/step C, 600 mg, 2.35 mmol) in hydrazine hydrate (5 mL) and EtOH (5 mL) was heated at 80°C for 3 h. After TLC (petroleum ether: EtOAc = 5:1, R_f = 0) showed that the reaction was completed, the solvent and hydrazine was removed under reduced pressure. The precipitated white solid was then washed with MTBE and air-dried to afford the title compound (600 mg, 100% yield) as a white solid.

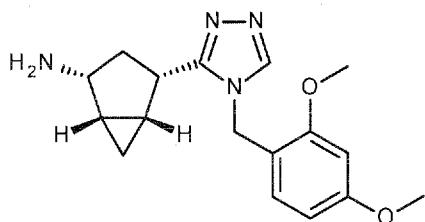
15 IB1 (+ or -)-teff-Butyl((1S,2R,4S,5R)-4-(4-(2,4-dimethoxybenzyl)-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-yl)carbamate



A solution of (+ or -)-tert-Butyl((1S,2R,4S,5R)-4-(hydrazinecarbonyl)bicyclo[3.1.0]hexan-2-yl)carbamate (550 mg, 2.16 mmol) in trimethoxymethane (2 mL) was stirred at 40°C for 2 h. After cooling down, (2,4-dimethoxyphenyl)methanamine (720 mg, 4.3 mmol), AcOH (0.5 mL), and MeCN (5 mL) was added and the resulting mixture solution was re-heated at 80°C for additional 10 h. After TLC (DCM: MeOH = 10:1, R_f = 0.2) showed that the reaction was

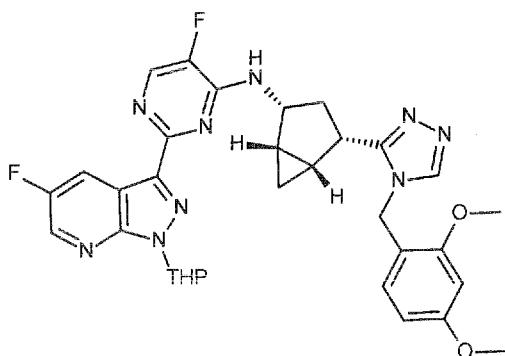
completed, the solvent was removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (DCM :MeOH = 10:1) to afford the title compound (400 mg, 44.8% yield) as yellow oil. MS: 415.1 [M+H]⁺.

5 [Cl⁻](1S,2R,4S,5R)-4-(4-(2,4-dimethoxybenzyl)-4H-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-amine



To a solution of (+ or -)-tert-butyl((1S,2R,4S,5R)-4-(4-(2,4-dimethoxybenzyl)-4H-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-yl)carbamate (400 mg, 0.97 mmol) in EtOAc (20 mL) was added HCl/EtOAc (10 mL) and the resulting mixture solution was stirred at room temperature for 2h. After TLC (DCM: MeOH = 10:1, R_f = 0) showed that the reaction was completed, the precipitated white solid was collected by filtration and further washed with EtOAc to afford the title compound (300 mg, 88.7% yield) as a white solid.

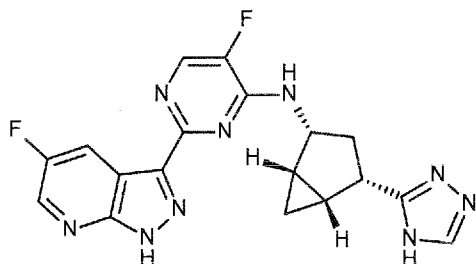
15 [D]₂ or -)-N-((1S,2R,4S,5R)-4-(4-(2,4-dimethoxybenzyl)-4H-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine



A mixture solution of (+ or -)-((1S,2R,4S,5R)-4-(4-(2,4-dimethoxybenzyl)-4H-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-amine (140 mg, 0.4 mmol) and DIPEA (103 mg, 0.795 mmol) in i-PrOH (10 mL) was stirred at room temperature for 15 min before 5-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (100 mg, 0.265 mmol) was added. The resulting mixture solution was then stirred at 80°C for 12 h. After TLC (EtOAc, R_f = 0.2) showed that the reaction was completed, the solvent was

removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography to afford the title compound (140 mg, 84.3% yield) as white oil. MS: 630.1 [M+H]⁺.

- 5 1ET (+ or -)-A/-((1S,2R,4S,5R)-4-(4H-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine

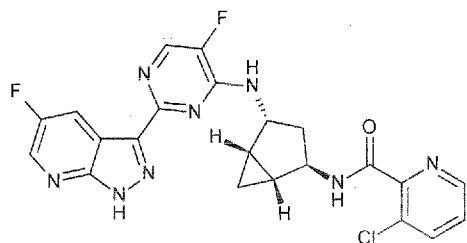


(+ or -)-/V-((1S,2R,4S,5R)-4-(4-(2,4-dimethoxybenzyl)-4H-1,2,4-triazol-3-yl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-

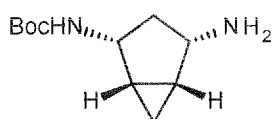
- 10 pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine (140.0 mg, 0.22 mmol) was dissolved in TFA (10.0 mL) and was stirred at 15°C for 12h. LC-MS showed the starting material was consumed. The solvent was removed to give the crude, which was purified by pre-HPLC (acid) to afford the title compound (12.0 mg, 84.3% yield) **as a** white solid. MS: 198.6 [M+H]⁺. ¹H NMR (400MHz, MeOH-d₄): δ ppm 8.69 (s, 1H), 8.50-8.52 (m, 1H), 8.35-8.38 (m, 2H), 5.34 (s, 1H), 3.86-3.91 (m, 1H), 2.56-2.61 (m, 1H), 2.02-2.03 (m, 1H), 1.97-1.98 (m, 1H), 1.78-1.84 (m, 1H), 1.00-1.03 (m, 1H), 0.61-0.66 (m, 1H).

Example 37

- 20 (+ or -)-3-Chloro-/V-[(1R,2R,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyridine-2-carboxamide

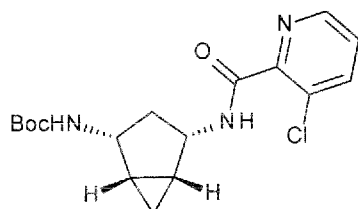


fA] rac)-tert-Butyl A/-f(1S,2R,4S,5R)-4-amino-2-bicyclo[3.1.0]hexanyl]pyridine-2-carboxamide



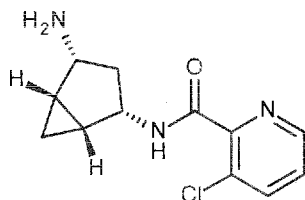
Under N₂ protection, to a mixture solution of (rac)-benzyl tert-butyl (1R,2S,4R,5S)-bicyclo[3.1.0]hexane-2,4-diyl dicarbamate (Example 19/Step B, 1.5 g, 4.33 mmol) in THF was added Pd/C (46.1 mg, 433 μmol). The resulting mixture was then stirred at room temperature under an atmosphere of H₂ (1 atm) for 2 h. Afterwards, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford a crude title compound (910 mg, 99% yield) as light yellow oil. MS: 213.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

10 (rac)-tert-butyl N-((1S,2R,4S,5R)-4-((3-chloro-2-pyridyl)amino)-2-bicyclo[3.1.0]hexan-2-yl)carbamate



To a mixture solution of (rac)-tert-butyl ((1S,2R,4S,5R)-4-aminobicyclo[3.1.0]hexan-2-yl)carbamate (450 mg, 2.12 mmol) in DCM (20 mL) was added HATU (1.21 g, 3.18 mmol), 3-chloropicolinic acid (501 mg, 3.18 mmol) and DIPEA (822 mg, 6.36 mmol). The resulting mixture was stirred at room temperature overnight before it was washed with brine. The separated organic layer was then dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (hexane ; EtOAc= 3 : 1 to 1 : 4) to afford the title compound (510 mg, 68% yield) as a off-white waxy solid. MS: 352.1 [M+H]⁺.

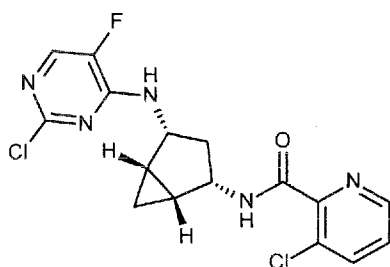
20 (rac)-N-((1R,2S,4R,5S)-4-amino-2-bicyclo[3.1.0]hexan-2-yl)-3-chloro-pyridine-2-carboxamide



A solution of (rac)-N-((1R,2S,4R,5S)-4-amino-2-bicyclo[3.1.0]hexan-2-yl)-3-chloropicolinamide (510 mg, 1.45 mmol) in 30% TFA/DCM (20 mL) was stirred at room temperature for 2 h. Afterwards, the reaction mixture was concentrated in vacuo to afford a crude title compound

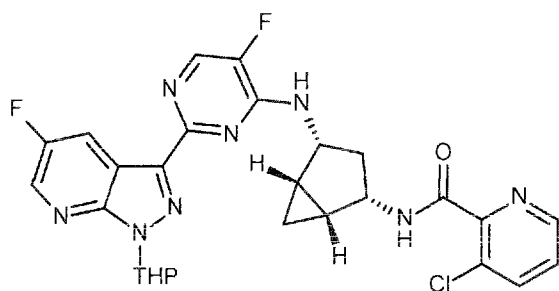
(365 mg, 100% yield) as an oil. MS: 252.1 $[M+H]^+$. This crude product was used directly in the next step without further purification.

JD] (rac)-3-Chloro-A-((1R,2S,4R,5S)-4-(2-chloro-5-fluoropyrimidin-4-yl)amino)-1,2-bicyclo[3.1.0]hexan-2-yl)pyridine-2-carboxamide



To a stirred solution of (rac)-A-((1R,2S,4R,5S)-4-aminobicyclo[3.1.0]hexan-2-yl)-3-chloropicolinamide (365 mg, 1.45 mmol) in THF (10 mL) was added DIPEA (562 mg, 4.35 mmol) and 2,4-dichloro-5-fluoropyrimidine (363 mg, 2.17 mmol) and the resulting mixture solution was heated at reflux temperature overnight. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (hexane:EtOAc = 3 : 1 to 1 : 4) to afford the title compound (140 mg, 25% yield) as light yellow oil. MS: 383.1 $[M+H]^+$.

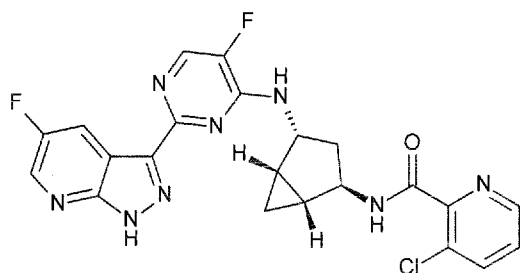
IE] (rac)-3-Chloro-A-((1R,2S,4R,5S)-4-(5-fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)amino)-1,2-bicyclo[3.1.0]hexan-2-yl)pyridine-2-carboxamide



To a stirred solution of (rac)-3-chloro-A-((1R,2S,4R,5S)-4-(2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)picolinamide (140 mg, 366 μ mol) in dioxane (10 mL) was added Bu_4Sn_2 (425 mg, 733 μ mol) and $\text{Pd}(\text{Ph}_3\text{P})$ (34.7 mg, 73.3 μ mol) and the resulting mixture solution was heated to 125 °C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (127 mg, 366 μ mol) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (84.7 mg, 73.3 μ mol) were added and the mixture solution was re-heated to 145 °C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was

concentrated under reduced pressure to give a crude product, which was then purified by silica gel flash chromatography (EtOAc/hexane, 70% to 100% gradient) to afford the title compound (100mg, 48% yield) as light yellow oil. MS: 567.9 [M+H]⁺

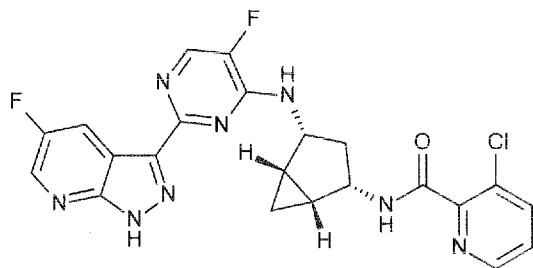
- 5 5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ylamino-1,2-bicyclo[3.1.0]hexan-2-ylpyridine-2-carboxamide



- A solution of 3-chloro-4-((1R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)picolinamide (100 mg, 176 μ mol) in 50% TFA/DCM (10 mL) was stirred at room temperature for 2 h. Afterwards, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (1 mg, 1.2% yield) as white powder. MS: 483.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.58 - 8.51 (m, 3 H), 8.18 (d, J = 4 Hz, 1 H), 8.02 (dd, J = 8, 4 Hz, 1 H), 7.56 (q, J = 4 Hz, 1 H), 5.36 - 5.30 (m, 1 H), 4.52 (d, J = 8 Hz, 1 H), 2.25 - 2.20 (m, 1 H), 2.06 - 1.98 (m, 1 H), 1.76 - 1.70 (m, 1 H), 1.35 - 1.31 (m, 1 H), 0.80 - 0.77 (m, 1 H), 0.69 - 0.63 (m, 1 H).

Example 38

- (- or +)-3-Chloro-4-((1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl)pyridine-2-carboxamide

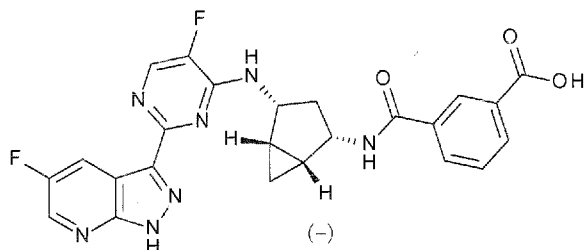


in the synthesis of Example 37, the title compound (1.8 mg, 2.1% yield) was obtained as another product after Prep-HPLC purification. MS: 483.2 [M+H]⁺; ¹H NMR (400 MHz, MeOH-d₄) δ 8.60 - 8.53 (m, 3 H), 8.18 (d, J = 4 Hz, 1 H), 8.00 (dd, J = 6, 4 Hz, 1 H), 7.53 (q,

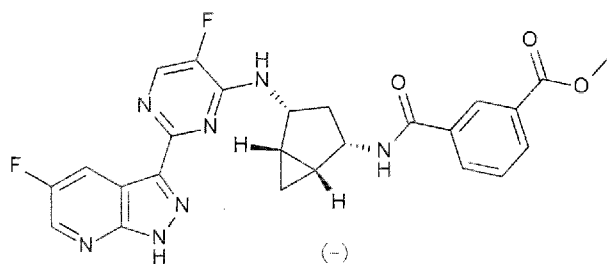
J = 4 Hz, 1 H), 5.16 - 5.09 (m, 1 H), 4.83 - 4.77 (m, 1 H), 2.62 - 2.54 (m, 1 H), 2.00 - 1.82 (m, 1 H), 1.40 - 1.31 (m, 2 H), 1.03(dd, J = 6, 4 Hz, 1 H), 0.58(dd, J = 10, 4 Hz, 1 H).

Example 39

- 5 (-)-3-[[[(1R,2S,4R,5S)-4-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl] carbamoyl] benzoic acid



1A1 (-)-Methyl 3-[[[(1R,2S,4R,5S)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl] carbamoyl] benzoate

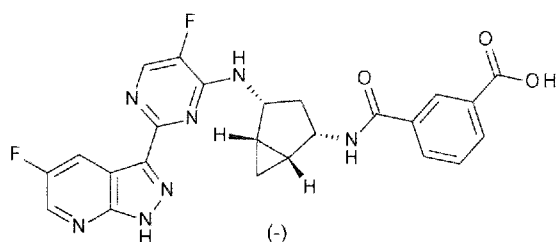


10

A mixture solution of (-)-(1S,2R,4S,5R)-A/2-[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]bicyclo[3.1.0]hexane-2,4-diamine (Example 35/Step B) (29.3 mg, 85 μ mol), HATU (64.9 mg, 171 μ mol), 3-(methoxycarbonyl)benzoic acid (30.7 mg, 171 μ mol) and triethylamine (34.5 mg, 341 μ mol) in DCM (5 mL) was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with satd. aq. NaHCO_3 solution and extracted with DCM (5 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (100 mg, 100% yield) as yellow gum. MS: 506.2 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification. Ms: 506.2 $[\text{M}+\text{H}]^+$

20

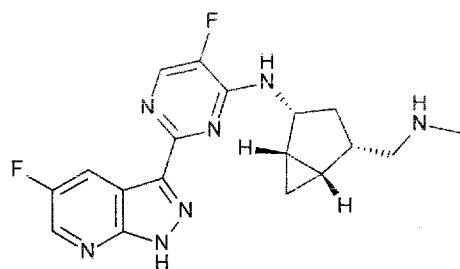
(-)-3-[[[(1R,2S,4R,5S)-4-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl] carbamoyl] benzoic acid



A mixture solution of LiOH monohydrate (35.8 mg, 853 μ mol) and (-)- methyl 3-(((1 R,2S,4R,5S)-4-((5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)carbamoyl)benzoate (43.1 mg, 85.3 μ mol) in THF (4 mL) and water (4 mL) was stirred at room temperature for 3 h. Afterwards, the reaction mixture was neutralized with 1 N HCl and concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (8 mg, 19% yield) as white foam. MS: 492.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 1.03 - 1.12 (m, 1 H) 1.39 - 1.53 (m, 1 H) 1.63 - 1.73 (m, 1 H) 1.76 - 1.86 (m, 1 H) 2.25 (dt, $J=12.86$, 7.62 Hz, 1 H) 4.61 - 4.73 (m, 1 H) 4.88 (br. s., 1 H) 7.61 (t, $J=7.78$ Hz, 1 H) 7.97 - 8.17 (m, 3 H) 8.34 (br. s., 1 H) 8.40 - 8.54 (m, 2 H) 8.58 - 8.75 (m, 2 H).

Example 40

(+ or -)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-W-((1S,2R,4S,5S)-4-((methylamino)methyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine

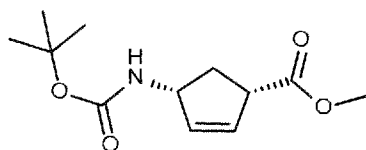


[AT (+ or -)-(1S,4R)-Methyl 4-aminocyclopent-2-enecarboxylate hydrochloride



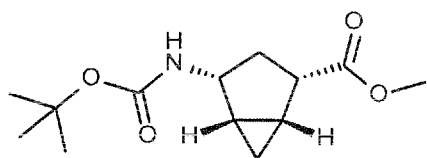
A solution of (1S,4R)-4-aminocyclopent-2-enecarboxylic acid hydrochloride (54 g, 0.33 mmol) in 4M HCl/MeOH(200 mL) was stirred at room temperature for 12 h. Afterwards, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude title compound (52.3 g, 99.6% yield) as a yellow solid.

[B] (+ or -)-(1S,4R)-Methyl 4-((fexi-butoxycarbonvi)amino)cyclopent-2-enecarboxylate



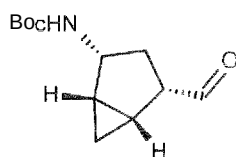
A mixture solution of (+ or -)-(1S,4R)-methyl 4-aminocyclopent-2-enecarboxylate hydrochloride (52.3 g, 328.6 mmol), trimethylamine (66.5 g, 657.2 mmol) and (Boc)₂O (86 g, 394.4 mmol) in DCM (400 mL) was stirred at room temperature overnight. Afterwards, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum: EtOAc = 10:1) to afford the title compound (63 g, 79% yield) as a white solid.

[C] (+ or -)-(1R,2S,4R,5S)-Methyl 4-((tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexane-2-carboxylate



To a stirred solution (+ or -)-(1S, 4R)-Methyl 4-((tert-butoxycarbonyl)amino)cyclopent-2-enecarboxylate (5 g, 20.7 mmol) in DCM (40 mL) was added ZnEt₂ (1 M in toluene, 41 mL) dropwise at 0°C. After stirred for 15 min, CH₂F₂ (6.75 mL) was added dropwise to the above mixture at 0°C, followed by 5 min later, another batch of ZnEt₂ (1 M in toluene, 41 mL) and CH₂I₂ (6.75 mL) were added sequentially at 0°C. The resulting reaction mixture was then allowed to warm up to 10°C and stirred at 10°C for 4 h. The reaction was quenched with NH₄Cl aqueous solution (50 mL) and extracted with DCM (100 mL × 3). Combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 15: 1) to afford the title compound (15 g, 27.2% yield) as a white solid.

[P] (+ or -)-tert-Butyl ((1S,2R,4S,5R)-4-formylbicyclo[3.1.0]hexan-2-yl)carbamate

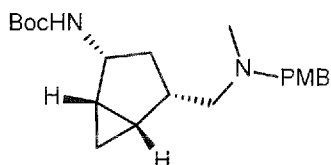


To a stirred solution of (+ or -)-(1R,2S,4R,5S)-methyl 4-((tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexane-2-carboxylate (2.6 g, 10.2 mmol) in toluene (20 mL) was added DIBAL-H (1.2 mL, 1.2 mmol) at -60°C and the resulting mixture solution was

stirred at at -60°C for 0.5 h. The reaction was quenched with Seignette salt aq. solution (50 mL) and extracted with EtOAc (50 mL x2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether : EtOAc = 10:1) to afford the

5 title compound (0.5 g, 21.7% yield as a white solid.

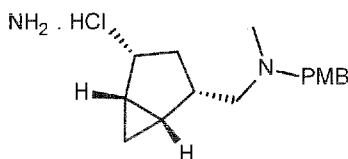
[E] _____ (+ _____ or _____ -)-tert-Butyl((1S,2R,4S,5S)-4-(((4-methoxybenzyl)(methyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)carbamate



- 10 To a solution of (+ or -)-tert-butyl((1S,2R,4S,5R)-4-formylbicyclo[3.1.0]hexan-2-yl)carbamate (0.5 g, 2.2 mmol) in DCE (5 mL) was added 1-(4-methoxyphenyl)-N-methylmethanamine (0.5 g, 3.3 mmol) and AcOH (0.19 g, 3.3 mmol). The resulting mixture solution was stirred at room temperature for 0.5 h before NaBH₃CN (0.27 g, 4.4 mmol) was added and the resulting mixture solution was stirred for at room temperature for additional 12h. Afterwards,
- 15 the reaction mixture was concentrated under reduced pressure to give a crude title compound (0.2 g). This crude product was used directly in the next step without further purification.

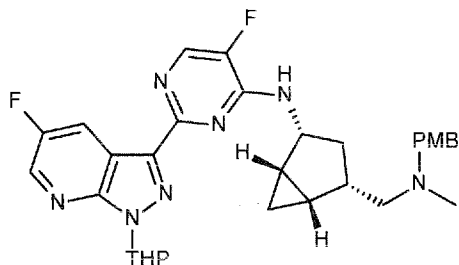
[F] (+ or -)-(1S,2R,4S,5S)-4-(((4-Methoxybenzyl)(methyl)amino)methyl)bicyclo[3.1.0]hexan-2-amine hydrochloride

20



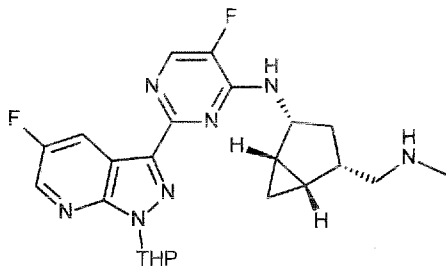
- A solution of tert-Butyl((1S,2R,4S,5S)-4-(((4-methoxybenzyl)(methyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)carbamate (0.4 g, 1.5 mmol) in HCl/EtOAc (5 mL) was stirred at room temperature for 2 h. Afterwards, the reaction mixture was concentrated under reduced
- 25 pressure to give a crude title compound (0.4 g) as yellow oil. This crude product was used directly in the next step without further purification.

FG1 f+ or -)-5-Fluoro-2-(5-fluoro-1 -(tetrahydro-2/-/pvrn-2-vl)-1 /-/pvrazolof3.4-b1pvridin-3-vl)-
/V-((1S,2R,4S,5S)-4-(((4-methoxybenzyl)(methyl)amino)methyl)bicyclo[3.1.0]hexan-2-
yl)pyrimidin-4-amine



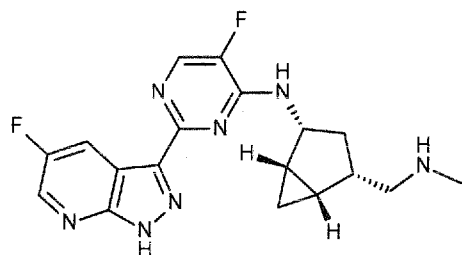
- 5 A mixture solution of (+ or -)-(1 S,2R,4S,5S)-4-(((4-methoxybenzyl)(methyl)amino)methyl)-bicyclo[3.1.0]hexan-2-aminehydrochloride (0.12 g, 0.39 mmol), 5-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1 -(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3.4-b]pyridine (0.15 g, 0.39 mmol), and DIPEA (0.1 g, 0.78 mmol) in THF (5 ml) was stirred at 70°C for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced
 10 pressure to give a crude title compound (0.18 g) as yellow oil. This crude product was used directly in the next step without further purification.

[H] (+ or -)-5-Fluoro-2-(5-fluoro-1-(tetrahydro-2/-/pvrn-2-vl)-1 H-pvrazolo[3.4-b]Dvridin-3-vl)-
N-((1S,2R,4S,5S)-4-((methylamino)methyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine



- 15 A solution of (+ or -)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-W-((1S,2R,4S,5S)-4-(((4-methoxybenzyl)(methyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine (0.12 g, 0.2 mmol) in acetyl chloride (4 mL) was stirred at room temperature for 0.5 h. Afterwards, the reaction mixture was concentrated under
 20 reduced pressure and the residue was re-dissolved in MeOH (5 ml) and the resulting solution was heated at 70°C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a crude title compound (70 mg) as yellow oil. This crude product was used directly in the next step without further purification.

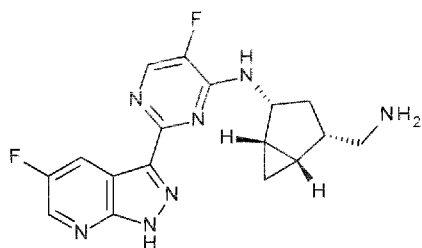
[(+ or -)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4S,5S)-4-((methylamino)methyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine



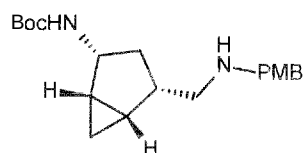
A solution of (+ or -)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4S,5S)-4-((methylamino)methyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine (70 mg, 0.15 mmol) in TFA (3 mL) was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (8.8 mg, 17.6% yield) as yellow foam. ¹H NMR (400MHz, MeOH-d₄) 8.64 (s, 1H), 8.49 - 8.21 (m, 1H), 5.20 (d, J=2.5 Hz, 1H), 3.16 - 3.03 (m, 2H), 2.77 (s, 3H), 2.45 - 2.23 (m, 1H), 1.97 (br. s., 1H), 1.80 - 1.57 (m, 1H), 1.32 - 1.07 (m, 1H), 0.96 - 0.75 (m, 1H), 0.66 - 0.45 (m, 1H).

Example 41

(+ or -)-N-((1S,2R,4S,5S)-4-((aminomethyl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine



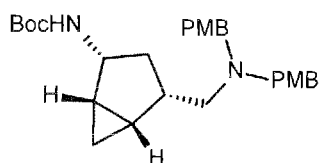
1 (+ or -)-tert-butyl ((1S,2R,4S,5S)-4-((4-methoxybenzyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)carbamate



To a stirred solution of (+ or -)-tert-butyl ((1S,2R,4S,5S)-4-formylbicyclo[3.1.0]hexan-2-yl)carbamate (Example 40/Step B, 2.1 g, 9.33 mmol) in MeOH (20 mL) was added PMBNH₂ (1.4 g, 10.26 mmol) and AcOH (112.3 mg, 1.87 mmol). After the mixture solution was stirred for 1 h NaBH₃CN (1.17 mg, 18.66 mmol) was added and the resulting mixture solution was

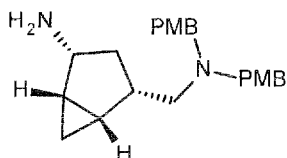
stirred at room temperature for additional 1 h. The reaction was quenched by the addition of satd. aq. NH_4Cl solution (50 mL) and extracted with DCM (50 mL three times). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography to afford the title compound (2 g, 61.9% yield) as a white solid. MS: 347.3 $[\text{M}+\text{H}]^+$.

[B] (+ or -)-tert-butyl ((1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)carbamate



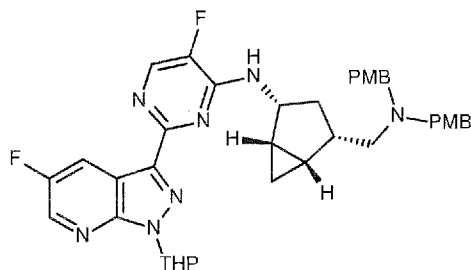
To a stirred solution of (+ or -)-tert-butyl ((1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)carbamate (1 g, 4.44 mmol) in DMF (10 mL) was added PMBCl (0.67 g, 4.88 mmol) and DIPEA (1.15 mg, 8.88 mmol) and the resulting mixture solution was stirred at 50°C for 12 h. The reaction was quenched by the addition of satd. aq. NH_4Cl solution (20 mL) and extracted with EA (20 mL three times). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether : EtOAc = 5:1) to afford the title compound (1.22 g, 58.9% yield) as yellow oil. MS: 427.3 $[\text{M}+\text{H}]^+$.

[C] (+ or -)-(1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)bicyclo[3.1.0]hexan-2-amine



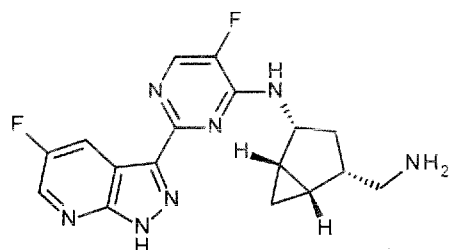
To a stirred solution of (+ or -)-tert-butyl ((1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)carbamate (1.22 g, 2.61 mmol) in EtOAc (10 mL) was added 4N HCl/EtOAc (10 mL) and the resulting mixture was stirred at room temperature for 2 h. Afterwards, the reaction mixture was concentrated under reduced pressure to give a crude title compound (0.9 g, 93.8% yield) as a white solid. MS: 367.3 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

1D1 (+ or -)-N-((1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine



- 5 A mixture solution of (+ or -)-(1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)-bicyclo[3.1.0]hexan-2-amine (0.35 g, 0.96 mmol), DIPEA (0.41 g, 3.2 mmol), and 5-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (0.3 g, 0.8 mmol) in THF (5 mL) was stirred at 70°C for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a
10 crude product, which was purified by silica gel flash chromatography (petroleum:EtOAc = 3:1) to afford the title compound (250 mg, 50.9% yield) as a yellow solid. MS: 682.3 [M+H]⁺.

1E1 (+ or -)-N-((1S,2R,4S,5S)-4-(aminomethyl)bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine

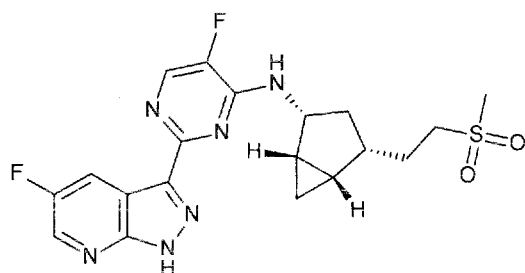


- 15 To a stirred solution of (+ or -)-N-((1S,2R,4S,5S)-4-((bis(4-methoxybenzyl)amino)methyl)-bicyclo[3.1.0]hexan-2-yl)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-amine (160 mg, 0.234 mmol) in MeCN (1.5 mL) and H₂O (0.5 mL) was added CAN (1.93 g, 3.520 mmol) and the resulting mixture solution was stirred at 50°C
20 for 4 h. The reaction was quenched with satd. aq. Na₂SO₃ solution (20 mL) and extracted with DCM (20 mL three times). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was re-dissolved in TFA (3 mL) and the resulting mixture solution was stirred at 30°C for 12 h. Afterwards, the reaction mixture was concentrated in vacuo to give a crude product, which was then purified
25 by Prep-HPLC to afford the title compound (5 mg, 4.1% yield) as a yellow solid. MS: 358.1 [M+H]⁺. ¹H NMR (400MHz, MeOH-d₄) δ 8.62 (s, 1 H), 8.35-8.41 (m, 1 H), 8.32 (d, J=4.77

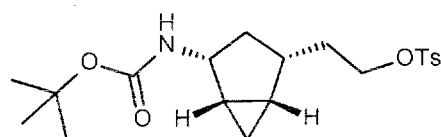
Hz, 1 H), 5.13-5.21 (m, 1 H), 2.96-3.09 (m, 2 H), 2.69-2.79 (m, 1 H), 2.26-2.37 (m, 1 H), 1.96 (d, J=3.01 Hz, 1 H), 1.64-1.74 (m, 1 H), 1.11-1.23 (m, 1 H), 0.82-0.90 (m, 1 H), 0.52-0.64 (m, 1 H).

5 Example 42

(+ or -)-5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-W-((1S,2R,4R,5S)-4-(2-(methylsulfonyl)ethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine



1A 1 (+ or -)-2-((1S,2R,4R,5S)-4-(tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexan-2-yl)ethyl 4-methylbenzenesulfonate



To a stirred solution of (+ or -)-tert-butyl ((1S,2R,4R,5S)-4-(2-hydroxyethyl)bicyclo[3.1.0]hexan-2-yl)carbamate (Example 24/Step B, 200 mg, 0.83 mmol) and Et₃N (161 mg, 1.6 mmol) in DCM (10 mL) was added TsCl (235 mg, 1.24 mmol) in an ice-water bath. After stirred at 0 °C for 10 min, the reaction was allowed to warm up to room temperature and stirred for another 12 h. Afterwards, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc=10:1) to afford the title compound (100 mg, 30% yield) as a white solid. MS: 395.2 [M+Hf.

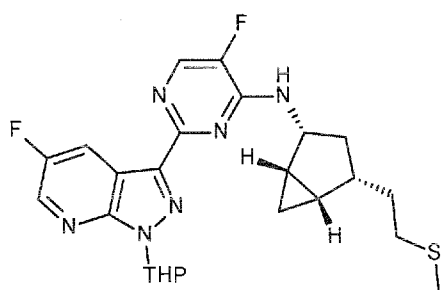
1B 1 (+ or -)-((1S,2R,4R,5S)-4-(2-(Methylthio)ethyl)bicyclo[3.1.0]hexan-2-amine hydrochloride



A mixture solution of (+ or -)-2-((1S,2R,4R,5S)-4-(tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexan-2-yl)ethyl 4-methylbenzenesulfonate (100 mg, 0.25 mmol) and sodium methanethiolate (35 mg, 0.5 mmol) in EtOH (5 mL) was stirred at room temperature for 2 h.

After TLC showed that the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (10 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was re-dissolved in 4N HCl/MeOH (10 mL) and the resulting mixture solution was stirred at room temperature for 2 h. Afterwards, the mixture solution was concentrated under reduced pressure and the precipitated solid was slurried with petroleum ether (10 mL) before filtration to afford the title compound (35 mg, 66.7% yield) as a yellow solid.

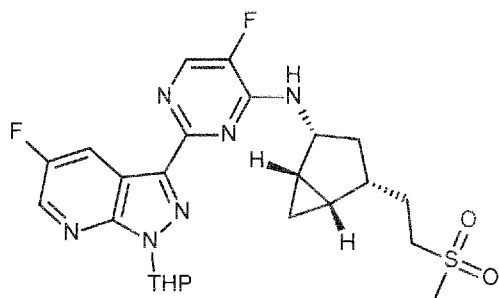
10 [CI (+ or -)-5-Fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4R,5S)-4-(2-(methylthio)ethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine



A mixture solution of (+ or -)-(1S,2R,4R,5S)-4-(2-(methylthio)ethyl)bicyclo[3.1.0]hexan-2-amine hydrochloride (35 mg, 0.17 mmol), 5-fluoro-3-(5-fluoro-4-(methylsulfonyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (70.5 mg, 0.18 mmol), and DIPEA (65.8 mg, 0.5 mmol) in THF (5 mL) was stirred at 70°C for 2 h. After TLC showed that the reaction was completed, the mixture solution was concentrated under reduced pressure. The crude product was then purified by silica gel flash chromatography (petroleum: EtOAc = 5:1) to afford the title compound (60 mg, 72.6% yield) as yellow oil.

20 MS: 487.2 $[\text{M}+\text{H}]^+$.

[PI (+ or -)-5-Fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrimidin-3-yl)-N-((1S,2R,4R,5S)-4-(2-(methylsulfonyl)ethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine

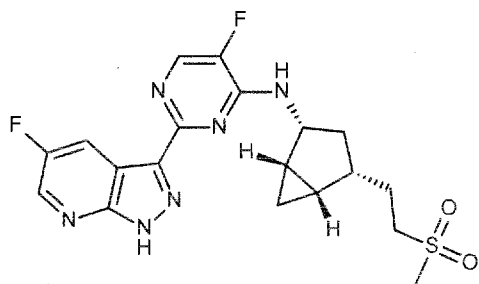


To a stirred solution of (+ or -)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4R,5S)-4-(2-(methylthio)ethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine (50 mg, 0.1 mmol) in DCM (5 mL) was added 3-chlorobenzoperoxoic acid (40 mg, 0.2 mmol) and the resulting mixture was stirred at room temperature for 1 h.

5 After TLC showed that the reaction was completed, the mixture was concentrated under reduced pressure and the residue was re-dissolved in MeOH (5 mL) followed by the addition of NH₄Cl (26 mg, 0.5 mmol) and Zn (19.5 mg, 0.3 mmol). The resulting reaction mixture was stirred at room temperature for 1 h before it was filtered. The filtrate was concentrated in vacuo to afford a crude title compound (40 mg, 70.8 % yield) as white oil.

10 MS: 519.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

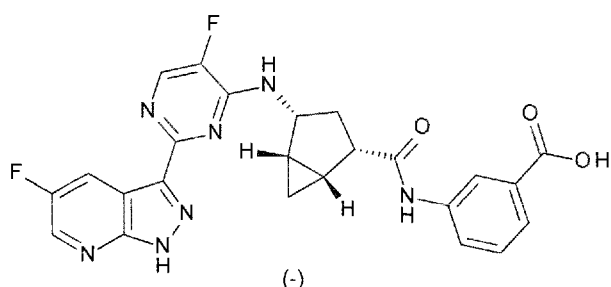
[E] (+ or -) 5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4R,5S)-4-(2-(methylsulfonyl)ethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine



A solution of (+ or -)-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-N-((1S,2R,4R,5S)-4-(2-(methylsulfonyl)ethyl)bicyclo[3.1.0]hexan-2-yl)pyrimidin-4-amine (40 mg, 0.07 mmol) in TFA (5 mL) was stirred at 50°C for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo, and the crude product was purified by Prep-HPLC (TFA) to afford a title compound (10 mg, 32.2% yield) as a yellow solid. MS: 435.1 [M+H]⁺. ¹H NMR (300 MHz, MeQH-d₄) δ 0.43 - 0.55 (m, 1 H) 0.73 - 0.87 (m, 1 H) 1.07 - 1.27 (m, 1 H) 1.59 - 1.71 (m, 1 H) 1.82 - 2.01 (m, 3 H) 2.17 - 2.33 (m, 1 H) 2.55 (dt, J=7.06, 3.63 Hz, 1 H) 3.01 (s, 3 H) 3.14 - 3.31 (m, 2 H) 5.07 - 5.20 (m, 1 H) 8.32 (d, J=5.09 Hz, 1 H) 8.36 - 8.42 (m, 1 H) 8.62 - 8.67 (m, 1 H).

Example 43

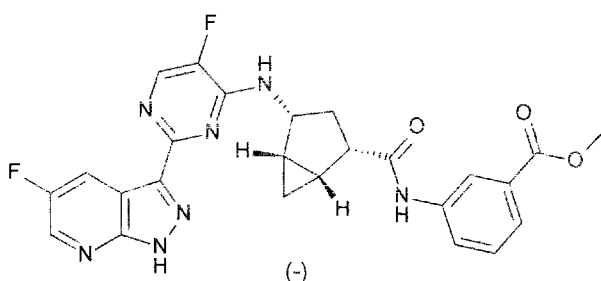
(-)-3-[[[(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]benzoic acid



In analogy to the synthesis of Example 34, methyl 3-aminobenzoate (19.9 mg, 131 μmol) was used in step A. Following subsequent ester hydrolysis (Step B) and de-protection of THP, the title compound (10 mg, 14% yield) was obtained after Prep-HPLC purification as a white solid. MS: 492.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 0.27 - 0.42 (m, 1 H) 0.99 (d, $J=4.52$ Hz, 1 H) 1.78 (dd, $J=8.03, 4.02$ Hz, 1 H) 1.85 - 2.05 (m, 2 H) 3.13 - 3.25 (m, 1 H) 4.96 (br. s., 1 H) 7.40 (t, $J=7.78$ Hz, 1 H) 7.61 (d, $J=7.78$ Hz, 1 H) 7.87 (t, $J=6.27$ Hz, 2 H) 8.23 (br. s., 1 H) 8.31 (d, $J=3.76$ Hz, 1 H) 8.50 (d, $J=7.78$ Hz, 1 H) 8.66 (br. s., 1 H) 10.13 (br. s., 1 H).

Example 44

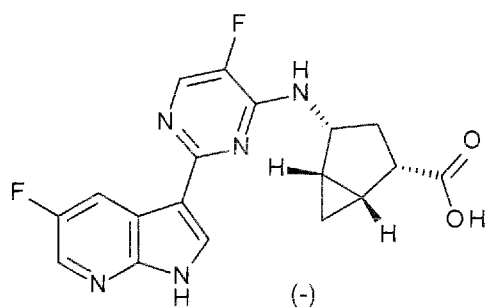
(-)-Methyl 3-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]benzoate



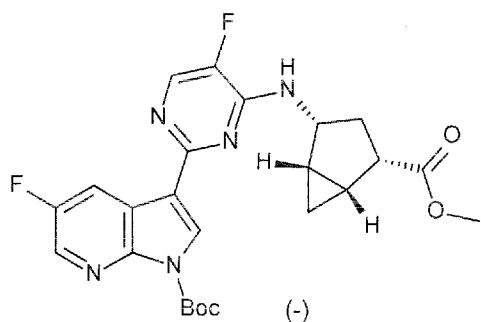
A solution of crude (-)-methyl 3-[[[(1S,2R,4S,5R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carbonyl]amino]benzoate (Example 43/Step A, 83 mg, 164 μmol) in TFA (4 mL) and DCM (4 mL) was stirred at room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (10 mg, 14% yield). MS: 506.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 0.29 - 0.41 (m, 1 H) 0.95 - 1.03 (m, 1 H) 1.78 (d, $J=3.76$ Hz, 2 H) 1.85 - 2.04 (m, 2 H) 3.15 - 3.24 (m, 1 H) 3.87 (s, 3 H) 4.97 (br. s., 1 H) 7.47 (t, $J=7.91$ Hz, 1 H) 7.64 (d, $J=7.78$ Hz, 1 H) 7.80 - 7.95 (m, 2 H) 8.26 - 8.40 (m, 2 H) 8.49 (d, $J=8.53$ Hz, 1 H) 8.64 (br. s., 1 H) 10.22 (s, 1 H).

Example 45

(-)-(1S,2R,4S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid

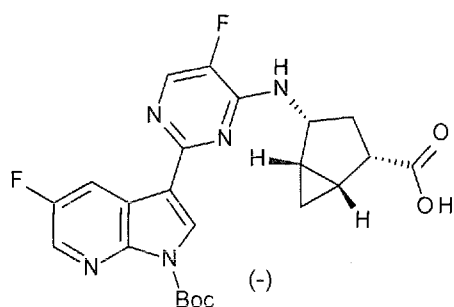


[A] (-)-tert-Butyl 5-fluoro-3-(5-fluoro-4-((1S,2R,4S,5R)-4-methoxycarbonyl-2-bicyclo[3.1.0]hexan-1-ylamino)pyrrolo[2,3-b]pyridine-1-carboxylate



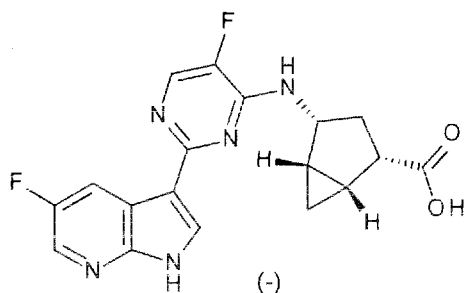
To a stirred mixture solution of tert-butyl 5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (70 mg, 0.19 mmol) and (-)-(1R,2S,4R,5S)-methyl 4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylate (Intermediate B-7/step B, 61 mg, 0.21 mmol) in dioxane (3 mL) was added $\text{Pd}_2(\text{dba})_3$ (18 mg, 0.012 mmol) and X-Phos (0.012 g, 0.025 mmol) under N_2 atmosphere. The resulting mixture was stirred at 110°C for 4 h. After cooling to room temperature, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the title compound (15 mg, 100% yield). MS: 486.2 $[\text{M}+\text{H}]^+$.

[B] (-)-(1R,2S,4R,5S)-4-((2-(1-(tert-butoxycarbonyl)-5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid



To a stirred solution of (-)-*tert*-butyl 5-fluoro-3-(5-fluoro-4-(((1S,2R,4S,5R)-4-(methoxycarbonyl)bicyclo[3.1.0]hexan-2-yl)amino)pyrimidin-2-yl)-1H-pyrrolo[2.3-b]pyridine-1-carboxylate (15 mg, 0.03 mmol) in THF (2 mL) and H₂O (0.5 mL) was added NaOH (13 mg, 0.3 mmol). The mixture was stirred at room temperature for 1 h and concentrated in vacuo to give a crude title compound (15 mg) as oil. This crude product was used directly in the next step without further purification.

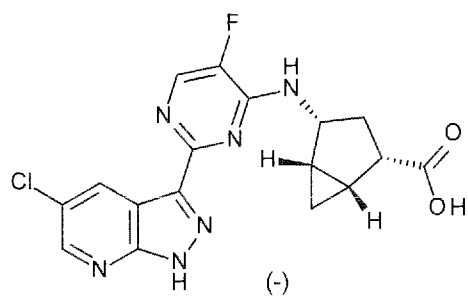
Example 45 (-)-((1S,2R,4S,5R)-2-(5-fluoro-1H-pyrrolo[2.3-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-4-carboxylic acid



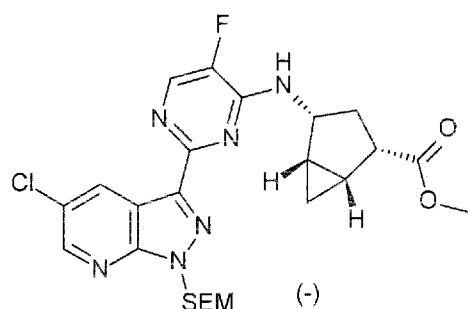
A solution of (-)-((1S,2R,4S,5R)-2-(5-fluoro-1H-pyrrolo[2.3-b]pyridin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid (15 mg, 0.03 mmol) in TFA (1 mL) and DCM (3 mL) was stirred at 30°C for 6 h under N₂ atmosphere. Afterwards, the mixture was concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (2 mg, 17% yield). MS: 372.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) 8.04 (q, J=5.19 Hz, 1 H) 0.56 (td, J=8.78, 4.77 Hz, 1 H) 1.09 - 1.22 (m, 1 H) 1.37 - 1.44 (m, 1 H) 1.63 - 1.79 (m, 1 H) 2.00 - 2.17 (m, 1 H) 2.25 - 2.39 (m, 1 H) 5.07 (d, J=4.77 Hz, 1 H) 7.81 (d, J=8.28 Hz, 1 H) 8.25 - 8.36 (m, 1 H) 8.57 (d, J=8.66 Hz, 1 H) 8.65 (s, 1 H) 12.21 (br. s., 1 H) 14.17 (br. s., 1 H).

Example 46

(-)-((1S,2R,4S,5R)-2-[[2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl]amino)bicyclo[3.1.0]hexane-4-carboxylic acid

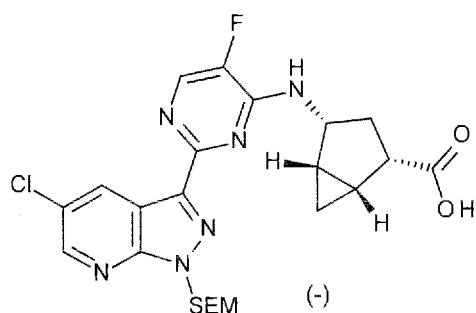


IA 1 (-)-Methyl (1S,2R,4S,5R)-2-(2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-4-carboxylate



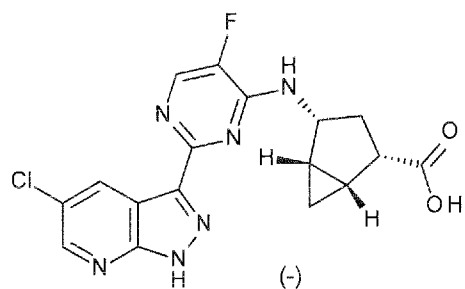
- 5 To a stirred mixture solution of (-)-(1R,2S,4R,5S)-methyl 4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylate (intermediate B-7/step B, 285 mg, 1 mmol) and Pd(PPh₃)₄ (120 mg, 0.1 mmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (960 mg, 870 μL, 1.65 mmol) at room temperature and the resulting reaction mixture was heated to 125°C for 2 h. After cooling down, 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (intermediate A-3, 409 mg, 1 mmol) and another batch of Pd(PPh₃)₄ (120 mg, 0.1 mmol) in dioxane (16 mL) were added into the above mixture. The combined reaction mixture was heated at 145°C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was diluted into water (2 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (45 mg, 8% yield) as yellow oil, MS: 533.2 [M+H]⁺

- 15 FBI (-)-(1S,2R,4S,5R)-2-(2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-4-carboxylic acid
- 20



To a stirred solution of (-)-methyl (1S,2R,4S,5R)-2-[[2-[5-chloro-1-(2-trimethylsilylethoxymethyl)pyrazolo[3,4-b]pyridin-3-yl]-5-fluoropyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylate (45 mg, 0.085 mmol) in THF (4 mL) and MeOH (4 mL) was added LiOH (12 mg, 0.254 mmol) pre-dissolved in H₂O (2 mL). The resulting reaction mixture was stirred at room temperature for 16 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH = 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (46 mg, 100% yield) as yellow oil. MS: 519.2 [M+H]⁺. It was used directly in next step without further purification.

(-)-(1S,2R,4S,5R)-2-[[2-[5-chloro-1-(2-trimethylsilylethoxymethyl)pyrazolo[3,4-b]pyridin-3-yl]-5-fluoropyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid

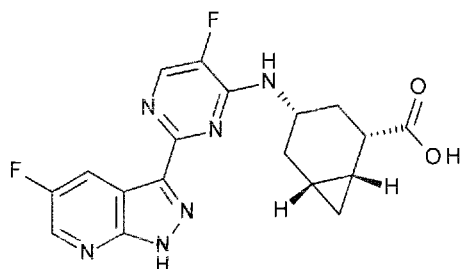


To a stirred solution of (-)-(1S,2R,4S,5R)-2-[[2-[5-chloro-1-(2-trimethylsilylethoxymethyl)pyrazolo[3,4-b]pyridin-3-yl]-5-fluoropyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-4-carboxylic acid (46 mg, 0.085 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (1 mL) at room temperature and stirred overnight. The reaction mixture was then concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (6 mg, 18% yield) as white foam. MS: 389.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.92 (d, J=2.26 Hz, 1 H) 8.55 - 8.58 (m, 1 H) 8.15 - 8.19 (m, 1 H) 5.02 - 5.10

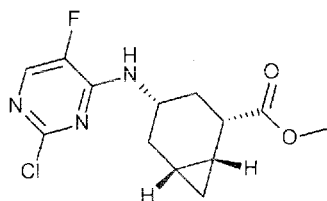
(m, 1 H) 2.22 - 2.31 (m, 1 H) 1.83 - 1.91 (m, 1 H) 1.72 - 1.82 (m, 1 H) 1.58 - 1.70 (m, 2 H) 0.91 - 0.97 (m, 1 H) 0.45 - 0.53 (m, 1 H).

Example 47

5 (rac)-(1R,2S,4S,6R)-4-((5-fluoro-2-((5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]norcarane-2-carboxylic acid



[A] (rac)-Methyl (1R,2S,4S,6R)-4-((2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-2-carboxylate

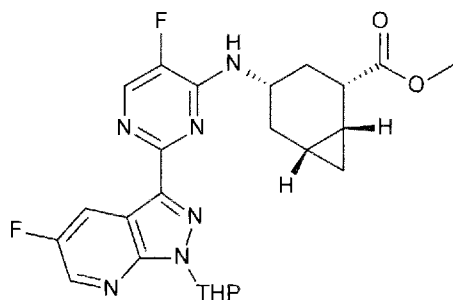


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To a stirred solution of (rac)-methyl (1R,2S,4S,6R)-4-aminonorcarane-2-carboxylate (intermediate B-15, 0.3 g, 1.6 mmol) in THF (20 mL) was added a solution of 2,4-dichloro-5-fluoropyrimidine (0.26 g, 1.6 mmol) in THF (10 mL) at -20°C, and then the solution was allowed to warm up to room temperature and stirred for another 16 h. The solvent was removed by evaporation to give a crude product, which was purified by Prep-TLC to give the title compound (0.3 g, 63.8% yield) as a white solid. ¹H NMR (400 MHz, CHCl₃-d₁) δ 7.96 - 7.79 (m, 1H), 5.11 (d, J=7.0 Hz, 1H), 4.09 - 3.95 (m, 1H), 3.74 (s, 3H), 3.27 - 3.17 (m, 1H), 2.57 - 2.42 (m, 1H), 1.95 (td, J=2.6, 12.9 Hz, 1H), 1.35 - 1.25 (m, 3H), 1.13 (ddd, J=2.0, 5.8, 8.5 Hz, 1H), 0.73 (dt, J=5.3, 8.9 Hz, 1H), 0.25 (q, J=5.4 Hz, 1H).

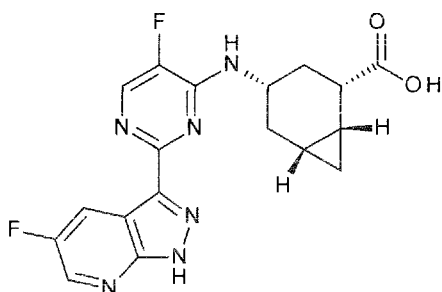
20

fBI (rac)-Methyl (1R,2S,4S,6R)-4-((5-fluoro-2-((5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]norcarane-2-carboxylate



To a solution of (rac)-methyl (1R,2S,4S,6R)-4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]norcarane-2-carboxylate (0.3 g, 1.0 mmol) and hexabutyliditin (0.86 g, 1.5 mmol) in dioxane (4 mL) was added Pd(PPh₃)₄ (115 mg, 0.1 mmol) under N₂ atmosphere, and the resulting mixture was stirred at 110°C for 2 h. Afterwards, the solution was cooled to room temperature, followed by the addition of 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1 a, 0.44 g, 1.3 mmol) and Pd(PPh₃)₄ (115.0 mg, 0.1 mmol) in one portion and the mixture solution was heated to 145°C under microwave heating for additional 1 h. The reaction was quenched with aq. KF solution (20 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-TLC separation to afford the title compound (0.1 g, 20.8% yield) as a yellow solid. ¹H NMR (400 MHz, MeOH-c/4) δ 8.61 - 8.48 (m, 2H), 8.14 (d, J=3.5 Hz, 1H), 6.18 (d, J=9.3 Hz, 1H), 4.18 (br. s., 1H), 4.09 (d, J=1.0 Hz, 1H), 3.85 (t, J=11.0 Hz, 1H), 3.73 (s, 3H), 3.68 - 3.62 (m, 1H), 2.81 (d, J=13.1 Hz, 1H), 2.63 - 2.49 (m, 1H), 2.20 (br. s., 1H), 2.05 (t, J=13.3 Hz, 2H), 1.97 - 1.74 (m, 2H), 1.70 (br. s., 1H), 1.67 (br. s., 1H), 1.51 (t, J=12.7 Hz, 1H), 1.44 - 1.29 (m, 2H), 1.23 (d, J=9.3 Hz, 1H), 0.82 - 0.70 (m, 1H), 0.40 - 0.27 (m, 1H).

[Cl] (racV(1R,2S,4S,6R)-4-r[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)]pyrimidin-4-ylaminonorcarane-2-carboxylic acid

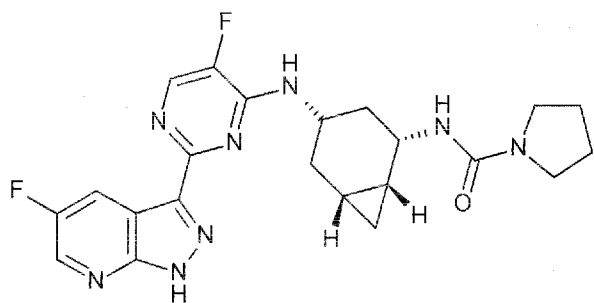


To a stirred solution of (rac)-methyl (1R,2S,4S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)]pyrimidin-4-yl]amino]norcarane-2-carboxylate (0.1 g, 0.14 mmol) in THF (5 mL) was added LiOH (33.6 mg, 1.4 mmol) and

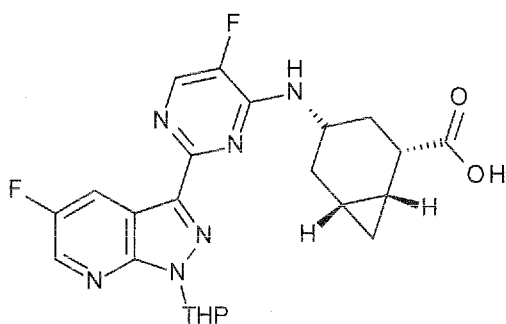
H₂O (1 mL), and the resulting mixture was stirred at 60°C for 6 h. After the solution was cooled to room temperature, 10 N aq. HCl solution (2 mL) was added slowly, and the resulting mixture was re-heated to 50°C for 2 days. The solvent was removed under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (22.3 mg, 28% yield) as a white solid of racemic mixture. ¹H NMR (400 MHz, MeOH-d₄) δ 8.65 (br. s., 1H), 8.42 (d, J=6.0 Hz, 1H), 8.29 (d, J=4.8 Hz, 1H), 4.34 (br. s., 1H), 3.32 - 3.26 (m, 1H), 2.59 (td, J=6.9, 13.6 Hz, 1H), 2.07 (d, J=12.8 Hz, 1H), 1.65 - 1.47 (m, 2H), 1.46 - 1.38 (m, 1H), 1.33 - 1.18 (m, 1H), 0.82 (dt, J=5.1, 8.7 Hz, 1H), 0.36 (q, J=5.3 Hz, 1H).

Example 48

(rac)-/V-[(1R,2S,6R)-4-[[5-fluoro-2-{5-fluoro-1W-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcaran-2-yl]pyrroliidine-1-carboxamide



(rac)-(1R,2S,6R)-4-[[5-fluoro-2-{5-fluoro-1-tetrahydropyran-2-yl}pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-2-carboxylic acid

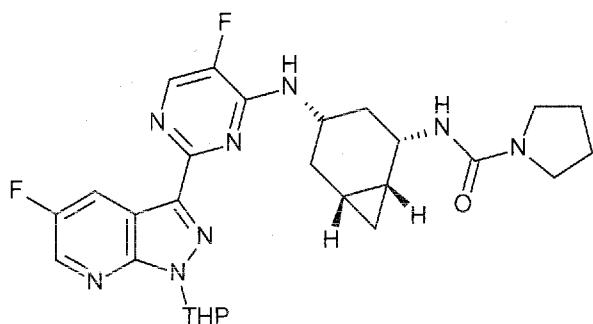


To a stirred solution of (rac)-methyl (1R,2S,4S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-2-carboxylate (0.2 g, 0.4 mmol) in THF (10 mL) was added LiOH (96 mg, 4 mmol) and H₂O (2 mL), and the resulting mixture was stirred at 60°C for 3 h. After TLC (petroleum ether: EtOAc = 1: 1) showed the starting material was consumed completely, the solution was cooled to 0°C, and adjusted pH = 4 by the addition of 1 N aq. HCl solution. The mixture was

extracted with DCM (30 mL three times), and the combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was co-evaporated with toluene 3 times to remove water to afford the title compound (0.16 g, 85% yield) as a white solid.

5

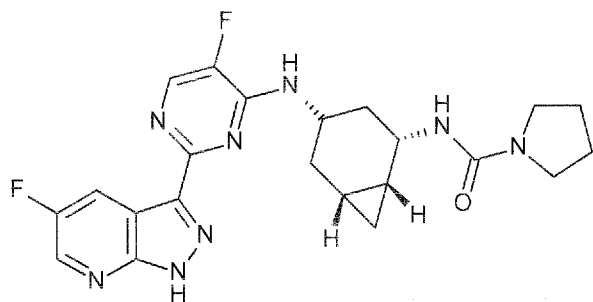
[B] (rac)-N-[(1R,2S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcaran-2-ylpyrrolidine-1-carboxamide



To a stirred solution of (rac)-(1R,2S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-2-carboxylic acid (0.16 g, 0.34 mmol) in toluene (10 mL) were added triethylamine (68.7 mg, 0.68 mmol) and diphenylphosphoryl azide (121.6 mg, 0.44 mmol) at room temperature and stirred for 30 min before the reaction temperature was raised to 90°C and heated for 2h. Afterwards, the reaction mixture was cooled to 0°C and pyrrolidine (48.3 mg, 0.68 mmol) was added, and the resulting mixture solution was stirred at room temperature for 16 h. The solvent was removed under reduced pressure to give a crude product, which was purified by Prep-TLC separation (DCM: MeOH) to afford the title compound (0.1 g, 55% yield) as a yellow solid.

fCl (rac)-N-[(1R,2S,6R)-4-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcaran-2-ylpyrrolidine-1-carboxamide

20

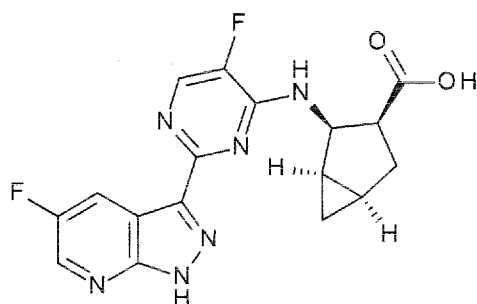


To a stirred solution of (rac)-N-[(1R,2S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcaran-2-ylpyrrolidine-1-carboxamide

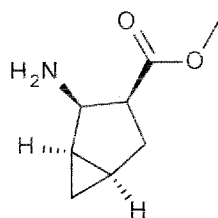
(0.1 g, 0.08 mmol) in DCM (10 mL) was added TFA (0.5 mL) and the mixture solution was stirred at 40°C for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (19.5mg, 21% yield) as a white solid. ¹H NMR (400 MHz, MeOH-d₄) δ 8.62 - 8.45 (m, 2H), 8.12 (br. s., 1H), 4.64 - 4.51 (m, 1H), 4.27 (d, J=4.8 Hz, 1H), 3.36 (d, J=7.3 Hz, 4H), 2.59 (d, J=6.5 Hz, 1H), 2.04 (d, J=10.0 Hz, 1H), 1.93 (t, J=6.5 Hz, 4H), 1.48 - 1.35 (m, 2H), 1.32 - 1.19 (m, 2H), 0.73 (dt, J=4.9, 8.7 Hz, 1H), 0.43 (q, J=5.2 Hz, 1H).

Example 49

10 **(rac-1R,2R,3S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid**

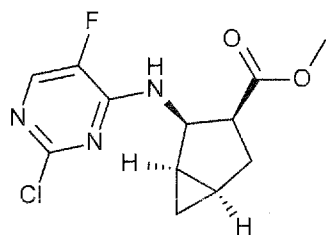


[A] (rac)-(1R,2R,3S,5R)-Methyl 2-aminobicyclo[3.1.0]hexane-3-carboxylate



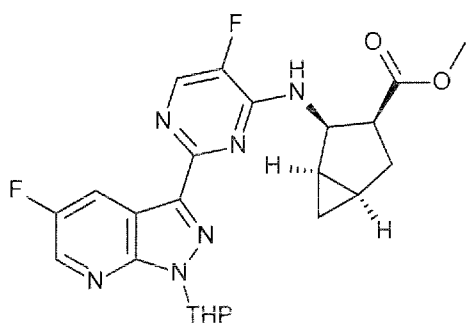
15 A solution of racemic mixture of (1R,2R,3S,5R)-methyl 2-((tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexane-3-carboxylate (Intermediate B-5, 4g, 8.3 mmol) in TFA/DCM (15 mL/15 mL) was stirred at room temperature for 2 h. Afterwards, the solvent was evaporated to dryness under reduced pressure to give a crude racemic mixture of a title compound (3 g) as yellow gum. MS: 156.1 [M+H]⁺. This crude product was used directly
20 in the next step without further purification.

[B] (rac)-Methyl (1R,2R,3S,5R)-2-((2-chloro-5-fluoro-pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-3-carboxylate



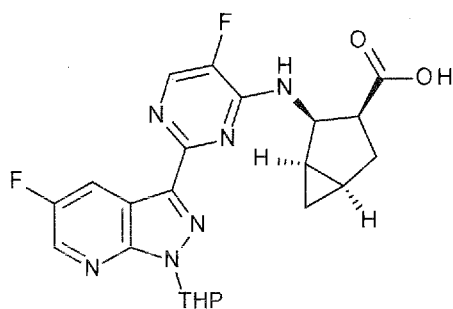
A stirred racemic mixture solution of (1R,2R,3S,5R)-methyl 2-aminobicyclo[3.1.0]hexane-3-carboxylate (3 g, 8.3 mmol), 2,4-dichloro-5-fluoro-pyrimidine (2 g, 11.9 mmol) and DIPEA (10 g, 77.5 mmol) in THF (20 mL) was heated at 60°C for 16 h. After cooling down, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the racemic mixture of title compounds (1g, 42% yield) as a yellow solid. MS: 286.1 [M+H]⁺.

[C] (rac)-Methyl (1R,2R,3S,5R)-2-[(2-fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ylamino]bicyclo[3.1.0]hexane-3-carboxylate



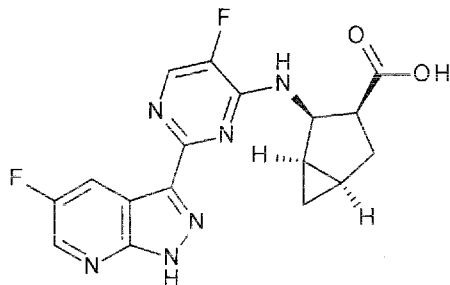
A stirred solution of racemic mixture of methyl (1R,2R,3S,5R)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]bicyclo[3.1.0]hexan-3-carboxylate (286 mg, 1.0 mmol), hexa-n-butyliditm (1 mL, 1.98 mmol) and Pd(PPh₃)₄ (150 mg) in dioxane (12 mL) was heated at 125°C for 1 h. After cooling down, 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 300mg, 0.9 mmol) and Pd(PPh₃)₄ (150 mg) were added and the resulting mixture was heated at 145°C for additional 1 h under microwave heating. The solvent was evaporated to dryness under reduced pressure and the crude product was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the racemic mixture of title compounds (80 mg, 15% yield) as a yellow solid. MS: 471.2 [M+H]⁺.

[D] (rac)-(1R,2R,3S,5R)-2-[(2-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ylamino]bicyclo[3.1.0]hexane-3-carboxylic acid



A solution of racemic mixture of methyl (1R,2R,3S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylate (80 mg, 0.17 mmol) and LiOH monohydrate (100 mg, 2.3 mmol) in THF/water (4 mL/4 mL) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to give a crude racemic mixture of title compounds (200 mg) as yellow gum. MS: 457.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

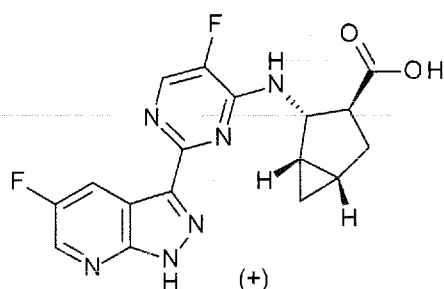
10 [El] (rac)-(1R,2R,3S,5R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid



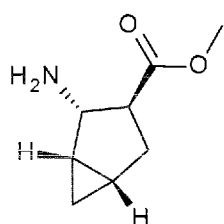
A solution of racemic mixture of (1R,2R,3S,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid (200 mg, 0.17 mmol) in TFA/DCM (5 mL/5 mL) was stirred at room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the racemic mixture of title compounds (10 mg, 16% yield) as a white solid. MS: 373.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.30 - 0.40 (m, 1 H) 0.63 - 0.72 (m, 1 H) 1.38 - 1.47 (m, 1 H) 1.70 - 1.80 (m, 1 H) 2.02 (td, J=1.73, 4.39 Hz, 1 H) 2.07 - 2.17 (m, 1 H) 2.64 - 2.78 (m, 1 H) 5.18 (br. s., 1 H) 7.79 (d, J=7.78 Hz, 1 H) 8.32 (d, J=3.51 Hz, 1 H) 8.53 (d, J=7.28 Hz, 1 H) 8.65 (br. s., 1 H) 12.29 (br. s., 1 H) 14.16 (br. s., 1 H).

Example 50

(+)-(1S,2S,3S,5S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid



[A] (rac)-Methyl (1S,2S,3S,5S)-2-aminobicyclo[3.1.0]hexane-3-carboxylate

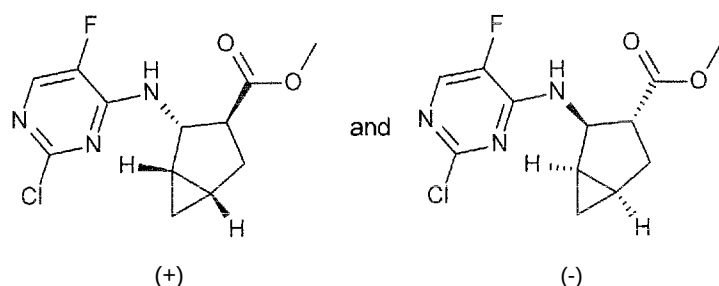


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In analogy to the synthesis of example 49/step A, a racemic mixture of (1S,2S,3S,5S)-methyl 2-((tert-butoxycarbonyl)amino)bicyclo[3.1.0]hexane-3-carboxylate (Intermediate B-6, 4 g, 8.3 mmol) was used. The crude title compound (3 g) obtained was used directly in the next step without further purification. MS: 156.1 [M+H]⁺.

10

IB 7 (+)-Methyl (1S,2S,3S,5S)-2-((2-chloro-5-fluoro-pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylate and (-)-methyl (1R,2R,3R,5R)-2-((2-chloro-5-fluoro-pyrimidin-4-yl)aminobicyclo[3.1.0]hexane-3-carboxylate

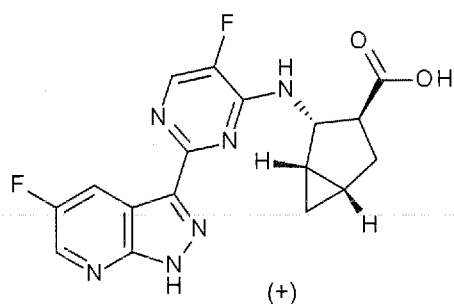


15 A stirred solution of racemic mixture of methyl (1S,2S,3S,5S)-2-aminobicyclo[3.1.0]hexane-3-carboxylate (3 g, 8.3 mmol), 2,4-dichloro-5-fluoro-pyrimidine (2 g, 11.9 mmol) and DIPEA (10 g, 77.5 mmol) in THF (20 mL) was heated at 60°C for 16 h. After cooling down, the solvent was evaporated to dryness under reduced pressure to give a crude product, which was purified by first silica gel flash chromatography and then SFC chiral separation (Chiral Pak. IC-H, 250 x 30 mm, 5 μm column, 30% EtOH in CO₂) to afford the title compound (+)-methyl (1S,2S,3S,5S)-2-((2-chloro-5-fluoro-pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-

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carboxylate (480 mg, 20% yield) and (-)-methyl (1R,2R,3R,5R)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-3-carboxylate (500 mg, 21% yield) as both white solids. MS: 286.1 [M+Hf.

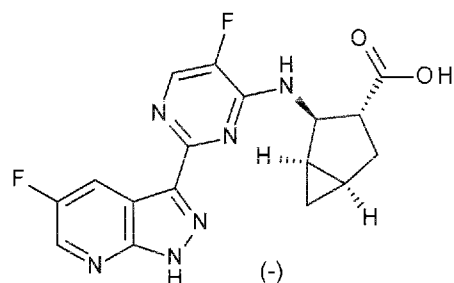
- 5 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 1040 1041 1042 1043 1044 1045 1046 1047 1048 1049 1050 1051 1052 1053 1054 1055 1056 1057 1058 1059 1060 1061 1062 1063 1064 1065 1066 1067 1068 1069 1070 1071 1072 1073 1074 1075 1076 1077 1078 1079 1080 1081 1082 1083 1084 1085 1086 1087 1088 1089 1090 1091 1092 1093 1094 1095 1096 1097 1098 1099 1100 1101 1102 1103 1104 1105 1106 1107 1108 1109 1110 1111 1112 1113 1114 1115 1116 1117 1118 1119 1120 1121 1122 1123 1124 1125 1126 1127 1128 1129 1130 1131 1132 1133 1134 1135 1136 1137 1138 1139 1140 1141 1142 1143 1144 1145 1146 1147 1148 1149 1150 1151 1152 1153 1154 1155 1156 1157 1158 1159 1160 1161 1162 1163 1164 1165 1166 1167 1168 1169 1170 1171 1172 1173 1174 1175 1176 1177 1178 1179 1180 1181 1182 1183 1184 1185 1186 1187 1188 1189 1190 1191 1192 1193 1194 1195 1196 1197 1198 1199 1200 1201 1202 1203 1204 1205 1206 1207 1208 1209 1210 1211 1212 1213 1214 1215 1216 1217 1218 1219 1220 1221 1222 1223 1224 1225 1226 1227 1228 1229 1230 1231 1232 1233 1234 1235 1236 1237 1238 1239 1240 1241 1242 1243 1244 1245 1246 1247 1248 1249 1250 1251 1252 1253 1254 1255 1256 1257 1258 1259 1260 1261 1262 1263 1264 1265 1266 1267 1268 1269 1270 1271 1272 1273 1274 1275 1276 1277 1278 1279 1280 1281 1282 1283 1284 1285 1286 1287 1288 1289 1290 1291 1292 1293 1294 1295 1296 1297 1298 1299 1300 1301 1302 1303 1304 1305 1306 1307 1308 1309 1310 1311 1312 1313 1314 1315 1316 1317 1318 1319 1320 1321 1322 1323 1324 1325 1326 1327 1328 1329



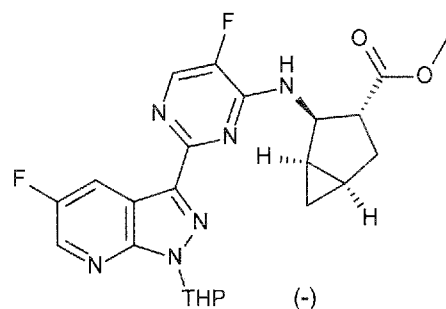
In analogy to the synthesis of example 49/step E, (+)-(1S,2S,3S,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid (400 mg, 0.35 mmol) was used to give a crude product, which was purified by Prep-HPLC to afford the title compound (20 mg, 15% yield) as a white solid. MS: 373.1 [M+H]⁺ ¹H NMR (400 MHz, DMSO-c₆) δ 0.27 - 0.41 (m, 1 H) 0.68 (q, J=3.89 Hz, 1 H) 1.36 - 1.49 (m, 1 H) 1.69 - 1.81 (m, 1 H) 1.96 - 2.07 (m, 1 H) 2.07 - 2.19 (m, 1 H) 2.61 - 2.79 (m, 1 H) 5.18 (d, J=3.26 Hz, 1 H) 7.78 (d, J=7.91 Hz, 1 H) 8.32 (d, J=3.76 Hz, 1 H) 8.53 (d, J=8.41 Hz, 1 H) 8.64 (s, 1 H) 12.27 (br. s., 1 H) 14.15 (br. s., 1 H).

Example 51

(-)-{1R,2R,3R,5R)-2-[15-Fluoro-2-(5-fluoro-1A_y-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid

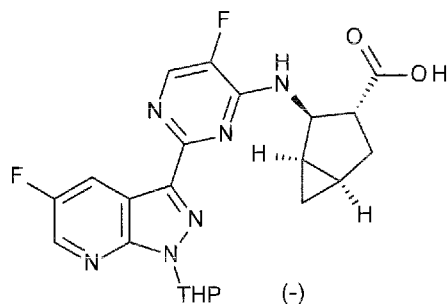


(-)-Methyl (1R,2R,3R,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydro pyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylate



In analogy to the synthesis of example 49/step C, (-)-methyl (1R,2R,3R,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-3-carboxylate was used to afford the title compound (150 mg, 24% yield) as a yellow solid. MS: 471.2 [M+H]⁺

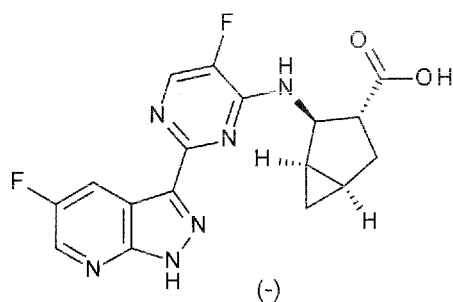
- 5 [B] (-)-(1R,2R,3R,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid



In analogy to the synthesis of example 49/step D, (-)-methyl (1R,2R,3R,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylate was used to afford the crude title compound (400 mg,

- 10 100% yield) as a yellow solid. MS: 457.2 [M+H]⁺.

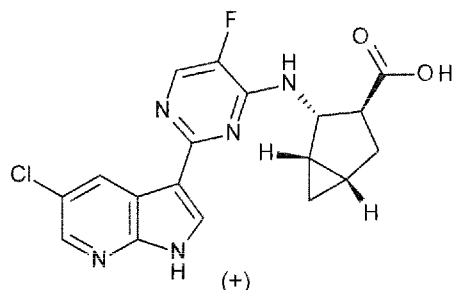
fCl (-)-(1R,2R,3R,5R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid



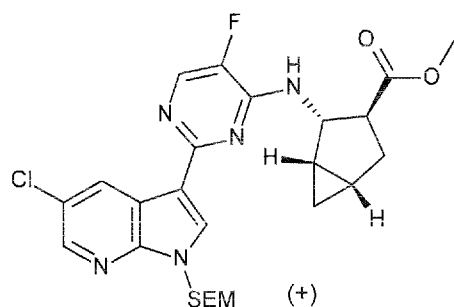
- 15 In analogy to the synthesis of example 49/step E, (-)-(1R,2R,3R,5R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid was used to afford the title compound (20 mg, 16% yield) as a white solid. MS: 373.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.29 - 0.39 (m, 1 H) 0.68 (q, J=4.02 Hz, 1 H) 1.38 - 1.48 (m, 1 H) 1.68 - 1.81 (m, 1 H) 1.95 - 2.07 (m, 1 H) 2.07 - 2.16 (m, 1 H) 2.62 - 2.77 (m, 1 H) 5.11 - 5.23 (m, 1 H) 7.79 (d, J=8.03 Hz, 1 H) 8.31 (d, J=3.76 Hz, 1 H) 8.53 (dd, J=8.66, 2.64 Hz, 1 H) 8.65 (dd, J=2.51, 1.51 Hz, 1 H) 14.16 (br. s., 1 H).
- 20

Example 52

(+)-(1S,2S,3S,5S)-2-[[2-(5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-5-fluoro-pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid

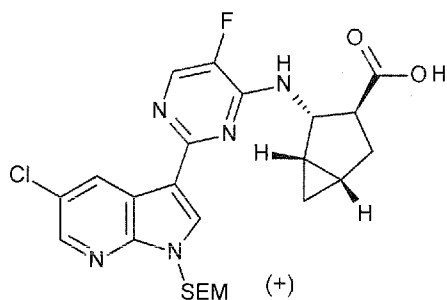


5 **IA 1 (+)-(1S,2S,3S,5S)-Methyl 2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylate**



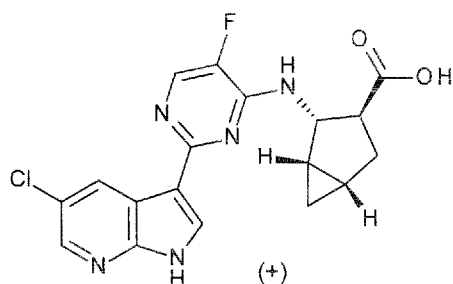
To a stirred mixture solution of 2-[[5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-*b*]pyridin-1-yl]methoxyethyl-trimethyl-silane (intermediate A-4b, 360 mg, 0.88 mmol) and (+)-methyl (1S,2S,3S,5S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-3-carboxylate (example 50/step B, 251 mg, 0.88 mmol) in dioxane/H₂O (5 mL/1 mL) was added Pd₂(dba)₃ (36 mg, 0.04 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (72 mg, 0.12 mmol) and K₃PO₄. The resulting reaction mixture solution was heated at 125°C for 2 h under microwave heating. After cooling down, the reaction mixture was poured into water (2 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (80 mg, 17% yield) as yellow oil. MS: 532.2 [M+Hf].

FBI (+)-(1S,2S,3S,5S)-2-((2-(5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylic acid



To a stirred solution of (+)-(1S,2S,3S,5S)-methyl 2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylate (80 mg, 0.15 mmol) in THF (4 mL) and MeOH (4 mL) was added LiOH (33 mg, 0.75 mmol) pre-dissolved in H₂O (2 mL). The reaction mixture was stirred at room temperature for 16 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The separated organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH = 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (81 mg) as yellow oil. MS: 518.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

(+)-(1S,2S,3S,5S)-2-((2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylic acid

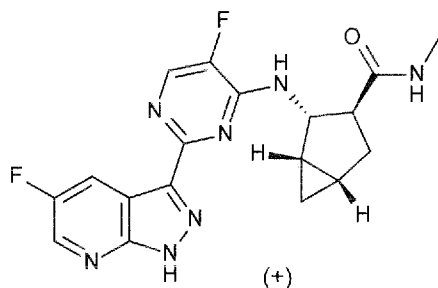


To a stirred solution of (+)-(1S,2S,3S,5S)-2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylic acid (81 mg, 0.15 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (1 mL) and the resulting mixture solution was stirred at room temperature for 12 h. The mixture was then concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (7.1 mg, 12% yield) as white foam. MS: 388.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-c₄) δ 8.90 (d, J=2.26 Hz, 1 H) 8.24 - 8.28 (m, 2 H) 8.10 (d, J=4.27 Hz, 1

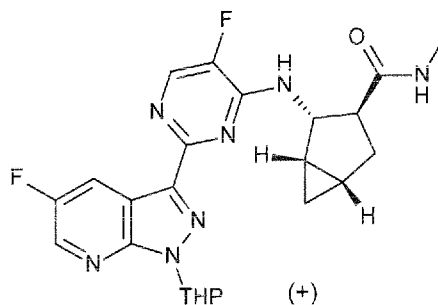
H) 5.35 - 5.41 (m, 1 H) 2.59 - 2.68 (m, 1 H) 2.21 - 2.30 (m, 2 H) 1.83 - 1.90 (m, 1 H) 1.52 - 1.59 (m, 1 H) 0.69 - 0.74 (m, 1 H) 0.47 - 0.54 (m, 1 H).

Example 53

- 5 **(+)-(1S,2S,3S,5S)-2-[[5-Fluoro-2-(5-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)pyrimidin-4-yl]amino]-4-methyl-bicyclo[3.1.0]hexane-3-carboxamide**



1A1 (+)-(1S,2S,3S,5S)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-*b*]pyridin-3-yl]amino]-4-methyl-bicyclo[3.1.0]hexane-3-carboxamide



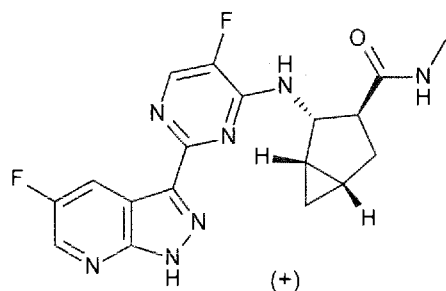
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A solution of (+)-methyl (1S,2S,3S,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-*b*]pyridin-3-yl]amino]-4-methyl-bicyclo[3.1.0]hexane-3-carboxylate (example 50/step C, 50 mg, 0.1 mmol) in 2M methylamine ethanol solution (15 mL) was stirred at room temperature for 70 h. Afterwards, the solvent was evaporated to dryness under reduced pressure to give a crude title compound (50 mg, 100% yield) as a yellow solid. MS: 470.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

15

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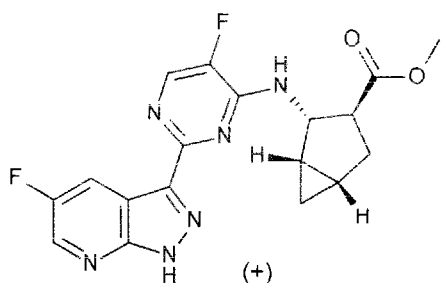
1B1 (+)-(1S,2S,3S,5S)-2-[[5-Fluoro-2-(5-fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)pyrimidin-4-yl]amino]-4-methyl-bicyclo[3.1.0]hexane-3-carboxamide



In analogy to the synthesis of example 49/step E, (+)-(1S,2S,3S,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-methylbicyclo[3.1.0]hexane-3-carboxamide (30 mg, 0.06 mmol) was used to give a crude product, which was purified by Prep-HPLC to afford the title compound (5 mg, 20% yield) as a white solid. MS: 386.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.27 - 0.40 (m, 1 H) 0.61 (q, J=3.85 Hz, 1 H) 1.35 - 1.45 (m, 1 H) 1.71 - 1.81 (m, 1 H) 1.93 - 2.08 (m, 2 H) 3.34(s, 3 H) 5.13 (td, J=8.41, 4.77 Hz, 1 H) 7.54 - 7.72 (m, 2 H) 8.30 (d, J=3.76 Hz, 1 H) 8.58 (d, J=7.28 Hz, 1 H) 8.64 (br. s., 1 H) 14.15 (br. s., 1 H).

Example 54

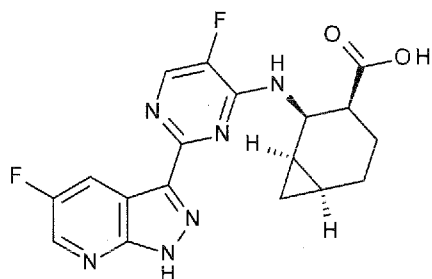
(+)-Methyl (1S,2S,3S,5S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylate



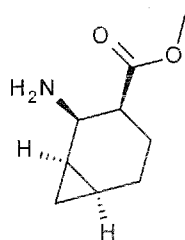
In analogy to the synthesis of example 49/step E, (+)-methyl (1S,2S,3S,5S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylate (example 50/step C, 30 mg, 0.06 mmol) was used. The crude product was purified by Prep-HPLC to afford the title compound (5 mg, 20%) as a white solid. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.32 - 0.44 (m, 1 H) 0.72 (q, J=4.02 Hz, 1 H) 1.40 - 1.50 (m, 1 H) 1.71 - 1.81 (m, 1 H) 2.00 - 2.17 (m, 2 H) 3.48 (s, 3 H) 5.19 (br. s., 1 H) 7.53 - 7.60 (m, 1 H) 7.61 - 7.69 (m, 1 H) 7.73 - 7.85 (m, 2 H) 8.33 (d, J=3.76 Hz, 1 H) 8.49 (d, J=7.28 Hz, 1 H) 8.65 (br. s., 1 H) 8.67 - 8.76 (m, 1 H) 14.17 (br. s., 1 H).

Example 55

(rac)-{1R,2R,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1*Ay*-pyrazolo[3,4-*b*]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



1A 1(rac)-{(1R,2R,3S,6S)-methyl 2-aminobicyclo[4. 1.0]heptane-3-carboxylate

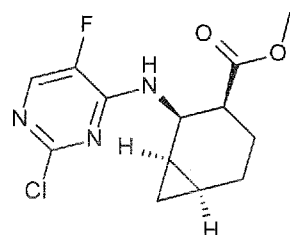


5

In analogy to the synthesis of example 49/step A, a racemic mixture of methyl (1*R*,2*R*,3*S*,6*S*)-2-(ferf-butoxycarbonylamino)norcarane-3-carboxylate (Intermediate B-8) and Intermediate B-10 (contained as a minor fraction from previous step of synthesis) (4g, 8.7 mmol) were used to give a crude title compound (3 g) as yellow gum. MS: 170.1 [M+H]⁺.

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

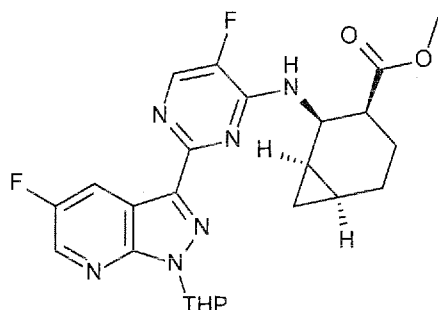
1B 1(rac)-Methyl (1*R*,2*R*,3*S*,6*S*)-2-((2-chloro-5-fluoro-1*Ay*-pyrazolo[3,4-*b*]pyridin-3-yl)amino)norcarane-3-carboxylate



15 In analogy to the synthesis of example 49/step B, a racemic mixture of (1*R*,2*R*,3*S*,6*S*)-methyl 2-aminobicyclo[4. 1.0]heptane-3-carboxylate (3 g, 8.7 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to give two pair of racemic mixture of compounds (2 g, 76% yield) as yellow solids. MS: 300.2 [M+H]⁺. This crude product was used directly in the next step without further purification. The title pair of racemic compound was obtained as major product.

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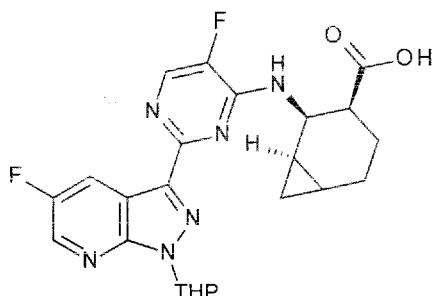
[C] (rac)-Methyl (1R,2R,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate



- 5 In analogy to the synthesis of example 49/step C, a racemic mixture of methyl (1R,2R,3S,6S)-2-[[2-chloro-5-fluoro-pyrimidin-4-yl]amino]norcaradiene-3-carboxylate (350 mg, 1.2 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the racemic mixture of title compounds (100 mg, 18% yield) as a yellow solid. MS: 485.1 [M+H]⁺.

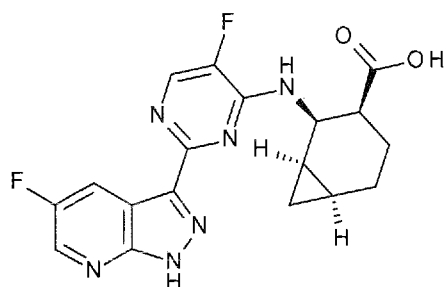
10

[D] (rac)-(1R,2R,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid



- 15 In analogy to the synthesis of example 49/step D, a racemic mixture of methyl (1R,2R,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate (100 mg, 0.21 mmol) was used to give a crude racemic mixture of title compound (200 mg) as yellow gum. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

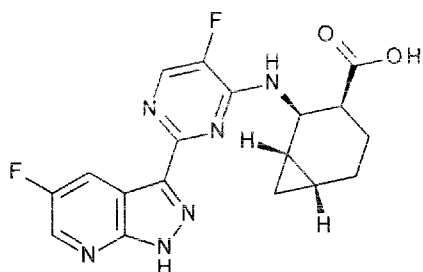
20 [E] (rac)-(1R,2R,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid



In analogy to the synthesis of example 49/step E, a racemic mixture of (1R,2R,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid (200 mg, 0.21 mmol) was used to give a crude product, which was purified by Prep-HPLC to afford the racemic mixture of title compounds (12 mg, 15% yield) as white solids. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.33 (d, J=4.77 Hz, 1 H) 0.69 (d, J=5.02 Hz, 1 H) 1.06 - 1.18 (m, 1 H) 1.38 - 1.56 (m, 2 H) 1.74 - 1.90 (m, 2 H) 2.54 (br. s., 1 H) 5.33 (br. s., 1 H) 8.30 (d, J=3.76 Hz, 1 H) 8.52 (d, J=8.28 Hz, 1 H) 8.65 (s, 1 H) 14.16 (br. s., 1 H).

Example 56

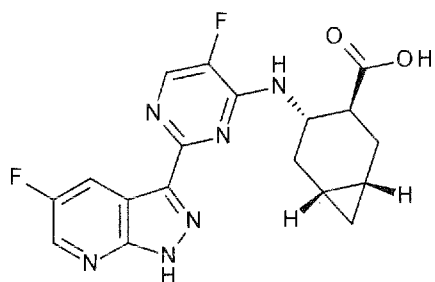
(rac)-(1S,2R,3S,6R)-2-[[5-Fluoro-2-{5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl}pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid



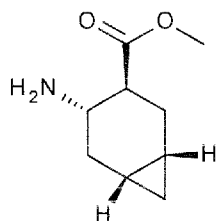
In the synthesis of example 55/step E, the title pair of racemic compound was obtained by Prep-HPLC separation as minor product (1.5 mg, 2% yield) that was derived from intermediate 10. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.23 - 0.30 (m, 1 H) 0.73 (dt, J=8.78, 4.39 Hz, 1 H) 0.98 (d, J=7.28 Hz, 1 H) 1.08 (br. s., 1 H) 1.28 (br. s., 1 H) 1.49 - 1.60 (m, 1 H) 1.86 - 1.94 (m, 1 H) 2.01 (dd, J=13.30, 6.53 Hz, 1 H) 6.61 (br. s., 1 H) 8.28 (d, J=3.51 Hz, 1 H) 8.64 (s, 2 H).

Example 57

(rac)-(1S,3S,4S,6R)-4-[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid



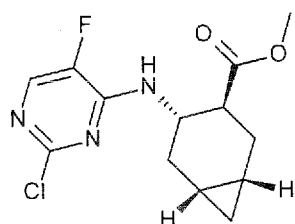
[A] (rac)-Methyl (1S,3S,4S,6R)-4-aminonorcaradiene-3-carboxylate and methyl (1R,3R,4R,6S)-4-aminonorcaradiene-3-carboxylate



- 5 In analogy to the synthesis of example 49/step A, a racemic mixture of methyl (1S,3S,4S,6R)-4-(tert-butoxycarbonylamino)norcaradiene-3-carboxylate (Intermediate B-11, 3 g, 3.9 mmol) was used to give a crude racemic mixture of title compound (3 g) as yellow gum. MS: 170.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

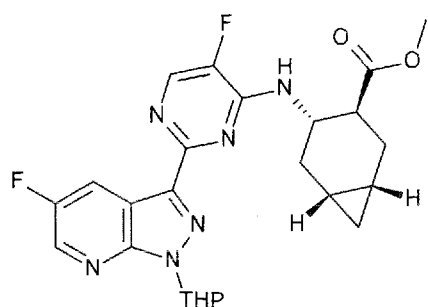
10

b) (rac)-Methyl (1S,3S,4S,6R)-4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]norcaradiene-3-carboxylate



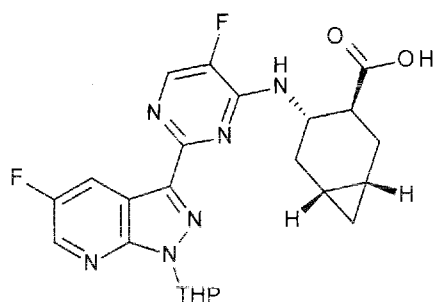
- 15 In analogy to the synthesis of example 49/step B, a racemic mixture of methyl (1S,3S,4S,6R)-4-aminonorcaradiene-3-carboxylate (3 g, 3.9 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-20% gradient) to afford the title compound (1 g, 85% yield) as a yellow solid. MS: 300.2 [M+H]⁺.

20 c) (rac)-Methyl (1S,3S,4S,6R)-4-[(5-fluoro-2-(5-fluoro-1-tetrahydro-2H-pyran-2-yl)-pyrazol-3-yl)amino]norcaradiene-3-carboxylate



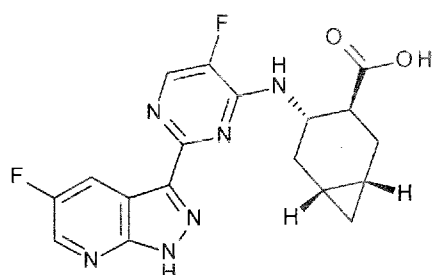
In analogy to the synthesis of example 49/step C, a racemic mixture of methyl (1S,3S,4S,6R)-4-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (300 mg, 1 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60%) to afford the racemic mixture of title compounds (100 mg, 20% yield) as yellow solids. MS: 485.3 [M+H]⁺.

[D] (rac)-(1S,3S,4S,6R)-4-[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-ylamino]norcarane-3-carboxylic acid



In analogy to the synthesis of example 49/stepD, a racemic mixture of methyl (1S,3S,4S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylate (100 mg, 0.17 mmol) was used to give a crude racemic mixture of title compounds (200 mg) as yellow gum. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

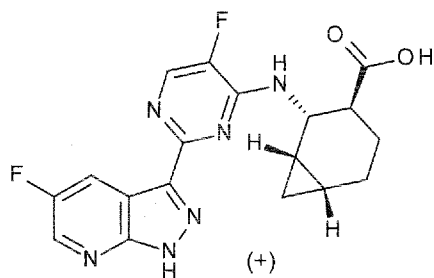
[E] (rac)-(1S,3S,4S,6R)-4-[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-ylamino]norcarane-3-carboxylic acid



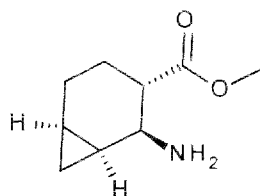
In analogy to the synthesis of example 49/step E, a racemic mixture of (1S,3S,4S,6R)-4-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid (200 mg, 0.17 mmol) was used to give a crude product, which was by Prep-HPLC to afford the racemic mixture of title compounds (16 mg, 25%) as white solids. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.01 - 0.16 (m, 1 H) 0.67 (td, J=8.66, 4.52 Hz, 1 H) 0.92 - 1.13 (m, 2 H) 1.52 (t, J=12.80 Hz, 1 H) 2.07 - 2.26 (m, 2 H) 2.29 - 2.46 (m, 2 H) 4.40 (br. s., 1 H) 7.64 (d, J=8.78 Hz, 1 H) 8.27 (d, J=3.76 Hz, 1 H) 8.59 (d, J=8.78 Hz, 1 H) 8.64 (s, 1 H) 12.17 (br. s., 1 H).

10 Example 58

(+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1H[^]pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

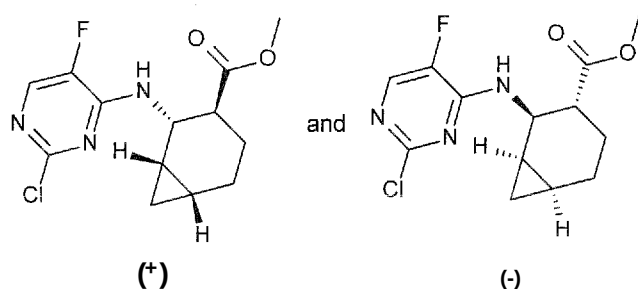


[A] (rac)-Methyl (1S,2S,3S,5K ¾-2-aminonorcarane-3-carboxylate



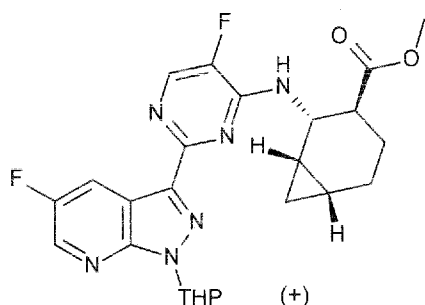
In analogy to the synthesis of example 49/step A, a racemic mixture of methyl (1S,2S,3S,6R)-2-(tert-butoxycarbonylamino)norcarane-3-carboxylate (Intermediate B-9, 3 g, 8.3 mmol) was used to give a crude racemic mixture of title compounds (3 g) as yellow gum. MS: 170.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

[B] (-)-Methyl (1S,2S,3S,6R)-2-((2-chloro-5-fluoro-pyrimidin-4-yl)amino)norcarane-3-carboxylate and (-)-methyl (1R,2R,3R,6S)-2-((2-chloro-5-fluoro-pyrimidin-4-yl)amino)norcarane-3-carboxylate



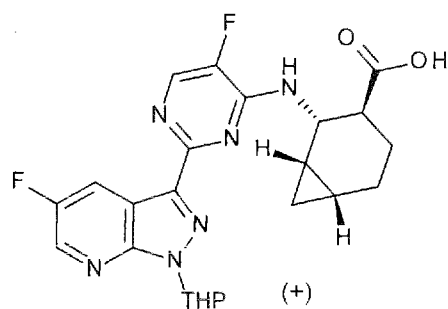
A stirred solution of racemic mixture of methyl (1S,2S,3S,6R)-2-aminonorcarane-3-carboxylate (3 g, 8.3 mmol) and TEA (8 g, 80 mmol) in THF (20 mL) was heated at 60°C for 16 h. After solvent was evaporated under reduce pressure, the crude product was purified first by silica gel flash chromatography (EtOAc/ petroleum ether, 0~20% gradient) and then SFC chiral separation (Chiral Pak, IC-H, 250 x 30 mm, 5 μm column, 20% MeOH in CO₂) to afford the title compound (+)-(1S,2S,3S,6R)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]norcarane-3-carboxylate (620 mg, 21% yield), MS: 300.2 [M+H]⁺ and (-)-(1R,2R,3R,6S)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]norcarane-3-carboxylate (650 mg, 26% yield), MS: 300.2 [M+H]⁺ as yellow solids.

[C] (+)-Methyl (1S,2S,3S,6R)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydro-2H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]norcarane-3-carboxylate



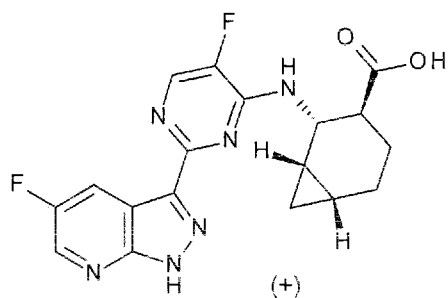
In analogy to the synthesis of example 49/step C, (+)-methyl (1S,2S,3S,6R)-2-[(2-chloro-5-fluoropyrimidin-4-yl)amino]norcarane-3-carboxylate (300 mg, 1 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60% gradient) to afford the title compound (100 mg, 20% yield) as a yellow solid. MS: 485.2 [M+H]⁺.

[D] (+)-(1S,2S,3S,6R)-2-[(5-Fluoro-2-(5-fluoro-1-tetrahydro-2H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]norcarane-3-carboxylic acid



In analogy to the synthesis of example 49/step D, (+)-methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylate (100 mg, 0.17 mmol) was used to give a crude title compound (200 mg) as yellow gum. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

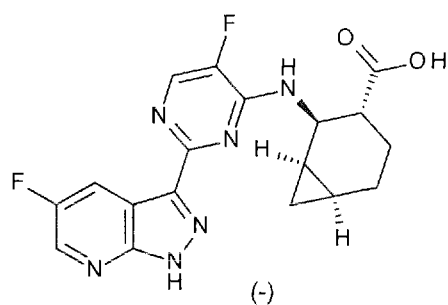
IE 1 (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



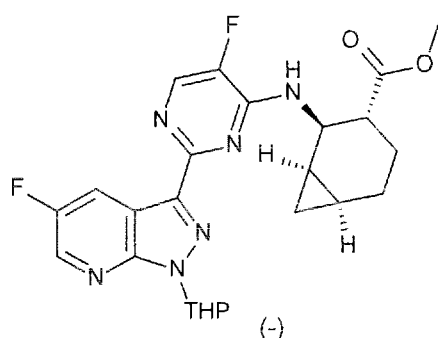
in analogy to the synthesis of example 49/step E, (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid (200 mg, 0.17 mmol) was used to give a crude product, which was by Prep-HPLC to afford the title compound (16 mg, 25% yield) as a white solid. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.43 (q, J=5.02 Hz, 1 H) 0.56 (td, J=8.66, 4.52 Hz, 1 H) 1.10 - 1.21 (m, 1 H) 1.32 - 1.50 (m, 3 H) 1.64 - 1.78 (m, 1 H) 2.02 - 2.15 (m, 1 H) 2.25 - 2.39 (m, 1 H) 5.06 (br. s., 1 H) 7.77 (d, J=8.28 Hz, 1 H) 8.30 (d, J=3.76 Hz, 1 H) 8.57 (d, J=8.03 Hz, 1 H) 8.65 (br. s., 1 H) 12.22 (br. s., 1 H) 14.15 (br. s., 1 H).

Example 59

(-)-(1R,2R,3R,6S)-2-[[5-Fluoro-2-{5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl}pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

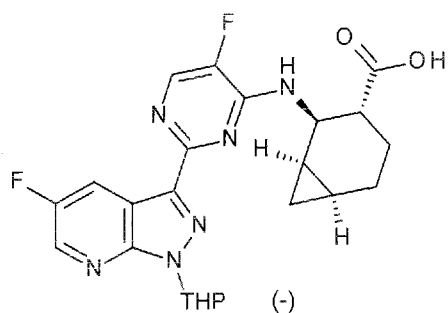


[A] (-)-Methyl (1R,2R,3R,6S)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate



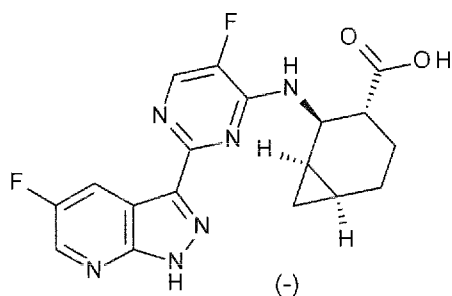
- 5 in analogy to the synthesis of example 58/step C, (-)-methyl (1R,2R,3R,6S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcaradiene-3-carboxylate was used to afford the title compound (150 mg, 19% yield) as a yellow solid. MS: 485.2 [M+H]⁺.

[B] (-)-[(1R,2R,3R,6S)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid



In analogy to the synthesis of example 58/step D, (-)-methyl (1R,2R,3R,6S)-2-[(5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate was used to give the crude title compound (500 mg, 100% yield) as yellow gum. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

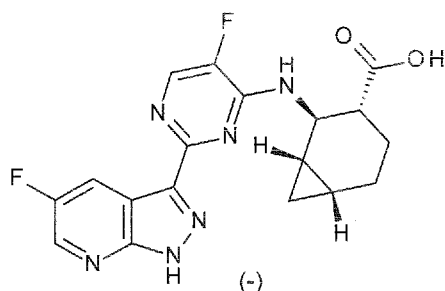
TCI (-)-(1R,2R,3R,6S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



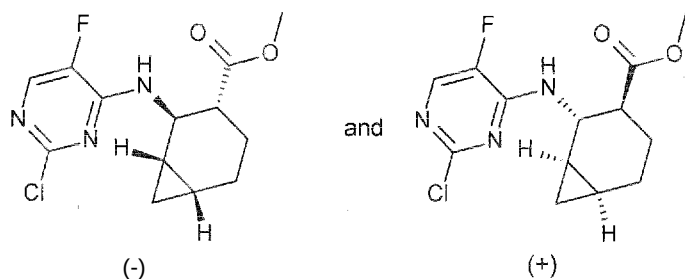
In analogy to the synthesis of example 58/step E, (-)-(1R,2R,3R,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid was used to afford the title compound (45 mg, 37% yield) as a white solid. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.43 (q, J=5.27 Hz, 1 H) 0.56 (td, J=8.72, 4.64 Hz, 1 H) 1.10 - 1.22 (m, 1 H) 1.31 - 1.47 (m, 3 H) 1.63 - 1.76 (m, 1 H) 2.01 - 2.15 (m, 1 H) 2.32 (t, J=9.66 Hz, 1 H) 5.06 (d, J=5.02 Hz, 1 H) 7.77 (d, J=8.53 Hz, 1 H) 8.29 (d, J=3.76 Hz, 1 H) 8.57 (d, J=9.04 Hz, 1 H) 8.64 (s, 1 H) 12.29 (br. s., 1 H) 14.15 (br. s., 1 H).

Example 60

(-)-{1S,2R,3R,6R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

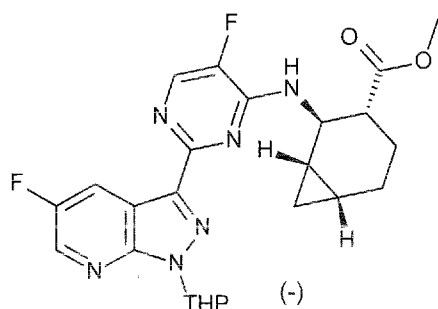


[A] (-)-Methyl (1³/₄,2R,3K,6R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate and (+)-methyl (1R,2S,3S,6S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate



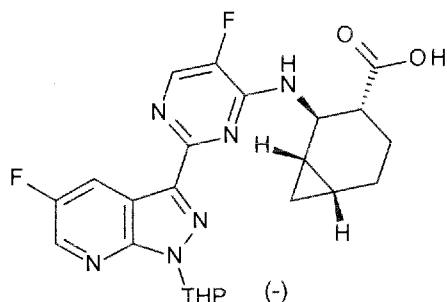
To a stirred solution of racemic mixture of methyl (1R,2S,3S,6S)-2-aminonorcarane-3-carboxylate (Intermediate B-13, 4 g, 4 mmol) and 2,4-dichloro-5-fluoropyrimidine (2 g, 11.9 mmol) in THF (40 mL) was added DIPEA (5 g, 38.5 mmol) dropwise at room temperature. After the addition, the resulting mixture was heated to 60°C and stirred for 16 h. After the solvent was evaporated under reduced pressure, the residue was re-dissolved in DCM and washed with satd. aq. NaHCO₃ solution. The organic layer was then dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was first purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60%) and then SFC chiral separation (Chiral Pak, IC-H, 250 x 30 mm, 5 μ m column, 25% EtOH in CO₂) to afford the title compound (-)-methyl (1S,2R,3R,6R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino] norcarane-3-carboxylate (44 mg, 3.6% yield), MS: 300.2 [M+H]⁺ and (+)-methyl (1R,2S,3S,6S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (44 mg, 3.6% yield), MS: 300.2 [M+H]⁺ as white solids.

1B1 (-)-Methyl (1S,2R,3R,6R)-2-[(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]amino]norcarane-3-carboxylate



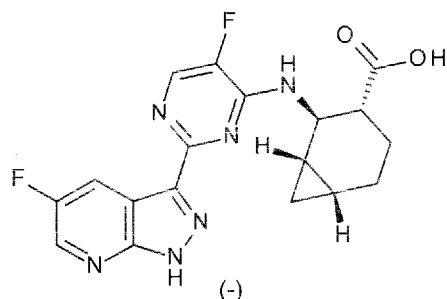
A stirred solution of (-)-methyl (1S,2R,3R,6R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino] norcarane-3-carboxylate (220 mg, 0.73 mmol), hexa-n-butyltin (0.51 mL, 0.88 mmol) and Pd(PPh₃)₄ (102 mg) in dioxane (12 mL) was heated at 125°C for 1 h. After cooling down, 5-fluoro-3-iodo-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 500 mg, 1.4 mmol) and Pd(PPh₃)₄ (102 mg) were added to the above mixture. The resulting reaction mixture was then heated at 145°C for another 1 h under microwave heating. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (EtOAc/ petroleum ether, 0-60%) to afford the title compound (95 mg, 27% yield) as a yellow solid. MS: 485.2 [M+H]⁺.

[C1] (-)-(1S,2R,3R,6R)-2-rr5-Fluoro-2-(5-fluoro-1-tetrahdropvran-2-vl-pyrazolof3.4-blpvridin-3-yr)pyrimidin-4-yllaminolnorcarane-3-carboxylic acid



A solution of (-)-methyl (1S,2R,3R,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylate (95 mg, 0.20 mmol) and LiOH monohydrate (123 mg, 2.9 mmol) in THF/water (8 mL/8 mL) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to give a crude title compound (200 mg) as yellow gum. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

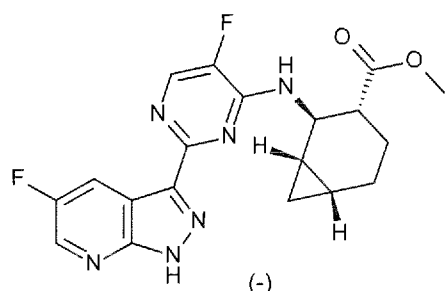
[D1] (-)-(1S,2R,3R,6R)-2-r[5-Fluoro-2-(5-fluoro-1 /-/-pyrazoloi3.4-b1pvridin-3-vl)Dvrimidin-4-yllaminolnorcarane-3-carboxyiic acid



A solution of (-)-(1S,2R,3R,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid (200 mg, 0.20 mmol) in TFA/DCM (5 mL/5 mL) was stirred at room temperature for 15 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (18 mg, 22% yield) as a white solid. MS: 387.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.29 - 0.40 (m, 1 H) 0.73 (td, J=9.03, 4.77 Hz, 1 H) 0.89 - 1.00 (m, 1 H) 1.08 - 1.19 (m, 1 H) 1.19 - 1.31 (m, 1 H) 1.73 (d, J=13.05 Hz, 1 H) 1.79 - 2.00 (m, 2 H) 4.55 (t, J=9.54 Hz, 1 H) 8.07 (d, J=7.78 Hz, 1 H) 8.30 (d, J=3.76 Hz, 1 H) 8.65 (br. s., 1 H) 8.76 (d, J=7.28 Hz, 1 H) 12.18 (br. s., 1 H) 14.16 (br. s., 1 H).

Example 61

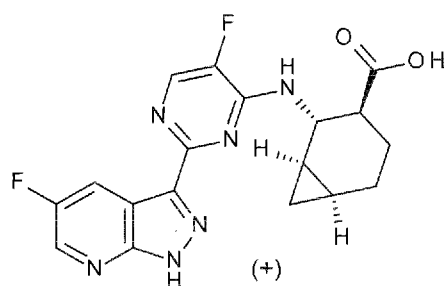
(-)-Methyl (1S,2R,3R,6R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate



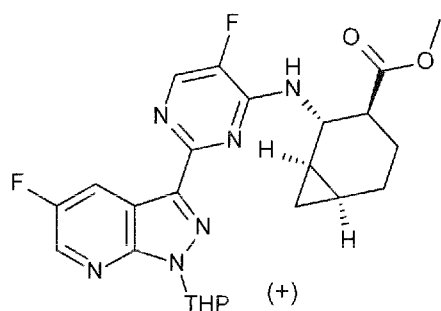
A solution of (-)-methyl (1S,2R,3R,6R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate (example 60/step B, 10 mg, 0.02 mmol) in TFA/DCM (10 mL/10 mL) was stirred at room temperature for 48 h. Afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (1.5 mg, 18% yield) as a white solid. MS: 401.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.36 (q, J=5.10 Hz, 1 H) 0.74 (td, J=9.03, 4.77 Hz, 1 H) 0.92 - 1.01 (m, 1 H) 1.09 - 1.19 (m, 1 H) 1.20 - 1.32 (m, 1 H) 1.71 (d, J=13.80 Hz, 1 H) 1.80 - 1.99 (m, 3 H) 2.57 - 2.66 (m, 1 H) 3.48 (s, 3 H) 4.52 - 4.63 (m, 1 H) 8.12 (d, J=8.28 Hz, 1 H) 8.31 (d, J=3.76 Hz, 1 H) 8.66 (s, 1 H) 8.69 (d, J=8.78 Hz, 1 H) 14.19 (br. s., 1 H).

Example 62

(+)-Methyl (1R,2S,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylic acid



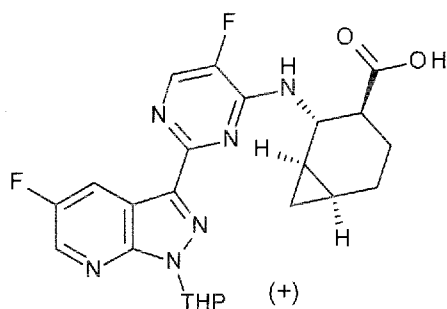
(+)-Methyl (1R,2S,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcaradiene-3-carboxylate



In analogy to the synthesis of example 49/step C, (+)-methyl (1R,2S,3S,6S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (example 60/step A) was used to afford the title compound (95 mg, 27% yield) as a yellow solid. MS: 485.2 [M+H]⁺.

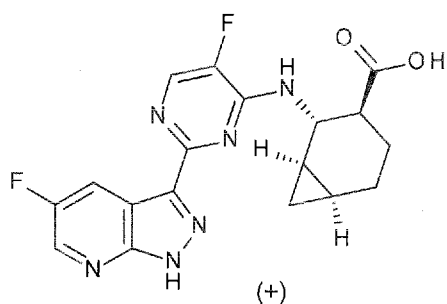
5

FBI (+)-(1R,2S,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-ylamino]norcarane-3-carboxylic acid



In analogy to the synthesis of example 49/step D, (+)-methyl (1R,2S,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-ylamino]norcarane-3-carboxylate was used to afford the crude title compound (200 mg) as a yellow solid. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

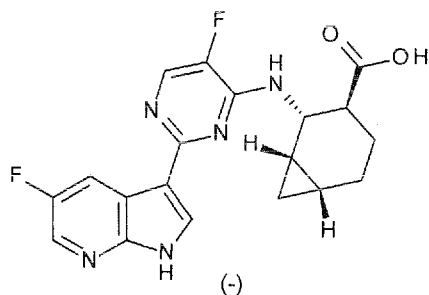
15 [Cl⁻](+)(1R,2S,3S,6S)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-ylamino]norcarane-3-carboxylic acid



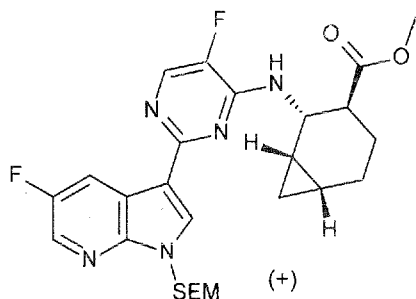
In analogy to the synthesis of example 49/step E, (+)-(1R,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid was used to afford the title compound (20 mg, 26% yield) as a white solid. MS: 387.2 [M+Hf. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.29 - 0.40 (m, 1 H) 0.73 (td, J=9.03, 4.77 Hz, 1 H) 0.89 - 1.00 (m, 1 H) 1.08 - 1.19 (m, 1 H) 1.19 - 1.31 (m, 1 H) 1.73 (d, J=13.05 Hz, 1 H) 1.79 - 2.00 (m, 2 H) 4.55 (t, J=9.54 Hz, 1 H) 8.07 (d, J=7.78 Hz, 1 H) 8.30 (d, J=3.76 Hz, 1 H) 8.65 (br. s., 1 H) 8.76 (d, J=7.28 Hz, 1 H) 12.18 (br. s., 1 H) 14.16 (br. s., 1 H).

10 Example 83

(+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

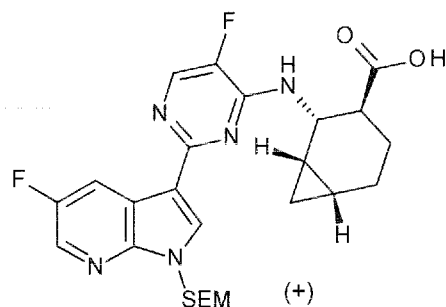


(+)-Methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-(2-trimethylsilyloxyethyl)pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylate



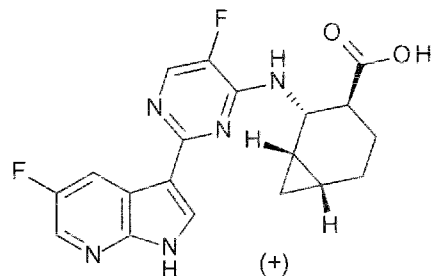
In analogy to the synthesis of example 49/step C, (+)-methyl (1S,2S,3S,6R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (example 58/step B, 299 mg, 998 μmol) and 2-[(5-fluoro-3-iodo-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (Intermediate A-2, 587 mg, 1.5 mmol) were used to give a crude product which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (90 mg, 17% yield) as yellow oil. MS: 530.2 [M+H]

IB1 (+)-(1S,2S,3S,6R)-2-rf5-Fluoro-2-r5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolor2.3-
blpvridin-3-yl]pvrimidin-4-vllaminolnorcarane-3-carboxylic acid



In analogy to the synthesis of example 49/step D, (+)-methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-
 5 [5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2.3-b]pyridin-3-yl]pyrimidin-4-
 yl]amino]norcarane-3-carboxylate (90 mg, 170 μ mol) was used to give the crude title
 compound (80 mg, 91% yield) as yellow oil. MS: 516.1 $[M+H]^+$. This crude product was
 used directly in the next step without further purification.

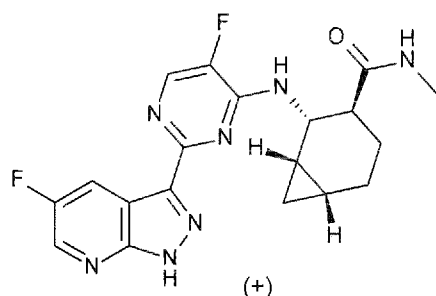
10 rci (+)-(1S,2S,3S,6R)-2-fr5-Fluoro-2-(5-fluoro-1 -/-pvrrolo[2.3-blpvridin-3-yl]pyrimidin-4-
vllaminolnorcarane-3-carboxylic acid



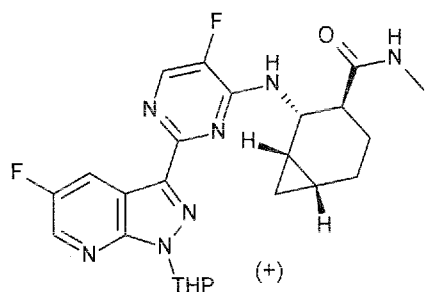
To a stirred solution of (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-[5-fluoro-1-(2-
 trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-
 15 carboxylic acid (80 mg, 155 μ mol) in DCM (3 mL) was added TFA (4.44 g, 38.9 mmol) and
 the reaction mixture was stirred at room temperature for 12 h. After solvent was removed
 under reduced pressure, the crude product was applied to Prep-HPLC separation to afford
 the title compound (5.7 mg, 10% yield) as white foam. MS: 386.1 $[M+H]^+$. ^1H NMR (400
 MHz, MeOH- d_4) δ 8.66 - 8.71 (m, 1 H) 8.17 - 8.24 (m, 2 H) 8.03 (d, $J=4.02$ Hz, 1 H) 5.26
 20 (dd, $J=10.54, 5.52$ Hz, 1 H) 2.33 (s, 1 H) 2.19 (d, $J=10.04$ Hz, 1 H) 1.76 - 1.84 (m, 1 H) 1.55
 (br. s., 3 H) 1.24 - 1.34 (m, 1 H) 0.66 - 0.74 (m, 1 H) 0.42 (d, $J=5.27$ Hz, 1 H).

Example 64

(+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1W-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-methyl-norcarane-3-carboxamide

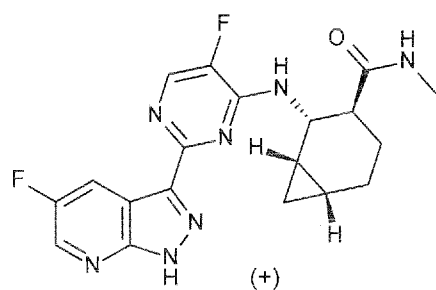


fA1 (+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-Dyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-N-methyl-norcarane-3-carboxamide



A stirred solution of (+)-methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylate (example 58/step C, 40 mg, 0.08 mmol) and methyl amine (2 M in ethanol, 20 mL) was stirred at room temperature for 70 h. Afterwards, the reaction mixture was concentrated in vacuo to give a crude title compound (40 mg) as oil. MS: 484.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

1B1 (+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-N-methyl-norcarane-3-carboxamide

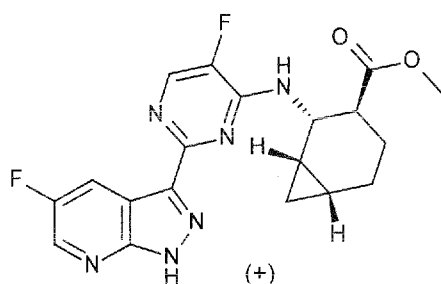


A crude material of (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]-N-methyl-norcarane-3-carboxamide (40 mg, 0.08 mmol) in TFA (20 mL) was stirred at room temperature for 4 h. After the solvent

was removed under reduced pressure, the crude product was purified by Prep-HPLC to afford the title compound (4 mg, 12% yield) as a white solid. MS: 400.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-c/6) δ 0.34 (q, J=5.10 Hz, 1 H) 0.57 (td, J=8.72, 4.64 Hz, 1 H) 1.09 - 1.20 (m, 1 H) 1.33 - 1.56 (m, 4 H) 2.02 - 2.13 (m, 1 H) 2.13 - 2.22 (m, 1 H) 3.14 (s, 3 H) 4.93 - 5.06 (m, 1 H) 7.45 - 7.60 (m, 2 H) 8.30 (d, J=3.76 Hz, 1 H) 8.61 (d, J=8.78 Hz, 1 H) 8.65 (s, 1 H) 13.96 - 14.33 (m, 1 H).

Example 65

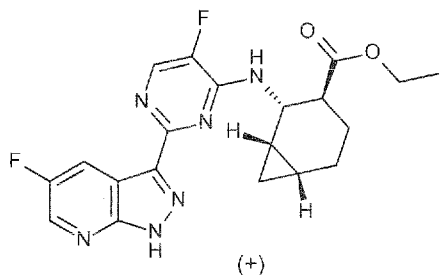
(+)-Methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylate



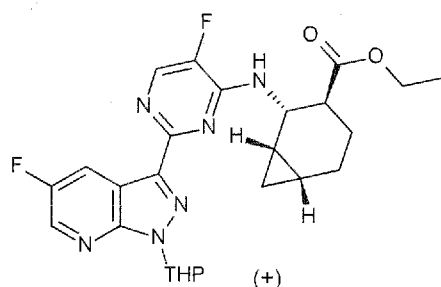
In the synthesis of example 64, the title compound (3 mg, 9% yield) was obtained as a white solid by-product. MS: 401.2 [M+Hf. ¹H NMR (400 MHz, DMSO-c/6) δ 0.46 (q, J=5.27 Hz, 1 H) 0.58 (td, J=8.78, 4.77 Hz, 1 H) 1.11 - 1.22 (m, 1 H) 1.35 - 1.46 (m, 3 H) 1.66 - 1.72 (m, 1 H) 2.02 - 2.13 (m, 1 H) 2.42 (t, J=9.91 Hz, 1 H) 3.47 (s, 3 H) 5.08 (d, J=5.27 Hz, 1 H) 7.73 (d, J=8.53 Hz, 1 H) 8.31 (d, J=3.76 Hz, 1 H) 8.54 (d, J=8.78 Hz, 1 H) 8.61 - 8.69 (m, 1 H) 14.17 (s, 1 H).

Example 66

(+)-Ethyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylate



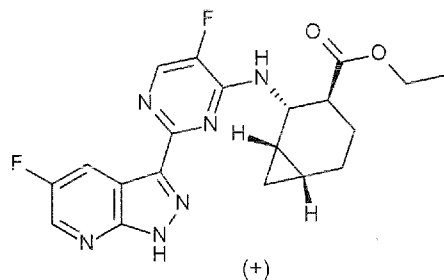
[A 1 Ethyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylate



In the synthesis of example 64/step A, the title compound was obtained as a by-product. MS: 499.2 $[M+H]^+$. This crude product was used directly in the next step without further purification.

5

FBI (+)-Ethyl (1S,2S,3S,6R)-2-[5-fluoro-2-(5-fluoro-1 H-Dvrazolo[3,4-b]pyridin-3-yl)Pvrimidin-4-yllamino]norcarane-3-carboxylate

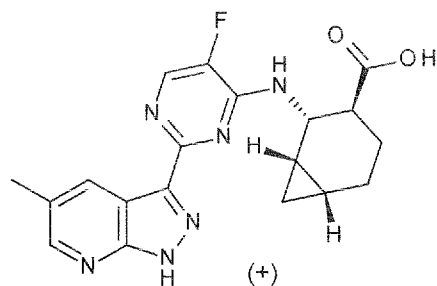


In the synthesis of example 64/step B, the title compound (1.5 mg, 4% yield) was obtained as a white solid by-product. MS: 415.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 0.49 (q, $J=5.27$ Hz, 1 H) 0.58 (td, $J=8.91, 4.52$ Hz, 1 H) 0.98 (t, $J=7.15$ Hz, 3 H) 1.12 - 1.21 (m, 1 H) 1.33 - 1.49 (m, 3 H) 1.68 (d, $J=8.78$ Hz, 1 H) 2.09 (t, $J=8.66$ Hz, 1 H) 2.31 - 2.42 (m, 1 H) 3.86 - 3.98 (m, 2 H) 5.10 (d, $J=5.27$ Hz, 1 H) 7.75 (d, $J=8.53$ Hz, 1 H) 8.31 (d, $J=3.76$ Hz, 1 H) 8.55 (d, $J=8.53$ Hz, 1 H) 8.65 (br. s., 1 H) 14.16 (br. s., 1 H).

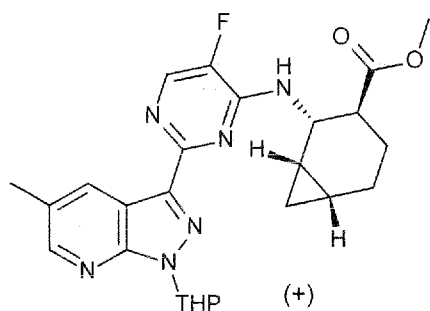
15

Example 8?

(+)-(1S,2S,3S,6R)-2-[5-Fluoro-2-(5-methyl-1H-vrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

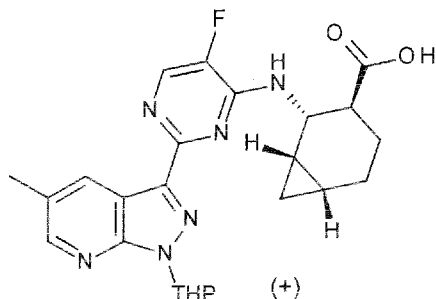


[A] (+)-Methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-methyl-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]aminonorcaradiene-3-carboxylate



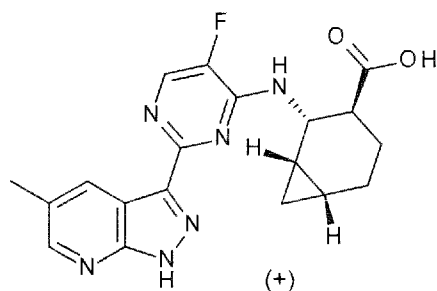
In analogy to the synthesis of example 58/step C, 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-7, 687 mg, 2 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (250 mg, 39% yield) as yellow oil. MS: 481.1 [M+H]⁺.

[B] (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-methyl-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]aminonorcaradiene-3-carboxylic acid



In analogy to the synthesis of example 49/step D, (+)-methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-methyl-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]aminonorcaradiene-3-carboxylate (250 mg, 520 μmol) was used to give a crude title compound (230 mg, 95% yield) as yellow oil. MS: 467 [M+H]⁺. This crude product was used directly in the next step without further purification.

[C] (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-methyl-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]aminonorcaradiene-3-carboxylic acid

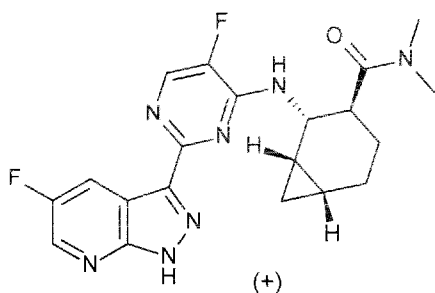


In analogy to the synthesis of example 49/step E, (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-methyl-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylic acid (230 mg, 493 μ mol) was used to give a crude product, which was purified by
 5 Prep-HPLC to afford the title compound (32 mg, 17% yield) as white foam. MS: 383.1 [M+Hf. ^{1} H NMR (400 MHz, MeOH-c/4) δ 8.90 (s, 1 H) 8.45 (d, J=1.76 Hz, 1 H) 8.14 (d, J=4.02 Hz, 1 H) 5.34 - 5.40 (m, 1 H) 2.57 (s, 3 H) 2.32 - 2.41 (m, 1 H) 2.16 - 2.25 (m, 1 H) 1.79 - 1.86 (m, 1 H) 1.50 - 1.71 (m, 3 H) 1.24 - 1.34 (m, 1 H) 0.67 - 0.75 (m, 1 H) 0.42 - 0.48 (m, 1 H).

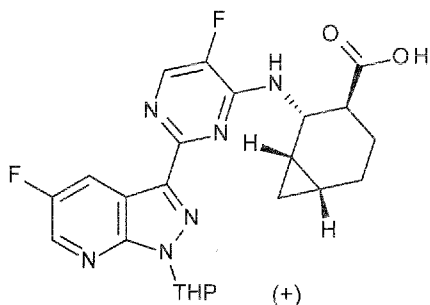
10

Example 68

(+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1W-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N,W-dimethyl-norcarane-3-carboxamide



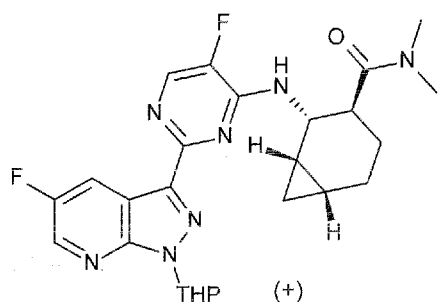
15 1A1 (+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



A solution of (+)-methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylate (example 58/step

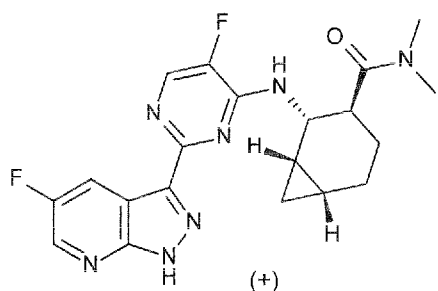
C, 30mg. 0.06 mmol) and LiOH monohydrate (10.4 mg, 0.24 mmol) in THF (4 mL) and H₂O (4 mL) was stirred at room temperature for 3 h. Afterwards, the mixture was neutralized with 1N HCl to pH = 6. The mixture was concentrated in vacuo to give a crude title compound (50 mg, 100% yield) as yellow gum. MS: 471.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

1B1 (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N,N-dimethyl-norcarane-3-carboxamide



- 10 A stirred mixture solution of dimethyl amine (5.58 mg, 0.12 mmol), *N,N*-diisopropylethylamine (40 mg, 0.31 mmol), HATU (47.1 mg, 0.12 mmol) and (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid (50 mg, 0.06 mmol) in DCM (4 mL) was stirred at room temperature for 16 h. Afterwards, the reaction was quenched with satd. aq.
- 15 NaHCO₃ solution and extracted with DCM (5 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (200 mg) as a white solid. MS: 498.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

20 1C1 (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N,N-dimethyl-norcarane-3-carboxamide

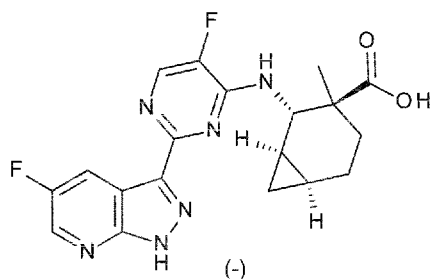


In analogy to the synthesis of example 49/step E, (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(5-fluoro-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N,N-dimethyl-

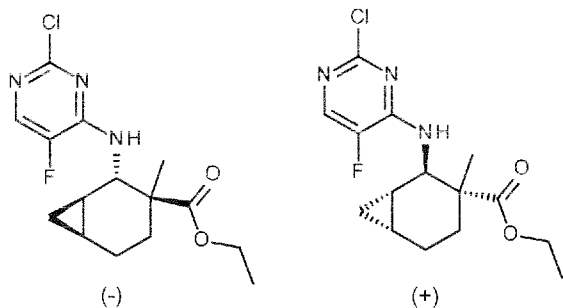
norcarane-3-carboxamide (200 mg, 0.06 mmol) was used to give a crude product, which was purified by Prep-HPLC to afford the title compound (5 mg, 20% yield) as a white solid. MS: 414.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-c/6) δ 0.45 (q, J=5.02 Hz, 1 H) 0.58 (td, J=8.78, 4.52 Hz, 1 H) 1.11 - 1.20 (m, 1 H) 1.21 - 1.35 (m, 2 H) 1.38 - 1.56 (m, 3 H) 2.03 - 2.14 (m, 1 H) 2.65 - 2.73 (m, 1 H) 2.74 (s, 3 H) 3.03 (s, 3 H) 5.08 - 5.23 (m, 1 H) 7.55 (d, J=8.03 Hz, 1 H) 8.27 (d, J=3.76 Hz, 1 H) 8.57 - 8.73 (m, 2 H) 14.13 (br. s., 1 H).

Example 69

(-)-1R,2S,3S,6S)-2-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid



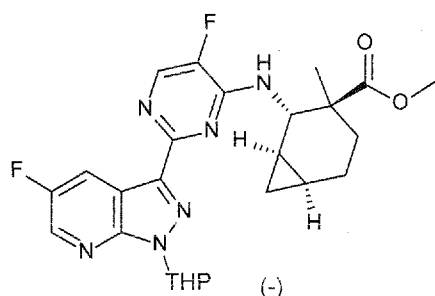
[A] (-)-1R,2S,3S,6S)-ethyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate & (+)-(1S,2R,3R,6R)-ethyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate



To a stirred solution of (-)-1R,2S,3S,6S)-ethyl 2-amino-3-methylbicyclo[4.1.0]heptane-3-carboxylate (intermediate B-16, 2.0 g, 10.1 mmol) in THF (20 mL) was added 2,4-dichloro-5-fluoropyrimidine (3.39 g, 20.3 mmol) and DIPEA (3.93 g, 30.4 mmol) and the resulting reaction mixture solution was stirred at 65°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified first by silica gel flash chromatography (0-40% EtOAc-hexane gradient) and then SFC chiral separation (DAICEL IC, 250 x 30 mm, 5 μm column, 30% MeOH in C0₂) to afford the title compound (-)-1R,2S,3S,6S)-ethyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]-

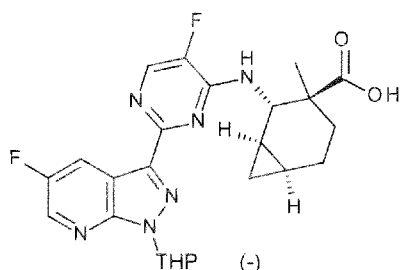
heptane-3-carboxylate (510 mg, 79% yield) as a light yellow solid, MS: 328.1 [M+H]⁺ and (+)-(1S,2R,3R,6R)-ethyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate (510 mg, 79% yield) as a light yellow solid. MS: 328.1 [M+H]⁺

- 5 IB1 (-)-(1R,2S,3S,6S)-ethyl 2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl))-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate



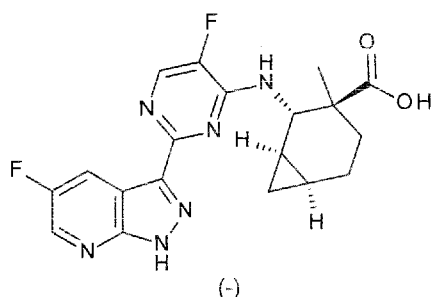
- To a stirred mixture solution of (-)-(1R,2S,3S,6S)-ethyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate (200 mg, 610 μ mol) and Pd(PPh₃)₄ (70.5 mg, 61 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (531 mg, 915 μ mol) and the resulting mixture solution was stirred at 125°C for 2 h. After cooling down, to the above mixture solution was added 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (318 mg, 915 μ mol) and Pd(PPh₃)₄ (70.5 mg, 61 μ mol) in dioxane (16 mL). Then the resulting mixture solution was re-heated at 145°C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (100 mg, 32% yield) as a yellow oil. MS: 513.1 [M+H]⁺

[C1] (-)-(1R,2S,3S,6S)-2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl))-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid



To a stirred mixture solution of (-)-(1R,2S,3S,6S)-ethyl 2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate (100 mg, 195 μ mol) in THF (4mL) and MeOH (2 mL) was added LiOH (23.4 mg, 976 μ mol) pre-dissolved in water (1mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (95 mg, 100% yield) as yellow oil. MS: 485.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

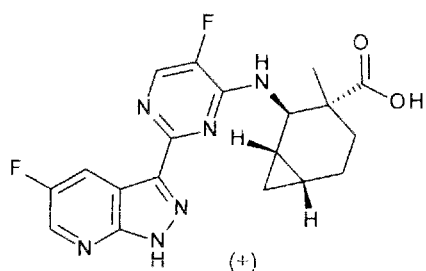
1D1 (-)-(1R,2S,3S,6S)-2-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid



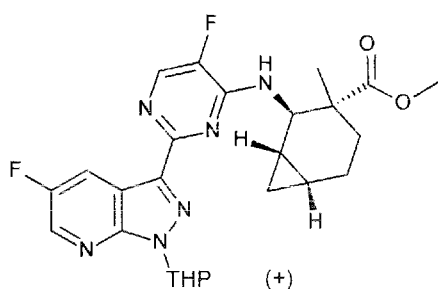
To a stirred solution of (-)-(1R,2S,3S,6S)-2-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid (95 mg, 196 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. Afterwards, the mixture solution was concentrated in vacuo to give a crude product, which was then purified by Prep-HPLC to afford the title compound (8 mg, 10.2% yield) as white foam. MS: 401.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.81 - 8.86 (m, 1 H) 8.53 - 8.55 (m, 1 H) 8.15 - 8.18 (m, 1 H) 5.14 - 5.16 (m, 1 H) 1.98 - 2.09 (m, 1 H) 1.85 - 1.93 (m, 1 H) 1.67 - 1.77 (m, 2 H) 1.55 - 1.63 (m, 1 H) 1.34 (s, 3 H) 1.13 - 1.20 (m, 1 H) 0.84 - 0.99 (m, 1 H) 0.30 - 0.35 (m, 1 H).

Example 70

(+)-(1S,2R,3R,6R)-2-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid



1A1 (+H1S,2R,3R,6R)-ethyl 2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate

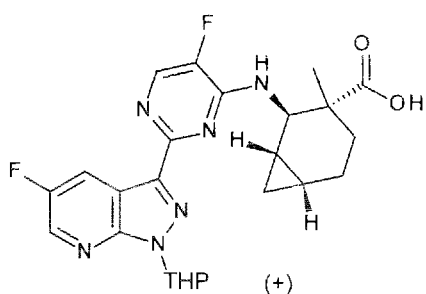


5

In analogy to the synthesis of Example 69/Step B, (+)-(1S,2R,3R,6R)-ethyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate (Example 69/Step A, 200 mg, 610 μ mol) was used to afford the title compound (100 mg, 32% yield) after silica gel flash chromatography separation as yellow oil. MS: 513.1 [M+H]⁺

10

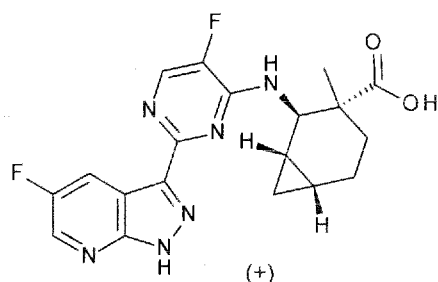
[BI_ (+H1S,2R,3R,6R)-2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid



15

In analogy to the synthesis of Example 69/Step C, (+)-(1S,2R,3R,6R)-ethyl 2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylate (100 mg, 195 μ mol) was used to afford a crude title compound (90 mg, 95.2%) as yellow oil. This crude product was used directly in the next step without further purification. 485.1 [M+H]⁺.

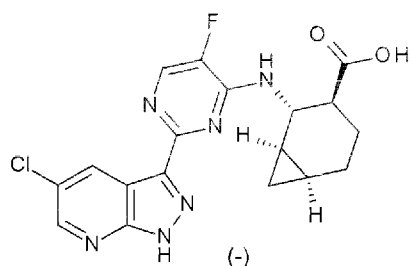
[C] (+)-(1S,2R,3R,6R)-2-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid



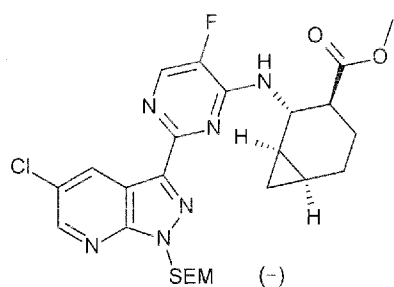
In analogy to the synthesis of Example 69/Step D, (+)-(1S,2R,3R,6R)-2-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)-3-methylbicyclo[4.1.0]heptane-3-carboxylic acid (95 mg, 196 μmol) was used to afford the title compound (4 mg, 5.1% yield) after Prep-HPLC purification as white foam. MS: 401.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.79 - 8.84 (m, 1 H) 8.53 - 8.59 (m, 1 H) 8.17 - 8.24 (m, 1 H) 5.16 - 5.20 (m, 1 H) 1.98 - 2.09 (m, 1 H) 1.84 - 1.94 (m, 1 H) 1.68 - 1.78 (m, 1 H) 1.54 - 1.64 (m, 1 H) 1.34 (s, 3 H) 1.14 - 1.22 (m, 1 H) 0.91 - 1.00 (m, 1 H) 0.84 - 0.91 (m, 1 H) 0.29 - 0.35 (m, 1 H).

Example 71

(-H1R,2S,3S,6S)-2-[[2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoro-pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

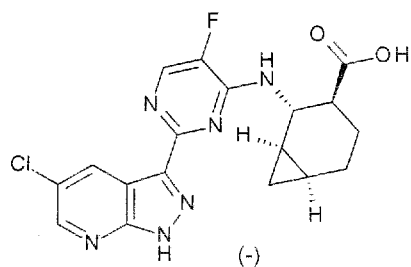


1A 1 (-)-Methyl (-1R,2S,3S,6S)-2-[[2-(5-chloro-1-(2-trimethylsilylethoxymethyl)pyrazolo[3,4-b]pyridin-3-yl)-5-fluoro-pyrimidin-4-yl]amino]norcarane-3-carboxylate



A mixture solution of (-)-(1R,2S,3S,6S)-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (Intermediate B-13a, 220 mg, 734 μmol), 1,1,1,2,2,2-hexabutyldistannane (511 mg, 881 μmol), and Pd(PPh₃)₄ (102 mg, 88.1 μmol) in 1,4-dioxane (12 mL) was heated at 125 °C for 2 h. After cooling down, to the above solution, 5 was added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (506 mg, 1.23 mmol) and second batch of Pd(PPh₃)₄ (102 mg, 88.1 μmol). The resulting reaction mixture solution was re-heated at 145 °C under microwave heating for another 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc : petroleum ether = 0 to 40% gradient) to afford the title compound (95 mg, 24% yield) as a white solid. MS: 547.2 [M+Hf].

IB1 (-)-(1R,2S,3S,6S)-2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



15

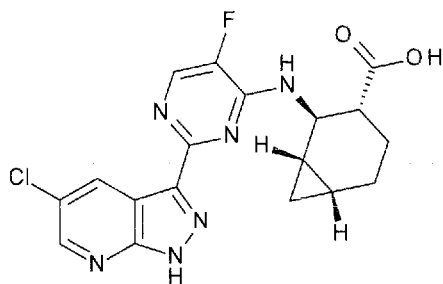
A solution of (-)-(1R,2S,3S,6S)-methyl 2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (90mg, 178 μmol) in THF (4 mL) and water (4 mL) was stirred at room temperature for 2 h. Afterwards, the reaction mixture was concentrated in vacuo. The residue was then re-dissolved in TFA (4 mL) and DCM (4 mL) and stirred at room temperature for 15 h, afterwards, the solvent was evaporated to dryness under reduced pressure. The crude product was purified by Prep-HPLC to afford the title compound (10 mg, 14% yield) as white foam. MS: 403.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 0.39 (q, J=5.10 Hz, 1 H) 0.76 (td, J=9.03, 4.52 Hz, 1 H) 0.88 - 0.98 (m, 1 H) 1.07 - 1.28 (m, 2 H) 1.73 (d, J=13.80 Hz, 1 H) 1.84 (ddd, J=18.07, 13.30, 5.02 Hz, 1 H) 1.90 - 1.99 (m, 1 H) 4.45 - 4.60 (m, 1 H) 8.11 (d, J=8.03 Hz, 1 H) 8.30 (d, J=3.51 Hz, 1 H) 8.62 (d, J=2.51 Hz, 1 H) 9.04 (d, J=2.26 Hz, 1 H) 12.27 (br. s., 1 H) 14.24 (br. s., 1 H).

25

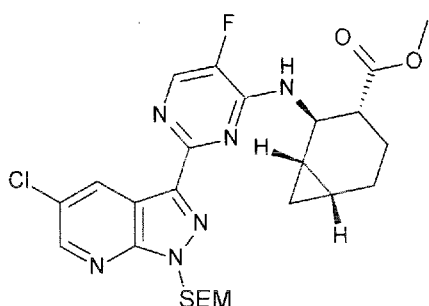
Example 72

30 **(+)-(1S,2R,3R,6R)-2-[[2-[5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-fluoropyrimidin-4-**

yl]amino]norcarane-3-carboxylic acid



1A] (+)-(1S,2R,3R,6R)-methyl 2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate

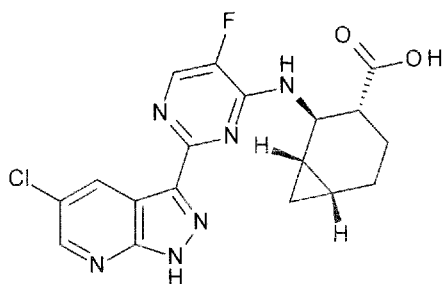


5

In analogy to the synthesis of Example 71/Step A, (+)-(1R,2S,3S,6S)-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (Intermediate B-13b) (220 mg, 734 μ mol) was used to afford the title compound (95 mg, 24% yield) as a white solid after silica gel flash chromatography purification. MS: 547.2 $[M+H]^+$.

10

1B] (+)-(1S,2R,3R,6R)-2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



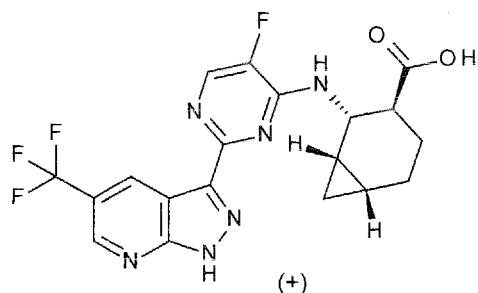
15

In analogy to the synthesis of Example 71/Step B, (+)-(1S,2R,3R,6R)-methyl 2-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (35.9 mg, 65.7 μ mol) was used to afford the title compound (5 mg, 19% yield) as a white solid after Prep-HPLC purification. MS: 403.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 0.33 - 0.44 (m, 1 H) 0.75 (td, $J=9.03$, 4.52 Hz, 1 H) 0.88 - 0.99 (m, 1 H) 1.06 - 1.27 (m, 2 H) 1.72 (d, $J=14.05$ Hz, 1 H) 1.78 - 1.90 (m, 1 H) 1.90

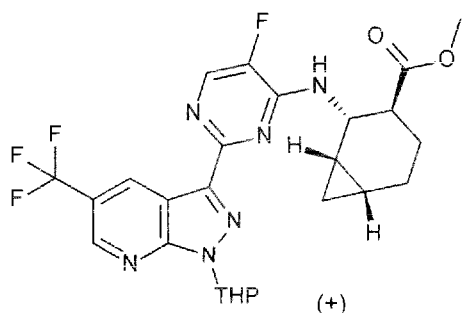
- 1.99 (m, 1 H) 4.50 (br. s., 1 H) 8.11 (d, J=7.53 Hz, 1 H) 8.29 (d, J=3.76 Hz, 1 H) 8.62 (d, J=2.26 Hz, 1 H) 9.05 (d, J=2.51 Hz, 1 H) 14.23 (br. s., 1 H).

Example 73

- 5 **(+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-[5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylic acid**



[A] (+)-Methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-[5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylate

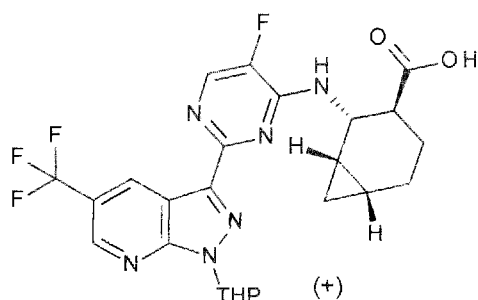


10

In analogy to the synthesis of example 58/step C, 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-5, 1.03 g, 2.6 mmol) was used to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (200 mg, 19% yield) as yellow oil. MS:

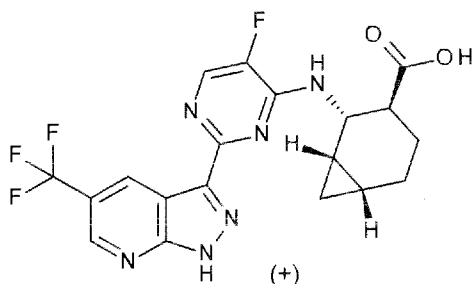
15 535.1 [M+H]⁺

[B] (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-[5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



In analogy to the synthesis of example 49/step D, (+)-methyl (1S,2S,3S,6R)-2-[[5-fluoro-2-[1-tetrahydropyran-2-yl-5-(trifluoromethyl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylate (200 mg, 374 μmol) was used to give a crude title compound (190 mg, 98% yield) as yellow oil. MS: 520.56 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

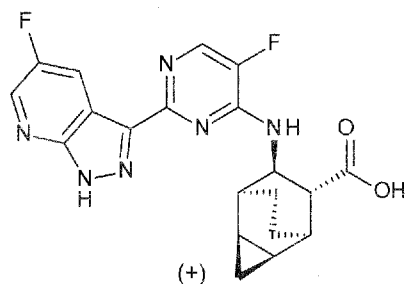
[c] (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



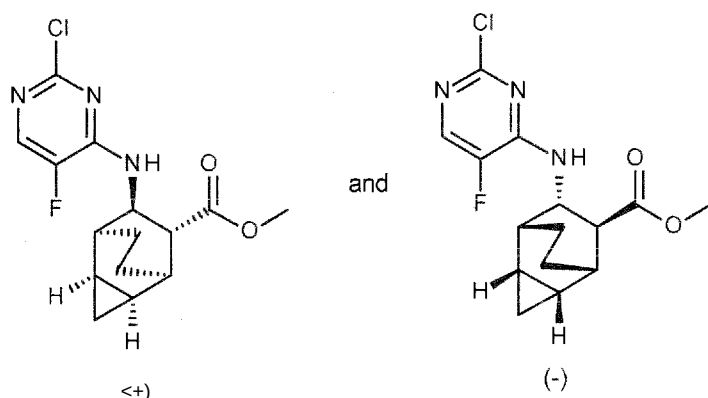
In analogy to the synthesis of example 49/step E, (+)-(1S,2S,3S,6R)-2-[[5-fluoro-2-[1-tetrahydropyran-2-yl-5-(trifluoromethyl)pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-yl]amino]norcarane-3-carboxylic acid (190 mg, 365 μmol) was used to give a crude product, which was purified by Prep-HPLC to afford the title compound (27 mg, 17% yield) as white foam. MS: 437.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 9.48 (d, $J=1.25$ Hz, 1 H) 8.86 (d, $J=1.76$ Hz, 1 H) 8.13 (d, $J=3.76$ Hz, 1 H) 5.17 (dd, $J=1.29, 5.52$ Hz, 1 H) 2.12 - 2.24 (m, 2 H) 1.75 - 1.82 (m, 1 H) 1.48 - 1.74 (m, 3 H) 1.21 - 1.32 (m, 1 H) 0.61 - 0.69 (m, 1 H) 0.36 - 0.41 (m, 1 H).

Example 74

(+)-(1S,2R,4S,5R,6R,7R)-7-[(5-fluoro-2-{5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl}pyrimidin-4-yl)amino]tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

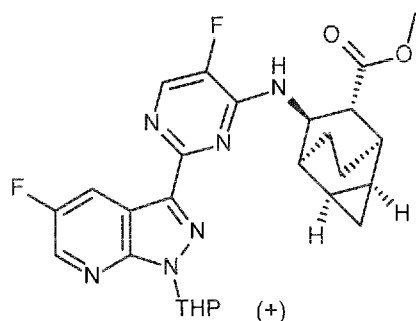


[A] (+)-(1S,2R,4S,5R,6R,7R)-Methyl 7-[(2-chloro-5-fluoropyrimidin-4-yl)amino]tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-[(2-chloro-5-fluoropyrimidin-4-yl)amino]tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of racemic mixture of (1S,2R,4S,5R,6R,7R)-methyl 7-aminotricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (Intermediate B-12, 20.4 g, 66 mmol) in THF (200 mL) was added 2,4-dichloro-5-fluoropyrimidine (22 g, 132 mmol) and DIPEA (25.6 g, 34.6 mL, 198 mmol) and the resulting reaction mixture was heated at 65°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was first purified by silica gel flash chromatography (0-40% EtOAc-hexane gradient) and then SFC chiral separation (DAICEL. IC, 250 x 30 mm, 5 μm column, 40% MeOH in CO₂) to afford the title compound (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (7.8 g, 92% yield) as a light yellow solid, MS: 326.1 (M+H)⁺ and (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (8 g, 94% yield) as a light yellow solid. MS: 326.1 [M+H]⁺.

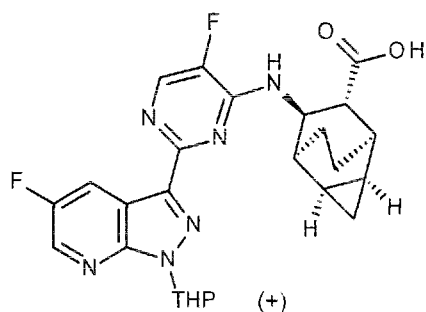
Example 1 (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((5-fluoro-2-((5-fluoro-1-(tetrahydro-2H-Dyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate



To a stirred mixture solution of (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (250 mg, 767 μmol) and Pd(PPh₃)₄ (88.7 mg, 76.7 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-

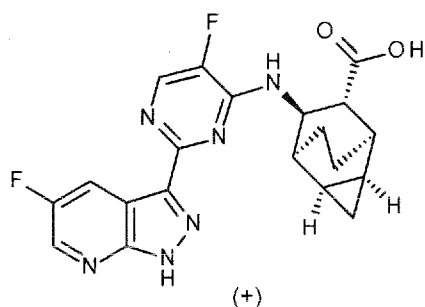
hexabutylstannane (668 mg, 1.15 mmol) and the reaction mixture was heated at 125°C for 2 h. After cooling down, 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 500 mg, 1.44 mmol) and second batch of Pd(PPh₃)₄ (88.7 mg, 76.7 μmol) in dioxane (16 mL) was added into above mixture. The resulting reaction mixture was stirred at 145°C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (2 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (94 mg, 24% yield) as a yellow solid. MS: 511.2 [M+H]⁺

[C] (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred solution of (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (94 mg, 0.184 mmol) in THF (4 mL) and MeOH (4 mL) was added LiOH (13.3 mg, 0.55 mmol) pre-dissolved in H₂O (2 mL). The reaction mixture was stirred at room temperature for 16 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH = 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (92 mg, 100% yield) as yellow oil. MS: 497.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

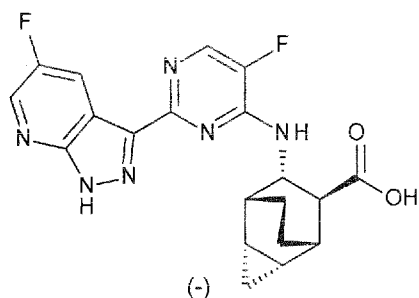
[D] (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



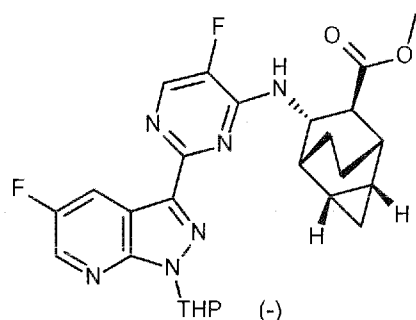
To a stirred solution of (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl))-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (92 mg, 0.184 mmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (1 mL) and the reaction mixture solution was stirred at room temperature for 12 h. The solvent was removed under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (11 mg, 15% yield) as white foam. MS: 413.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.60 - 8.65 (m, 1 H) 8.54 - 8.57 (m, 1 H) 8.14 - 8.19 (m, 1 H) 4.70 - 4.75 (m, 1 H) 2.77 - 2.82 (m, 1 H) 2.64 - 2.69 (m, 1 H) 2.52 - 2.59 (m, 1 H) 1.77 - 1.97 (m, 2 H) 1.64 - 1.76 (m, 2 H) 1.11 - 1.19 (m, 1 H) 0.97 - 1.03 (m, 1 H) 0.89 - 0.97 (m, 1 H) 0.41 - 0.51 (m, 1 H).

Example 75

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

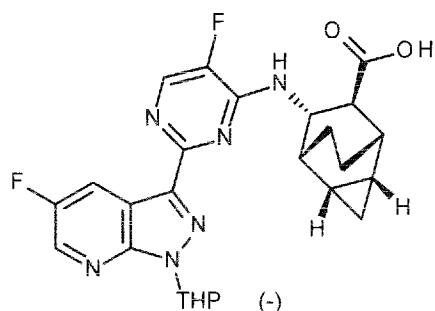


(-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl))-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



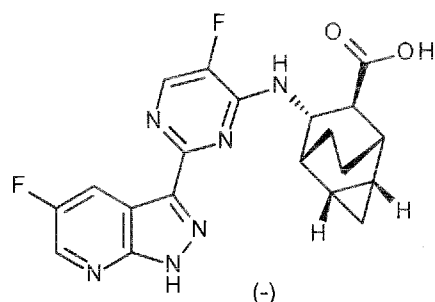
In analogy to the synthesis of example 74/step B, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate was used to afford the title compound (94 mg, 24% yield) as a yellow solid after silica gel flash chromatography purification. MS: 511.2 [M+H]⁺

[B] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



10 In analogy to the synthesis of example 74/step C, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate was used to afford a crude title compound (94 mg, quant.) as a yellow solid. MS: 497.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

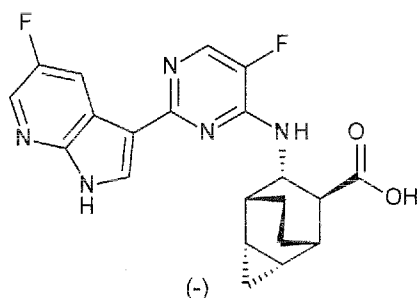
[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



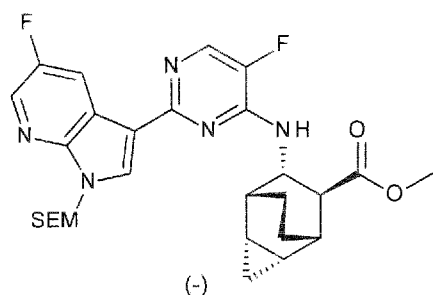
In analogy to the synthesis of example 74/step D, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid was used to afford the title compound (13 mg, 18% yield) as a yellow solid after Prep-HPLC purification. MS: 413.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.63 (dd, J=2.64, 1.38 Hz, 1 H) 8.46 - 8.54 (m, 1 H) 8.25 (d, J=3.89 Hz, 1 H) 7.33 - 7.43 (m, 1 H) 4.51 (br. s., 1 H) 2.61 - 2.69 (m, 1 H) 2.54 - 2.61 (m, 1 H) 2.43 (d, J=1.88 Hz, 1 H) 1.40 - 1.77 (m, 3 H) 1.05 - 1.13 (m, 1 H) 0.91 - 1.01 (m, 1 H) 0.68 - 0.78 (m, 1 H) 0.17 - 0.27 (m, 1 H).

Example 76

(-)-{1R,2S,4R,5S,6S,7S}-7-((5-fluoro-2-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

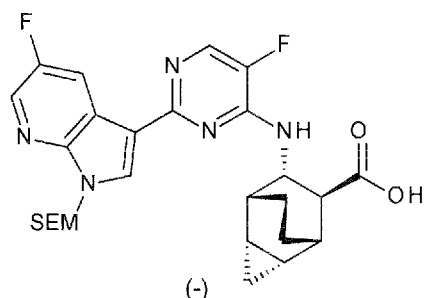


[A] (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



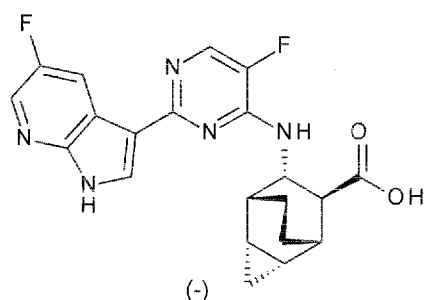
In analogy to the synthesis of example 74/step B, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (example 74/step A, 660 mg, 2.03 mmol) and 5-fluoro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate A-2, 1.59 g, 4.05 mmol) were used to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (193 mg, 17% yield) as yellow oil. MS: 556.2 [M+H]⁺.

[BI] (-)-(1 R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2.3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



In analogy to the synthesis of example 74/step C, (-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2.3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (192 mg, 346 μ mol) was used to give a crude title compound (180 mg, 96% yield) as yellow oil. MS: 542.2 $[M+H]^+$. This crude product was used directly in the next step without further purification.

10 [CI] (-H1 R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-fluoro-1H-pyrrolo[2.3-b]Pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

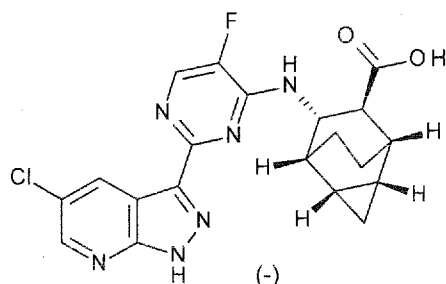


To a stirred solution of (-)-(1 R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2.3-b]pyridin-3-yl)pyrimidin-4-

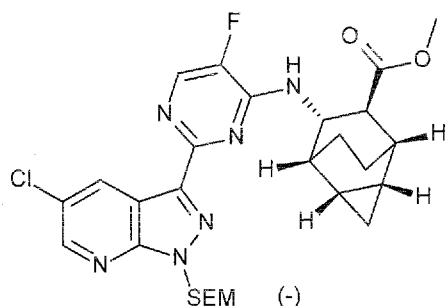
15 yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (180 mg, 332 μ mol) in DCM (3 mL) was added TFA (4.44 g, 3 mL, 38.9 mmol) and the reaction mixture solution was stirred at room temperature for 12 h. After the solvent was removed under reduced pressure, the crude product was purified by Prep-HPLC to afford the title compound (4 mg, 3% yield) as white foam. MS: 412.1 $[M+H]^+$. ¹H NMR (400 MHz, MeOH-d₄) δ 8.62 (dd, J=9.66, 2.89 Hz, 1 H) 8.27 (s, 1 H) 8.17 (br. s., 1 H) 8.05 (d, J=4.02 Hz, 1 H) 4.53 (br. s., 1 H) 2.66 (br. s., 1 H) 2.57 (br. s., 1 H) 2.47 (br. s., 1 H) 1.55 - 1.93 (m, 4 H) 1.11 - 1.19 (m, 1 H) 0.91 - 1.00 (m, 2 H) 0.42 - 0.51 (m, 1 H).

Example 77

(-H1R,2S,4R,5S,6S,7S)-7-((2-{5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

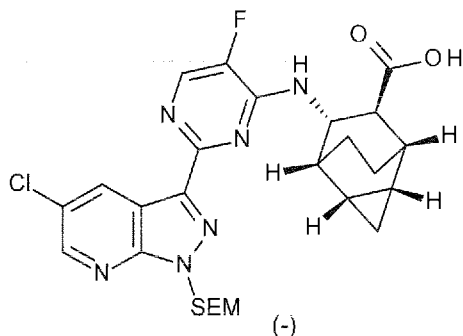


(-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



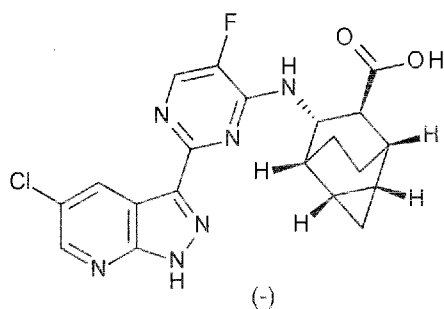
To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (example 74/step A (-) enantiomer, 220 mg, 675 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (78 mg, 67.5 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (588 mg, 532 μL , 1.01 mmol) and the resulting reaction mixture solution was stirred at 125°C for 2 h. After cooling down, to the above mixture was added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-3), 360 mg, 878 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (78 mg, 67.5 μmol) in dioxane (16 mL). The reaction mixture solution was stirred at 145°C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (70 mg, 18.1% yield) as yellow oil. MS: 573.1 $[\text{M}+\text{H}]^+$

IB] (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



- 5 To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (70 mg, 122 μ mol) in THF (4 mL) and MeOH (2 mL) was added LiOH (14.6 mg, 611 μ mol) pre-dissolved in water (1 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with
- 10 water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated HCl to pH = 4 and then extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude title compound (68 mg, 99.6% yield) as yellow oil. MS: 559.1 [M+H]⁺. This crude product was used directly
- 15 in the next step without further purification.

[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

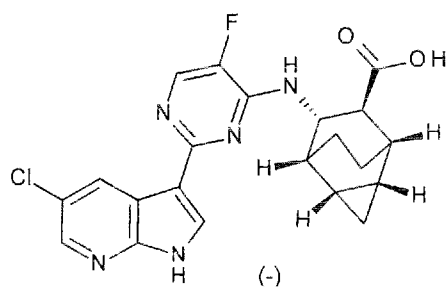


- 20 To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (68 mg, 122 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol). The reaction mixture solution was stirred at room temperature for 12 h. Afterwards, the reaction mixture was concentrated in

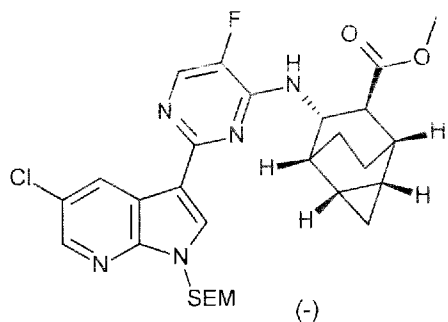
vacuo to give a crude product, which was then purified by Prep-HPLC to afford the title compound (6.8 mg, 13% yield) as white foam. MS: 429.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-*c*/4) δ 8.97 (d, *J*=2.26 Hz, 1 H) 8.55 (d, *J*=2.26 Hz, 1 H) 8.13 (d, *J*=3.76 Hz, 1 H) 4.70 - 4.77 (m, 1 H) 2.71 - 2.77 (m, 1 H) 2.65 - 2.71 (m, 1 H) 2.54 - 2.60 (m, 1 H) 1.96 - 2.07 (m, 1 H) 1.59 - 1.89 (m, 3 H) 1.09 - 1.17 (m, 1 H) 0.98 - 1.06 (m, 1 H) 0.86 - 0.96 (m, 1 H) 0.39 - 0.49 (m, 1 H).

Example 78

(-)-(1*R*,2*S*,4*R*,5*S*,6*S*,7*S*)-7-((2-{5-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



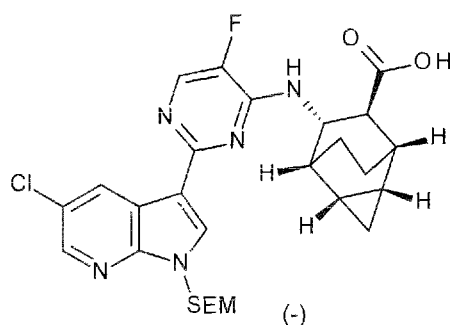
(-)-(1*R*,2*S*,4*R*,5*S*,6*S*,7*S*)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1*R*,2*S*,4*R*,5*S*,6*S*,7*S*)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (example 74/step A (-) enantiomer, 220 mg, 675 μ mol, Eq: 1) and $Pd(PPh_3)_4$ (78 mg, 67.5 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (588 mg, 1.01 mmol) at room temperature. The resulting reaction mixture was stirred at 125°C for 2 h. After cooling down, to the above mixture solution was added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Intermediate A-4a, 359 mg, 878 μ mol) and $Pd(PPh_3)_4$ (78 mg, 67.5 μ mol) in dioxane (16 mL). Then the reaction mixture solution was stirred at 145°C for additional 1 h under microwave heating. After cooling to room temperature, the reaction

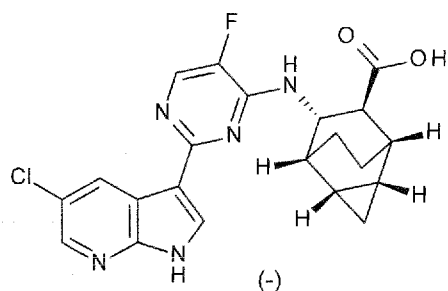
mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (100 mg, 25.9% yield) as a yellow oil. MS: 572.1 $[\text{M}+\text{H}]^+$

IB] (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (100 mg, 175 μmol) in THF (4 mL) and MeOH (2 mL) was added lithium hydroxide (20.9 mg, 874 μmol , Eq: 5) pre-dissolved in water (1 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (97.5 mg, 100% yield) as yellow oil. MS: 558.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

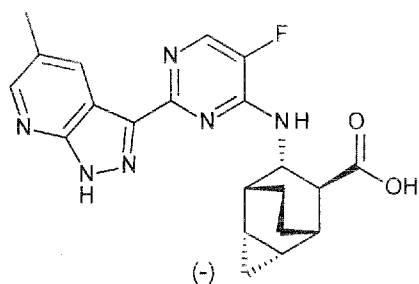
[C] f)-((1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



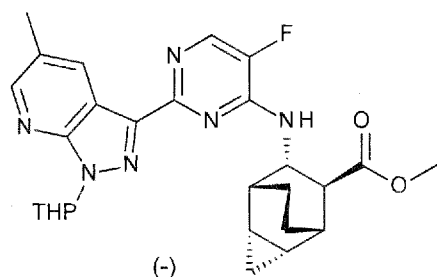
To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid (97.5 mg, 175 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol) at room temperature. The reaction mixture solution was stirred at room temperature for 12 h before being concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (3.5 mg, 4.6% yield) as white foam. MS: 428.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.89 (d, J=2.51 Hz, 1 H) 8.24 (s, 1 H) 8.21 - 8.23 (m, 1 H) 8.05 (d, J=4.02 Hz, 1 H) 4.53 - 4.57 (m, 1 H) 2.64 - 2.68 (m, 1 H) 2.54 - 2.59 (m, 1 H) 2.45 - 2.50 (m, 1 H) 1.90 - 1.98 (m, 1 H) 1.69 - 1.87 (m, 3 H) 1.59 - 1.68 (m, 1 H) 1.11 - 1.18 (m, 1 H) 0.90 - 0.99 (m, 1 H) 0.43 - 0.51 (m, 1 H).

Example 79

{-H 1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid

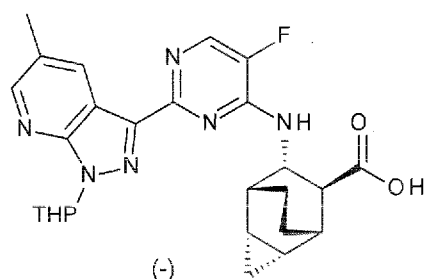


[A] (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate



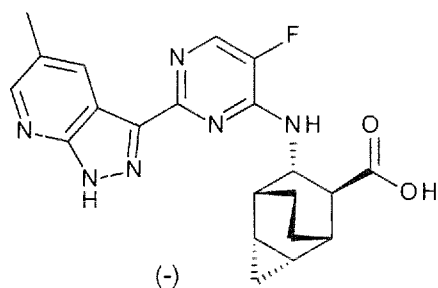
in analogy to the synthesis of example 74/step B, (-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (example 74/step A, 660 mg, 2.03 mmol) and 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3.4-b]pyridine (Intermediate A-7, 1.04 g, 3.04 mmol) were used to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (400 mg, 39% yield) as a yellow solid. MS; 507.1 [M+Hf

10 FBI (-)-(1 R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-PVr3Zoiof3,4-b1pyTidin-3-yl)pyrimidin-4-YO^ amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



In analogy to the synthesis of example 74/step C, (-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (400 mg, 790 μmol) was used to give a crude title compound (350 mg, 90% yield) as a yellow solid. MS: 493.1 [M+Hf. This crude product was used directly in the next step without further purification.

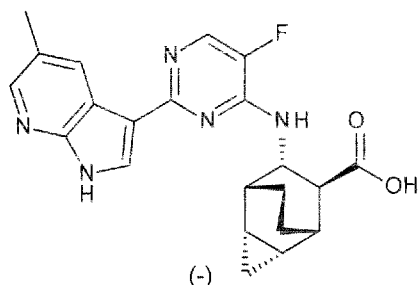
15 [C] (-)-(1 R,2S,4R,5S,6S,7S)-7-f(5-Fluoro-2-(5-methyl-1 H-pvrazolo3,4-b1pvridin-3-yl)pvrimidin^vl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



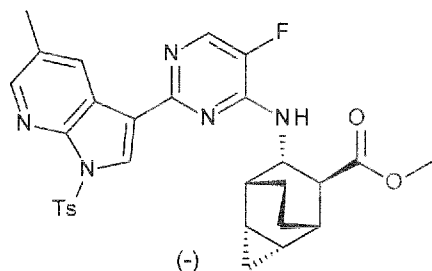
In analogy to the synthesis of example 74/step D, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (350 mg, 711 μ mol) was used to give a crude product, which was then purified by Prep-HPLC to afford the title compound (45 mg, 16% yield) as white foam. MS: 409.1 [M+H]⁺ ¹H NMR (400 MHz, MeOH-d₄) δ 8.64 - 8.91 (m, 1 H) 8.21 - 8.50 (m, 1 H) 7.91 - 8.21 (m, 1 H) 4.79 (d, J=6.02 Hz, 1 H) 3.12 - 3.48 (m, 3 H) 2.73 - 2.81 (m, 1 H) 2.58 - 2.68 (m, 1 H) 2.48 - 2.53 (m, 1 H) 1.58 - 1.97 (m, 4 H) 1.13 (dd, J=7.91, 3.64 Hz, 1 H) 0.85 - 1.05 (m, 2 H) 0.46 (d, J=7.28 Hz, 1 H).

Example 80

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-{5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl}pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid



15 1A1 (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate

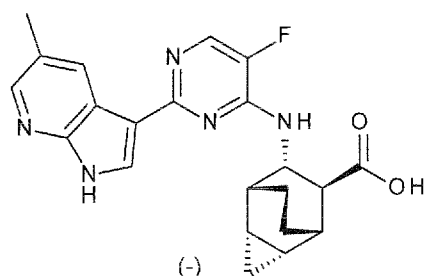


In analogy to the synthesis of example 74/step B, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (example

74/step A, (-) enantiomer, 220 mg, 675 μmol) and 3-iodo-5-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridine (Intermediate A-8, 362 mg, 878 μmol) were used to give a crude product, which was purified by silica gel flash chromatography (0-40% EtOAc-hexane gradient) to afford the title compound (50 mg, 13% yield) as a white solid. MS: 576.1 $[\text{M}+\text{H}]^+$

5

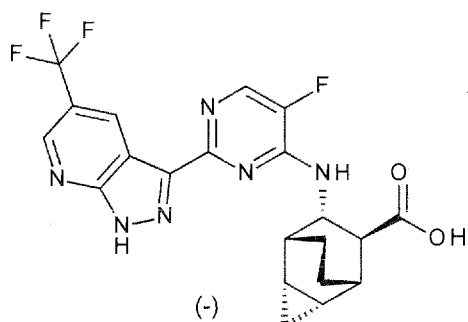
[B] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



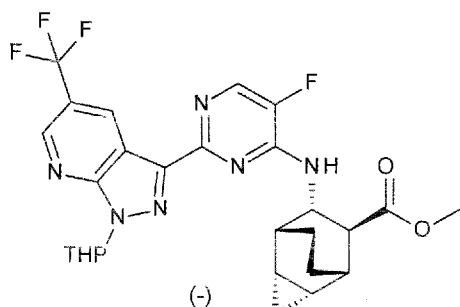
To a stirred solution of ((-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (50 mg, 86.9 μmol) in THF (8 mL) and MeOH (4 mL) was added LiOH (10.4 mg, 434 μmol) pre-dissolved in H₂O (2 mL). The reaction mixture was stirred at room temperature for 48 h before being diluted with water (10 mL), and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH = 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (1 mg, 3% yield) as white foam. MS: 408.1 $[\text{M}+\text{H}]^+$. ¹H NMR (400 MHz, MeOH-d₄) δ ppm 8.74 - 8.78 (m, 1 H) 8.15 (s, 1 H) 8.08 - 8.13 (m, 1 H) 8.02 (d, J=4.02 Hz, 1 H) 4.61 - 4.66 (m, 1 H) 3.08 (s, 1 H) 2.63 - 2.70 (m, 1 H) 2.55 - 2.61 (m, 1 H) 2.51 (s, 4 H) 1.70 - 1.94 (m, 3 H) 1.21 - 1.27 (m, 1 H) 1.09 - 1.18 (m, 1 H) 0.89 - 1.00 (m, 2 H) 0.43 - 0.50 (m, 1 H).

Example 81

(-)-(1R,2S,4R,5S,6S,7S)-7-((S-Fluoro-2-(S-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



1A1 (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate



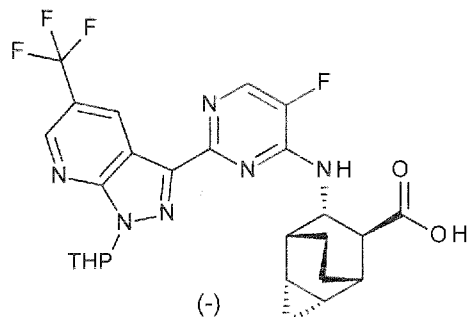
5

In analogy to the synthesis of example 74/step B, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (example 74/step A, 660 mg, 2.03 mmol) and 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-5, 1.21 g, 3.04 mmol) were used to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (200 mg, 18% yield) as yellow oil. MS: 561.1 [M+H]⁺

10

1B1 (-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid

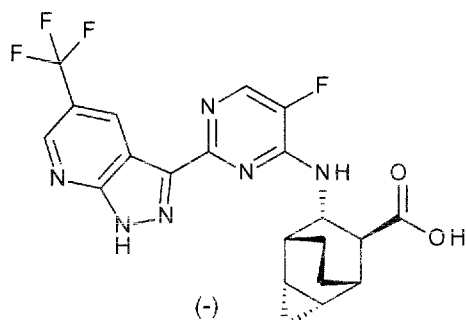
15 acid



In analogy to the synthesis of example 74/step C, (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (200 mg, 357 μ mol) was used to give a crude title compound (190 mg, 97% yield) as yellow oil. MS: 546.6 [M+H]⁺.

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

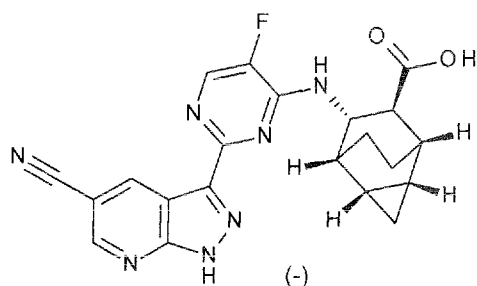
fC] (-)-d R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-(trifluoromethyl)-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



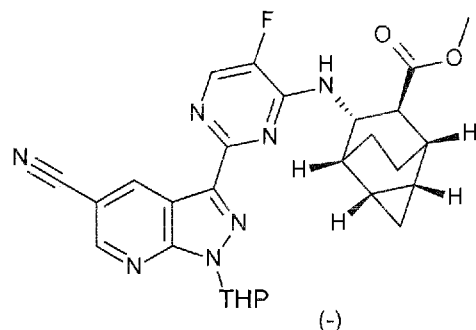
10 In analogy to the synthesis of example 74/step D, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (190 mg, 348 μ mol) was used to give a crude product, which was then purified by Prep-HPLC to afford the title compound (64 mg, 40% yield) as white foam. MS: 463.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.11 - 9.13 (m, 1 H) 6.95 - 6.97 (m, 1 H) 6.35 - 8.37 (m, 1 H) 7.50 - 7.54 (m, 1 H) 4.53 - 4.60 (m, 1 H) 2.85 - 2.89 (m, 1 H) 2.41 - 2.46 (m, 1 H) 1.43 - 1.66 (m, 5 H) 1.10 - 1.15 (m, 1 H) 0.97 - 1.05 (m, 1 H) 0.73 - 0.81 (m, 1 H) 0.25 - 0.34 (m, 1 H).

Example 82

20 **(-)-(1R,2S,4R,5S,6S,7S)-7-((2-{5-cyano-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid**

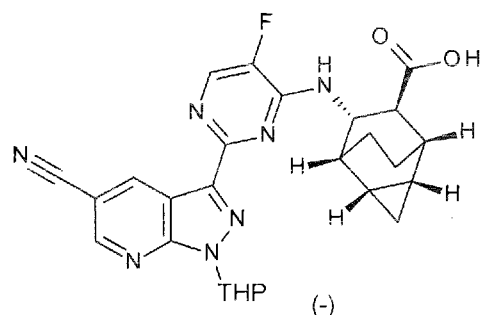


IA 1 (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



- 5 To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (example 74/step A, (-) enantiomer, 440 mg, 1.35 mmol) and Pd(PPh₃)₄ (156 mg, 135 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (1.18 g, 1.06 mL, 2.03 mmol) and the reaction mixture was stirred at 125 °C for 2h. After cooling to room temperature, to the above mixture solution was added 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (Intermediate A-10, 526 mg, 1.49 mmol) and Pd(PPh₃)₄ (156 mg, 135 μmol) in dioxane (16 mL). The resulting reaction mixture was then re-heated at 145 °C for additional 1.5 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (100 mg, 17.2% yield) as yellow oil. MS: 518.1 [M+H]⁺

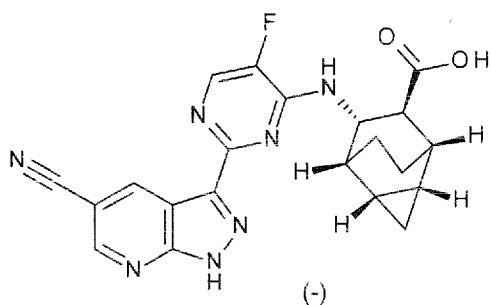
IB 1 (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)-5-fluoropyrimidin-4-

yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (100 mg, 193 μ mol) in THF (4mL) was added LiOH (23.1 mg, 966 μ mol) pre-dissolved in water (4mL). The reaction mixture solution was stirred at room temperature for 4 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated HCl to pH = 4 and then extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (98 mg, 100% yield) as yellow oil. MS: 504.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

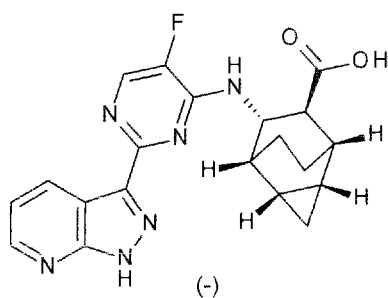
[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-cyano-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



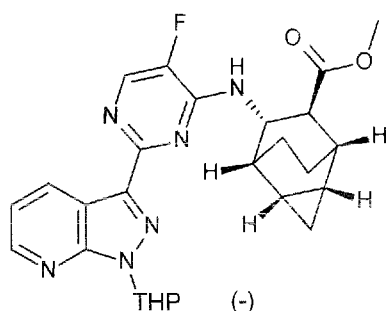
To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (100 mg, 199 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. Afterwards, the mixture solution was concentrated in vacuo to give a crude product, which was then purified by Prep-HPLC to afford the title product (1.5 mg, 1.8% yield) as white foam. MS: 420.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.35 - 9.38 (m, 1 H) 8.85 - 8.87 (m, 1 H) 8.15 - 8.18 (m, 1 H) 4.72 - 4.77 (m, 1 H) 2.73 - 2.77 (m, 1 H) 2.64 - 2.69 (m, 1 H) 2.52 - 2.58 (m, 1 H) 1.83 - 2.00 (m, 2 H) 1.64 - 1.77 (m, 2 H) 1.11 - 1.19 (m, 1 H) 0.98 - 1.03 (m, 1 H) 0.89 - 0.97 (m, 1 H) 0.42 - 0.49 (m, 1 H).

Example 83

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

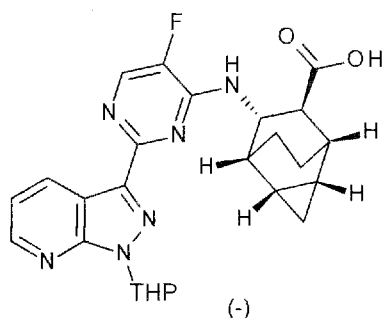


1A 1 (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate



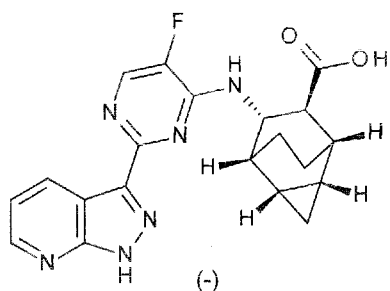
- 5 To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate (example 74/step A (-) enantiomer, 440 mg, 1.35 mmol) and Pd(PPh₃)₄ (156 mg, 135 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (1.18 g, 1.06 mL, 2.03 mmol) and the resulting reaction mixture solution was stirred at 125°C for 2 h. After cooling to room temperature, to
- 10 the above mixture solution was added 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-11, 667 mg, 2.03 mmol) and Pd(PPh₃)₄ (156 mg, 135 μmol) in dioxane (16 mL). The resulting reaction mixture solution was then re-heated at 145°C for 1.5 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic
- 15 layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (180 mg, 27.1% yield) as yellow oil. MS: 493.1 [M+H]⁺

- 20 **1B 1** (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylic acid



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (180 mg, 365 μ mol) in THF (4 mL) and MeOH (2 mL) was added LiOH (43.8 mg, 1.83 mmol, Eq: 5) pre-dissolved in water (1 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated HCl to pH = 4 and then extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound (175 mg, 100% yield) as yellow oil. MS: 479.1 [M+H]⁺. It was used directly in the next step without more purification.

fC] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

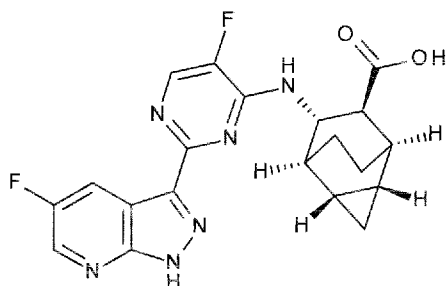


To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (175 mg, 366 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. Afterwards, the reaction mixture was concentrated in vacuo to give a crude product, which was then purified by Prep-HPLC to afford the title product (40 mg, 27.7% yield) as white foam. MS: 395.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.97 (dd, J=8.03, 1.51 Hz, 1 H) 8.60 (dd, J=4.52, 1.51 Hz, 1 H) 8.18 (d, J=4.02 Hz, 1 H) 7.37 (dd,

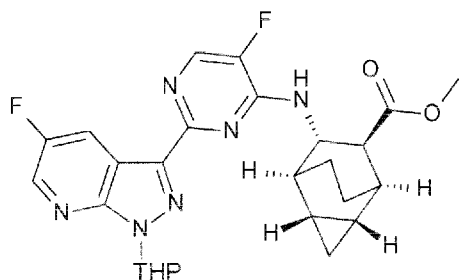
J=8.16, 4.64 Hz, 1 H) 4.75 (d, J=6.78 Hz, 1 H) 2.78 - 2.84 (m, 1 H) 2.64 - 2.69 (m, 1 H) 2.52 - 2.58 (m, 1 H) 1.77 - 1.93 (m, 2 H) 1.61 - 1.76 (m, 2 H) 1.10 - 1.19 (m, 1 H) 0.99 (br. s., 1 H) 0.87 - 0.96 (m, 1 H) 0.43 - 0.50 (m, 1 H).

5 Example 84

(rac)-(1S,2S,4R,5R,6S,7S)-7-((S-fluoro-2-(S-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

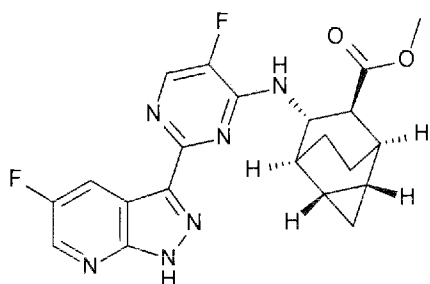


IA 1 (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-Dyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



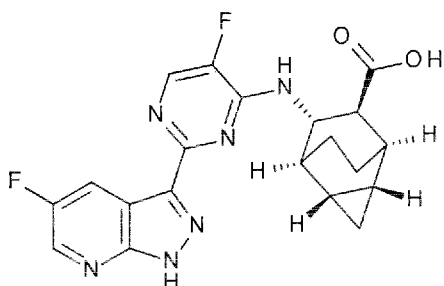
A mixture solution of 5-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-9, 300 mg, 0.8 mmol), (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate B-18, 234mg, 1.2 mmol) and DIPEA (206 mg, 1.6 mmol) in THF (10 mL) was stirred at 60 °C for 10 h. After TLC (petroleum ether:EtOAc = 10:1) showed that the reaction was completed, the solvent was removed under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (petroleum ether : EtOAc = 3:1 to DCM : MeOH = 30:1) to afford the title compound (300 mg, 75% yield) as a yellow solid.

[B] (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



A solution of (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (250 mg, 0.49 mmol) in TFA (5 mL) and DCM (5 mL) was stirred at room temperature for 10 h. After TLC (petroleum ether:EtOAc = 2:1) showed that the reaction was completed, the solvent was removed under reduced pressure to give a crude title compound. This crude product was used directly in the next step without further purification.

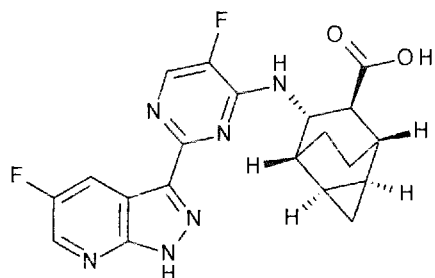
[C] (rac)-(1S,2S,4R,5R,6S,7S)-7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid



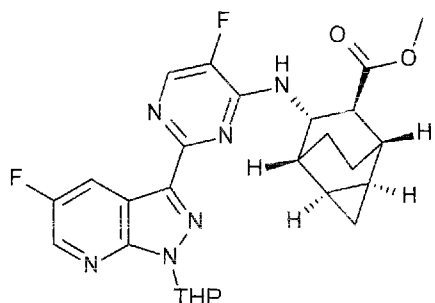
A solution of (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (200 mg, 0.48 mmol) in 2N aq. NaOH solution (5 mL) and THF (2 mL) was stirred at room temperature for 3 h. Afterwards, the reaction mixture was neutralized with 2N HCl to pH = 4 and extracted with EtOAc (50 mL three times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (52 mg, 22% yield) as a white solid. MS: 413.1, [M+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 0.40 - 0.58 (m, 1 H) 0.75 (br. s., 1 H) 0.89 - 1.23 (m, 3 H) 1.28 - 1.43 (m, 1 H) 1.52 (d, J=8.29 Hz, 2 H) 2.32 (br. s., 1 H) 2.40 (br. s., 1 H) 2.84 (d, J=5.09 Hz, 1 H) 4.91 (br. s., 1 H) 7.96 (d, J=6.59 Hz, 1 H) 8.30 (d, J=3.77 Hz, 1 H) 8.50 - 8.58 (m, 1 H) 8.64 (s, 1 H).

Example 85

(rac)-(1R,2R,4S,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo [3.2.2.0^{2,4}]nonane-6-carboxylic acid

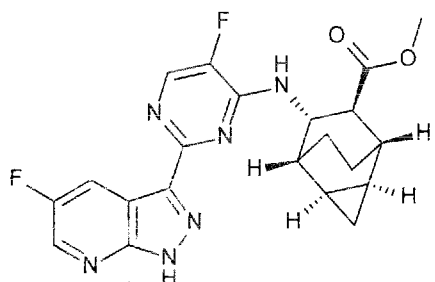


1A1 (rac)-(1 R,2R,4S,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



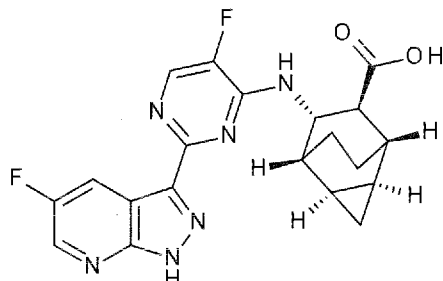
In analogy to the synthesis of Example 84/Step A, (rac)-(1 R,2R,4S,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate B-19, 93 mg, 0.475 mmol) was used to afford the title compound (120 mg, 74.5 % yield) as a yellow solid after silica gel flash chromatography purification.

1B1 (rac)-(1 R,2R,4S,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1 H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



In analogy to the synthesis of Example 84/Step B, (rac)-(1 R,2R,4S,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2 -yl)-1 /-y-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2 .0^{2,4}]nonane-6-carboxylate (120 mg, 0.235 mmol) was used to give a crude title compound (120 mg, 100% yield) as a white solid. MS: 427.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

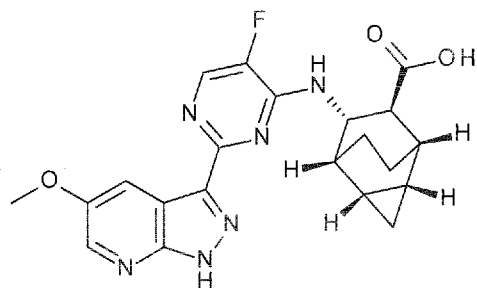
[C] (rac)-(1 R,2R,4S,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



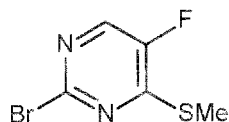
- 5 in analogy to the synthesis of Example 84/Step C, (rac)-(1 R,2R,4S,5S,6S,7S)-methyl-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (120 mg, 0.235 mmol) was used to give a crude product, which was purified by Prep-HPLC to afford the title compound (12 mg, 12.5% yield) as a white solid. MS: 413.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.41 - 0.46 (m, 1 H) 0.68-0.69 (br. s., 1 H) 1.02 - 1.04 (m, 3 H) 1.15 - 1.24 (m, 3 H) 1.41 (m, 2 H) 2.34-2.39 (m, 2 H) 2.97 (br. s., 1 H) 4.87 (br. s., 1 H) 7.72-7.79 (m, 1 H) 8.28-8.29 (d, J=3.6 Hz, 1 H) 8.49-8.51 (d, J=3.6 Hz, 1 H) 8.63 - 8.64 (m, 1 H).

Example 86

- 15 (rac)-{1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-methoxy-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



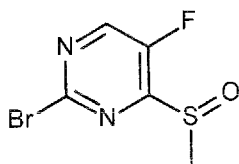
IAI 2-Bromo-5-fluoro-4-(methylthio)pyrimidine



- 20 A solution of 2-chloro-5-fluoro-4-(methylthio)pyrimidine (10.8 g, 60.4 mmol) in HBr/acetic acid (100 mL) was stirred at room temperature for 72 h. Afterwards, the reaction mixture was adjusted to pH = 8 with satd. aq. NaHCO₃ solution and extracted with EtOAc (200 mL)

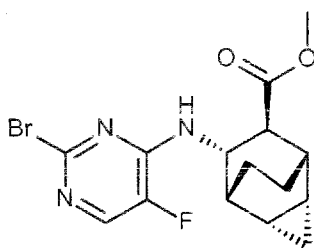
three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to afford a crude title compound (12.15 g, 90.1% yield) as a white solid. MS: 225.0 $[\text{M}+2+\text{H}]^+$.

5 1B 12-Bromo-5-fluoro-4-(methylsulfinyl)pyrimidine



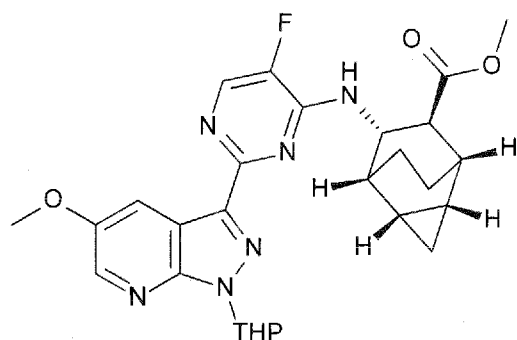
To a stirred solution of 2-bromo-5-fluoro-4-(methylthio)pyrimidine (1.4 g, 6.2 mmol) in DCM (20 mL) was added m-CPBA (1.17 g, 6.8 mmol) at 0-5 °C and stirred for 1 h. Afterwards, the reaction was allowed to warm up to room temperature and filtered. The filtrate was concentrate under reduced pressure to give a crude title compound (1.43 g, 95.3% yield) as a white solid. MS: 240.0 $[\text{M}+2+\text{H}]^+$. This crude product was used directly in the next step without further purification.

15 [C] (rac)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((2-bromo-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



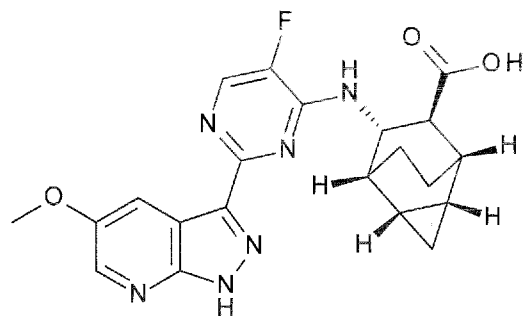
To a stirred solution of 2-bromo-5-fluoro-4-(methylsulfinyl)pyrimidine (550 mg, 2.3 mmol) in THF (10 mL) was added (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (500 mg, 2.5 mmol) and DIPEA (890 mg, 6.9 mmol) and the resulting reaction mixture was stirred at 85 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residual was purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1) to afford the title compound (430 mg, 50.5% yield) as colorless oil. MS: 370.0 $[\text{M}+\text{H}]^+$.

25 [P] (rac)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of 5-methoxy-1-(tetrahydro-2H-pyran-2-yl)-3-(tributylstannyl)-1H-pyrazolo[3,4-b]pyridine (240 mg, 0.48 mmol) in THF (4 mL) was added (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-bromo-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (160 mg, 0.44 mmol). PdCl₂(dtbpf) (26 mg, 0.04 mmol) and the reaction mixture was stirred at 80°C for 12 h. After TLC showed that the reaction was completed, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the title compound (130 mg, 56% yield) as brown oil. MS: 523.0 [M+H]⁺

[E] (rac)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methoxy-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid

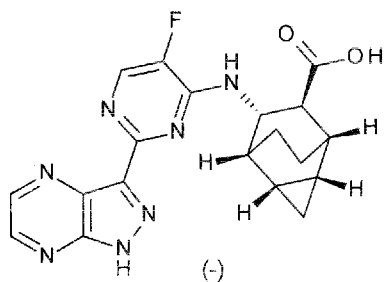


A solution of (rac)-(2S,4R,6S,7S)-methyl 7-((5-fluoro-2-(5-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (125 mg, 0.22 mmol) in TFA/DCM (5 mL, 1:2) was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was re-dissolved in THF/water (5 mL: 4:1), added with LiOH (72 mg, 3 mmol), and the resulting mixture was stirred at room temperature for 2 h. After LC-MS showed that the reaction was completed, the reaction mixture was neutralized using TFA to pH = 4, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (54.6 mg, 61% yield) as a white solid. MS: 425.0

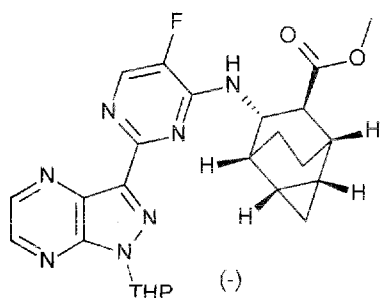
$[M+H]^+$. ^1H NMR (400 MHz, MeOH-*d*(4)) δ 8.40 (d, J = 2.4 Hz, 1H), 8.28 (d, J = 4.8 Hz, 1H), 8.24 (d, J = 2.8 Hz, 1H), 5.04 (d, J = 6.0 Hz, 1H), 4.02 (s, 3H), 2.81 (d, J = 6.4 Hz, 1H), 2.53-2.50 (m, 2H), 1.80-1.62 (m, 4H), 1.21-0.49 (m, 4H).

5 Example 87

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

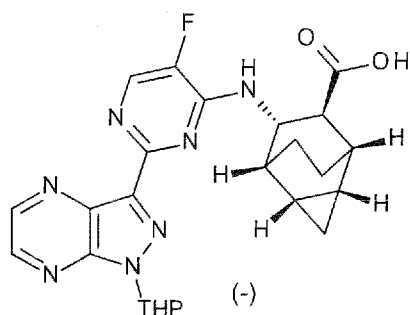


IA 1 (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



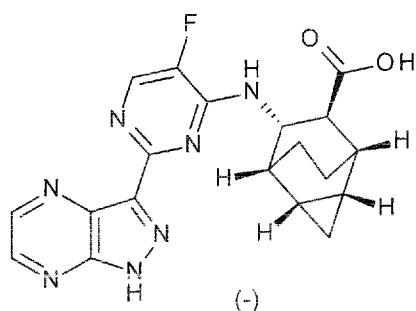
In analogy to the synthesis of Example 74/Step B, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (Intermediate C-1, 1.03 g, 3.65 mmol) was used to afford the title compound (200 mg, 20% yield) as a yellow solid after silica gel flash chromatography purification. MS: 494.2 $[M+H]^+$.

IB 1 (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



In analogy to the synthesis of Example 74/Step C, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (200 mg, 405 μ mol) was used to give a crude title compound (200 mg, 100% yield) as yellow oil. MS: 480.2 $[M+H]^+$. This crude product was used directly in the next step without further purification.

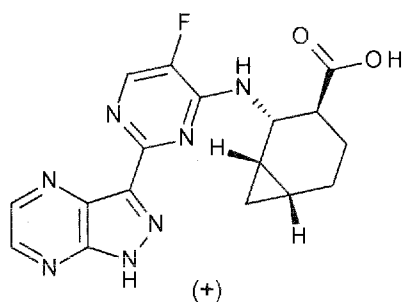
IC1 (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid



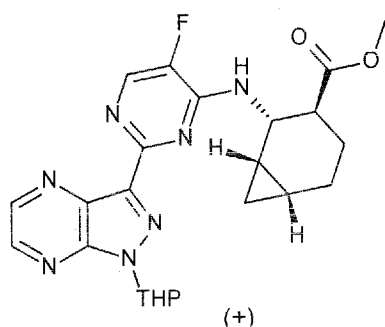
In analogy to the synthesis of Example 74/Step D, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (190 mg, 396 μ mol) was used to afford the title compound (16 mg, 10.2 % yield) as white foam after Prep-HPLC purification. MS: 396.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 8.75 (d, $J=2.26$ Hz, 1 H) 8.60 - 8.66 (m, 1 H) 8.16 - 8.22 (m, 1 H) 4.54 - 4.59 (m, 1 H) 2.73 - 2.80 (m, 1 H) 2.66 - 2.71 (m, 1 H) 2.45 - 2.50 (m, 1 H) 1.85 - 1.94 (m, 1 H) 1.54 - 1.80 (m, 4 H) 1.07 - 1.16 (m, 1 H) 0.86 - 0.99 (m, 2 H) 0.39 - 0.49 (m, 1 H).

Example 88

(+H1S,2S,3S,6R)-2-((5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid

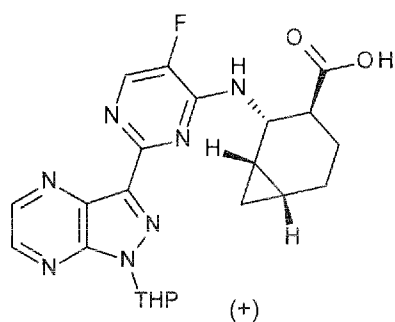


1A 1 (+)-(1S,2S,3S,6R)-methyl 2-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate



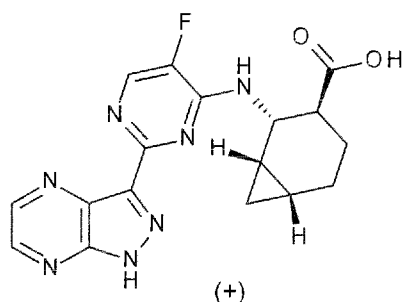
- 5 In analogy to the synthesis of Example 58/Step C, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (Intermediate C-1, 367 mg, 1.3 mmol) was used to afford the title compound (160 mg, 34.3% yield) as yellow oil after silica gel flash chromatography purification. MS: 468.1 [M+H]⁺

10 [B] (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



- In analogy to the synthesis of Example 58/Step D, (+)-(1S,2S,3S,6R)-methyl 2-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (160 mg, 342 μmol) was used to give a crude title compound (140 mg, 100% yield) as yellow oil. MS: 454.1 [M+H]⁺. This crude product was used directly in the next step without further purification.
- 15

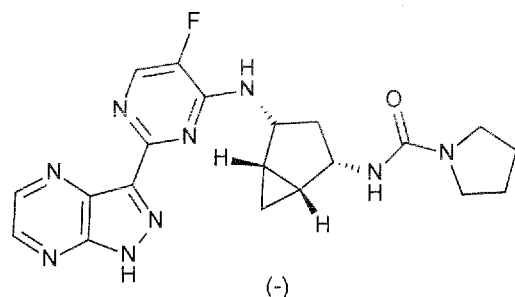
[C] (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



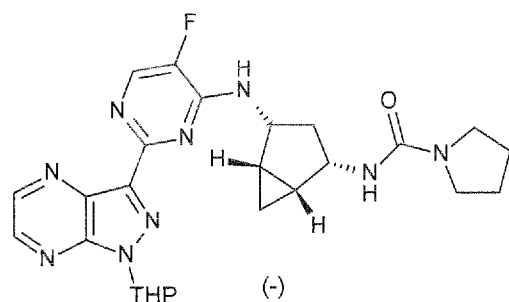
In analogy to the synthesis of Example 58/Step E, (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid (140 mg, 309 μmol) was used to afford the title compound (6 mg, 5.3% yield) as white foam after Prep-HPLC purification. MS: 370.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.76 (d, $J=2.26$ Hz, 1 H) 8.63 (d, $J=2.01$ Hz, 1 H) 8.15 - 8.20 (m, 1 H) 5.20 - 5.28 (m, 1 H) 2.32 - 2.40 (m, 1 H) 2.12 - 2.21 (m, 1 H) 1.69 - 1.79 (m, 2 H) 1.47 - 1.65 (m, 2 H) 1.22 - 1.29 (m, 1 H) 0.64 - 0.71 (m, 1 H) 0.36 - 0.43 (m, 1 H).

Example 89

(-)-yV-[(1R,2S,4R,5S)-4-[[5-fluoro-2-{1H-pyrazolo[3,4-b]pyrazin-3-yl}pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide

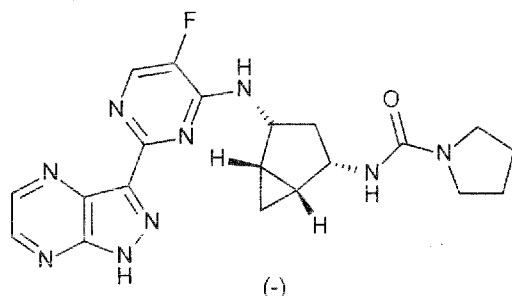


[A] (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydro-2H-pyran-2-yl)pyrazolo[3,4-b]pyrazin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide



To a stirred mixture solution of (-)-N-((1R,2S,4R,5S)-4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide (Example 6/Step A, 220 mg, 647 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (112 mg, 97.1 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (563 mg, 971 μmol) and the resulting reaction mixture was stirred at 125°C for 2 h. After cooling down, to the above mixture solution was added 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (Intermediate C-1, 367 mg, 1.29 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (112 mg, 97.1 μmol) in dioxane (16 mL). The reaction mixture solution was then re-heated at 145°C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-10% MeOH-DCM gradient) to afford the title compound (40 mg, 12% yield) as a white solid. MS: 508.2 $[\text{M}+\text{H}]^+$.

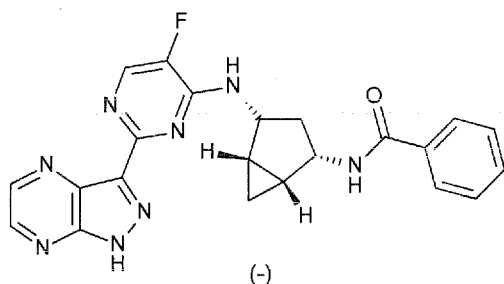
(-)-N-((1R,2S,4R,5S)-4-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide



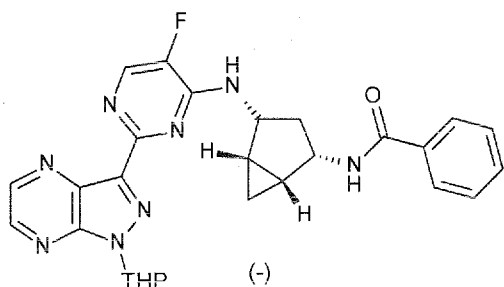
A solution of N-((1R,2S,4R,5S)-4-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide (40mg, 78.8 μmol) in TFA (5mL) and DCM (5 mL) was stirred at room temperature for 16 h. Afterwards, solvent was evaporated under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (2 mg, 6% yield) as white foam. MS: 424.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 0.24 - 0.36 (m, 1 H) 0.94 (d, $J=4.52$ Hz, 1 H) 1.24 (d, $J=12.80$ Hz, 1 H) 1.53 (d, $J=6.53$ Hz, 1 H) 1.75 - 1.84 (m, 4 H) 2.10 - 2.23 (m, 1 H) 3.18 - 3.29 (m, 4 H) 4.28 (br. s., 1 H) 4.67 (br. s., 1 H) 5.74 (d, $J=7.03$ Hz, 1 H) 7.69 (d, $J=6.02$ Hz, 1 H) 8.32 (d, $J=3.76$ Hz, 1 H) 8.61 (d, $J=2.26$ Hz, 1 H) 8.74 (d, $J=2.01$ Hz, 1 H) 14.30 (s, 1 H).

Example 90

(-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide

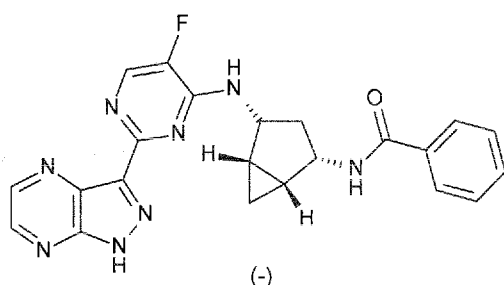


IA 1 (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyrazin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide



In analogy to the synthesis of Example 89/Step A, (-)-N-[(1R,2S,4R,5S)-4-[[2-chloro-5-fluoropyrimidin-4-yl]amino]bicyclo[3.1.0]hexan-2-yl]benzamide (Example 7/step A, 220 mg, 634 μ mol) was used to afford the title compound (100 mg, 31% yield) as a white solid after silica gel flash chromatography purification. MS: 515.2 $[M+H]^+$.

IB (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide

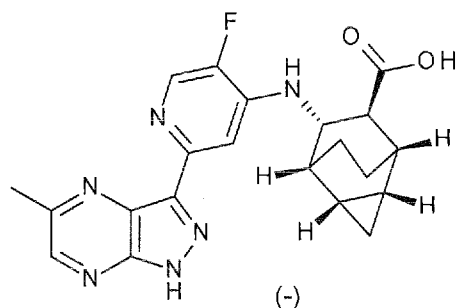


In analogy to the synthesis Example 89/Step B, (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydropyran-2-yl)pyrazolo[3,4-b]pyrazin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide (100 mg, 195 μ mol) was used to afford the title compound (30 mg, 36% yield) as a white solid. MS: 431.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 0.32 - 0.46 (m, 1 H) 1.05 (d, $J=4.52$ Hz, 1 H) 1.30 - 1.47 (m, 1 H) 1.57 - 1.70 (m, 1 H) 1.90 (br. s., 1 H) 2.20 - 2.37 (m, 1 H) 4.60 (d, $J=2.26$ Hz, 1 H) 4.78 (br. s., 1 H) 7.41 - 7.50 (m, 2

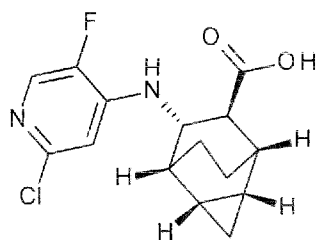
H) 7.50 - 7.58 (m, 1 H) 7.80 - 7.95 (m, 3 H) 8.34 (d, J=3.76 Hz, 1 H) 8.40 (d, J=7.28 Hz, 1 H) 8.63 (s, 1 H) 8.76 (d, J=2.01 Hz, 1 H) 14.11 - 14.55 (m, 1 H).

Example 91

- 5 (rac)-(1 R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



[A] (rac)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

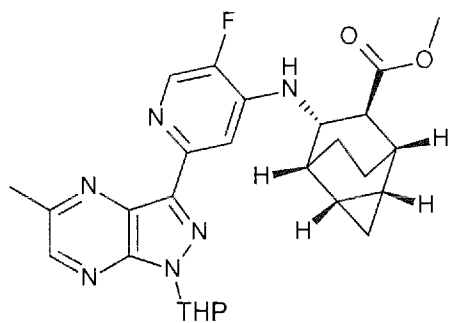


10

To a stirred solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate B-12, 350 mg, 1.68 mmol) and 2-chloro-5-fluoro-4-iodopyridine (453 mg, 1.76 mmol) in dioxane (15 mL) was added Xant-phos (194 mg, 0.336 mmol), Pd₂(dba)₃ (153 mg, 0.168 mmol) and Cs₂CO₃ (1.64 g, 5.04 mmol) and the resulting mixture solution was stirred at 90°C for 18 h. After TLC (petroleum ether: EtOAc = 3:1) showed that the reaction was completed, solvent was removed under reduced pressure to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether: EtOAc = 10:1 to 1:1) to afford the title compound (410 mg, 75.1% yield) as a white solid. MS: 325.1 [M+H]⁺.

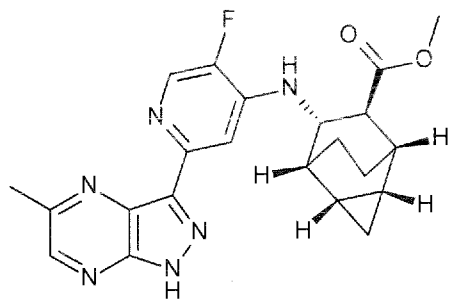
20

[B] (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



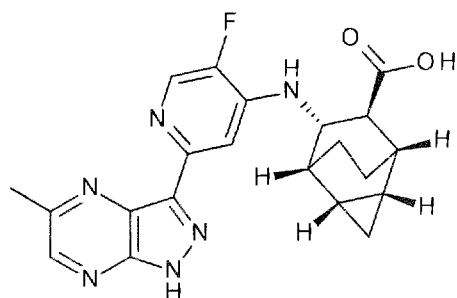
To a stirred solution of 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-3-(tributylstannyl)-1H-pyrazolo
[3,4-b]pyrazine (150 mg, 0.3 mmol) in dioxane (6 mL) was added (rac)-
(1R,2S,4R,5S,6S,7S)-methyl7-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0]nonane-
5 6-carboxylate (107.1 mg, 0.33 mmol), Pd₂(dba)₃ (27.5 mg, 0.03 mmol), X-phos (43 mg,
0.09 mmol) and CuI (3 mg, 0.015 mmol) at room temperature. The resulting reaction
mixture was stirred at 140°C under microwave heating for 3 h. After cooling to room
temperature, the reaction mixture was concentrated in vacuo to give a crude product, which
was purified by silica gel flash chromatography (petroleum ether: EtOAc = 1:1) to afford the
10 title compound (12 mg, 8% yield) as a yellow solid. MS: 507.4 [M+H]⁺

[Cl] (rac)-(1R,2S,4R,5S,6S,7S)-Methyl7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-
1H-pyrazolo[3,4-b]pyrazine-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0]nonane-6-carboxylate



15 To a stirred solution of (1R,2S,4R,5S,6S,7S)-methyl7-((5-fluoro-2-(5-methyl-1 - (tetrahydro-
2H
-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyrazine-3-yl)pyridin-4-
yl)amino)tricyclo[3.2.2.0,4]nonane-6-carboxylate (36 mg, 0.07 mmol) in DCM (15 mL) was
added TFA (3 mL) and the mixture solution was stirred at room temperature for 12 h. After
TLC (petroleum ether: EtOAc = 1:1) showed that the reaction was completed, the solvent
20 was removed under reduced pressure to give a crude title compound (30 mg) as an oil. MS:
423.1 [M+H]⁺. This crude product was used directly in the next step without further
purification.

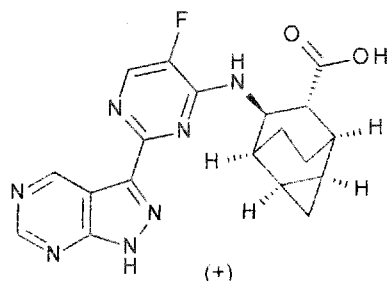
ID] (rac)-(1R,2S,4R,5S,6S,7S)-7-(5-fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



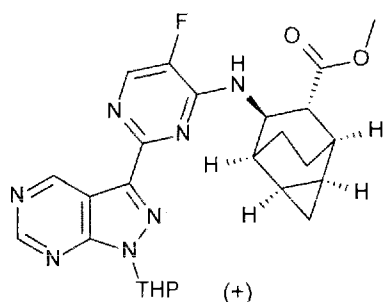
To a solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-
 5 -pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (30 mg, 0.07 mmol) in MeOH (5 mL) was added aq. NaOH solution (4 N, 5 mL) and the reaction mixture was stirred at room temperature for 3 h. After TLC (petroleum ether:EtOAc = 1:1) showed that the reaction was completed, the mixture solution was concentrated to remove MeOH and followed by the addition of AcOH to adjust pH to 5-6.
 10 The reaction mixture was extracted with DCM (20 mL three times), and the organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (2.5 mg, 9% yield) as a white solid. MS: 409.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄): δ ppm 8.63 (s, 1 H) 8.41 (d, J=7.03 Hz, 1 H) 8.30 (br. s., 1 H) 4.27 (d, J=5.02 Hz, 1 H) 2.90 (d, J=5.52 Hz, 1 H) 2.81 (s, 3 H) 2.57-2.67 (m, 2 H) 1.85-1.99 (m, 2 H) 1.68 (d, J=10.79 Hz, 2 H) 1.17 (d, J=4.77 Hz, 1 H) 0.94 (d, J=4.27 Hz, 2 H) 0.41-0.51 (m, 1 H).

Example 92

(+)-(1S,2R,4S,5R,6R,7R)-7-(5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

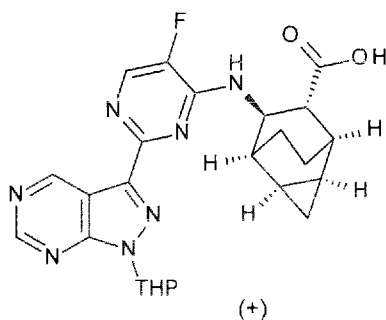


1A1 (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-(5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



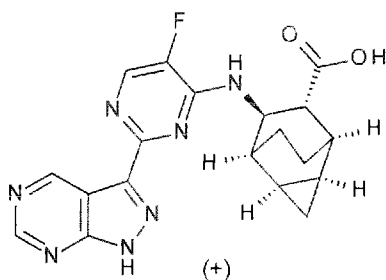
In analogy to the synthesis of 74/Step B, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediate D-1, 1.03 g, 3.65 mmol) was used afford the title compound (200 mg, 20% yield) as a white solid after silica gel flash chromatography purification. MS: 494.2 [M+H]⁺.

IB1 (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,2,0.4]nonane-6-carboxylic acid



In analogy to the synthesis of Example 74/Step C, (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,2,0.4]nonane-6-carboxylate (190 mg, 385 μmol) was used to give a crude title compound (185 mg, 100% yield) as yellow oil. MS: 480.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

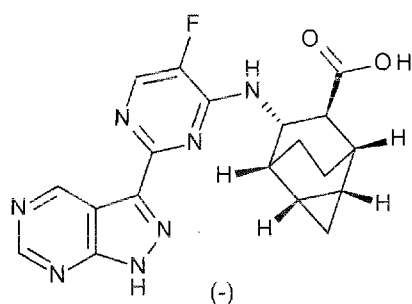
[Cl (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,2,0.4]nonane-6-carboxylic acid



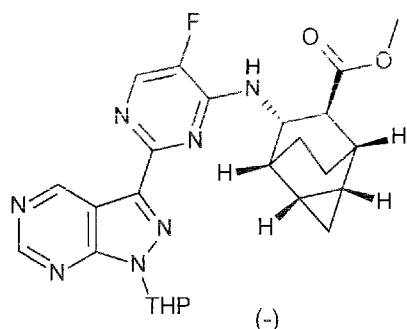
In analogy to the synthesis of Example 74/Step D, (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (185 mg, 193 μmol) was used to afford the title compound (1.5 mg, 2% yield) as white foam after Prep-HPLC purification. MS: 396.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.94 - 9.96 (m, 1 H) 9.01 - 9.03 (m, 1 H) 8.15 - 8.19 (m, 1 H) 4.74 - 4.78 (m, 1 H) 2.69 - 2.74 (m, 1 H) 2.62 - 2.66 (m, 1 H) 2.52 - 2.57 (m, 1 H) 1.59 - 1.94 (m, 4 H) 1.10 - 1.18 (m, 1 H) 0.97 - 1.04 (m, 1 H) 0.87 - 0.95 (m, 1 H) 0.41 - 0.49 (m, 1 H).

Example 93

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

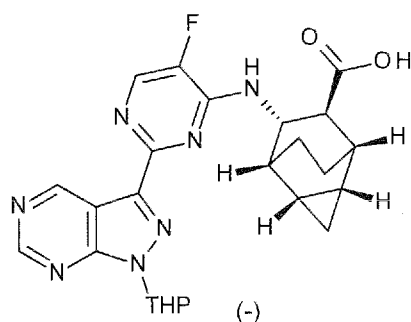


(-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



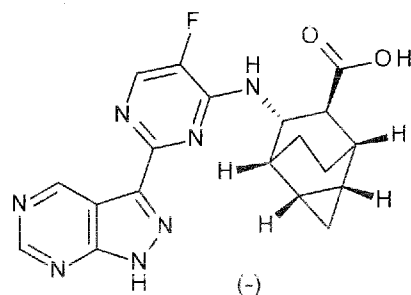
In analogy to the synthesis of Example 75/Step A, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediate D-1, 1.03 g, 3.65 mmol) was used to afford the title compound (200 mg, 20% yield) as a yellow solid after silica gel flash chromatography purification. MS: 494.2 [M+H]⁺.

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



In analogy to the synthesis of Example 75/Step B, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (160 mg, 113 μ mol) was used to give a crude title compound (131 mg, 100% yield) as yellow oil. This crude product was used directly in the next step without further purification. MS: 480.2 $[M+H]^+$

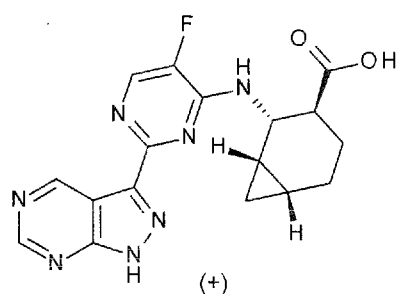
[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid



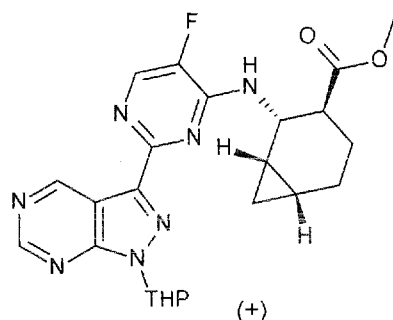
In analogy to the synthesis of Example 75/Step C, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (131 mg, 95.6 μ mol) was used to afford the title compound (3 mg, 7.9% yield) as white foam after Prep-HPLC purification. MS: 396.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 9.94 (s, 1 H) 9.01 - 9.03 (m, 1 H) 8.16 - 8.20 (m, 1 H) 4.73 - 4.78 (m, 1 H) 2.73 - 2.77 (m, 1 H) 2.60 - 2.64 (m, 1 H) 2.51 - 2.56 (m, 1 H) 1.57 - 1.93 (m, 4 H) 1.11 - 1.18 (m, 1 H) 0.97 - 1.03 (m, 1 H) 0.38 - 0.96 (m, 1 H) 0.43 - 0.50 (m, 1 H).

Example 94

(+H1S,2S,3S,6R)-2-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid

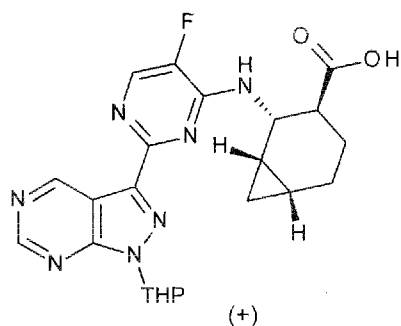


1A 1 (+)-(1S,2S,3S,6R)-methyl 2-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate



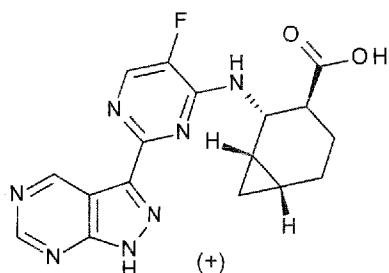
- 5 In analogy to the synthesis of Example 58/Step C, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediate D-1, 425 mg, 1.5 mmol) was used to afford the title compound (300 mg, 22.5% yield) as a white powder after silica gel flash chromatography purification. MS: 468.2 [M+H].

10 [B] (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



- In analogy to the synthesis Example 58/Step D, (+)-(1S,2S,3S,6R)-methyl 2-((5-fluoro-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (300 mg, 225 μ mol) was used to give a crude title compound (300 mg, 100% yield) as yellow oil. MS: 454.2 [M+H]⁺. This crude product was used directly in the next step without further purification.
- 15

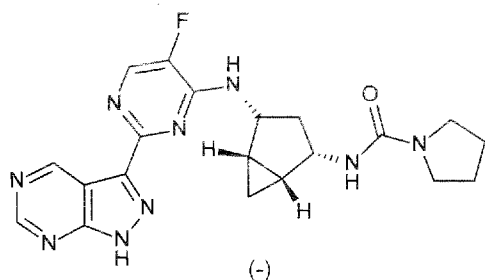
[C] (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



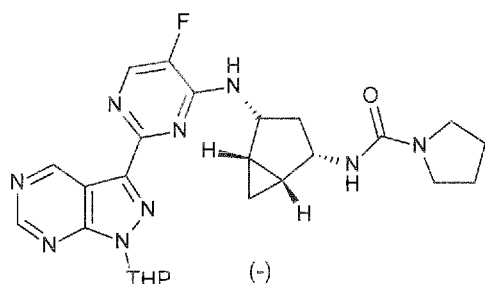
In analogy to the synthesis of Example 58/Step E, (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1-
 5 (tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid (300 mg, 232 μ mol) was used to afford the title compound (23 mg, 27%) yield as white foam after Prep-HPLC purification. MS: 370.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 10.03 (s, 1 H) 9.03 (s, 1 H) 8.16 - 8.20 (m, 1 H) 5.29 - 5.36 (m, 1 H) 2.31 - 2.39 (m, 1 H) 2.17 - 2.26 (m, 1 H) 1.78 - 1.85 (m, 1 H) 1.49 - 1.72
 10 (m, 3 H) 1.24 - 1.34 (m, 1 H) 0.68 - 0.75 (m, 1 H) 0.42 - 0.47 (m, 1 H).

Example 95

(-)-W-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide



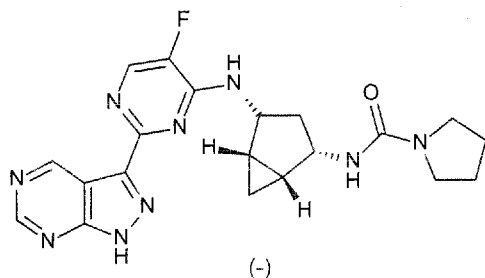
[A] (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydropyran-2-yl)pyrazolo[3,4-d]pyrimidin-3-yl]pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide



In analogy to the synthesis of Example 89/Step A, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-
 20 1H-pyrazolo[3,4-d]pyrimidine (Intermediate D-1, 367 mg, 1.29 mmol) was used to afford the

title compound (100 mg, 31% yield) as a white solid after silica gel flash chromatography purification. MS:508.2 [M+H]⁺

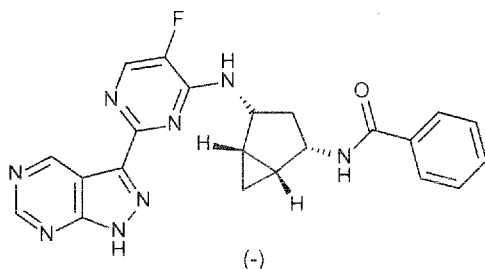
[B] (-)-A-((1R,2S,4R,5S)-4-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide



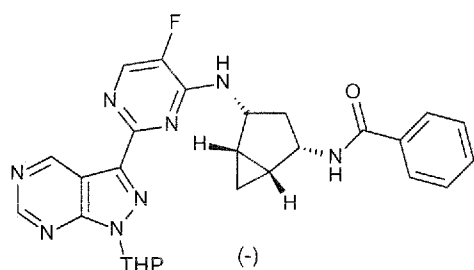
In analogy to the synthesis of Example 89/Step B, (-)-A-((1R,2S,4R,5S)-4-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide (100mg, 197 μmol) was used to afford the title compound (5 mg, 6% yield) as white foam after Prep-HPLC purification. MS:424.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.25 - 0.37 (m, 1 H) 0.97 (d, J=4.02 Hz, 1 H) 1.21 - 1.36 (m, 1 H) 1.57 (br. s., 1 H) 1.69 - 1.85 (m, 5 H) 2.06 - 2.18 (m, 1 H) 3.23 (t, J=6.65 Hz, 4 H) 4.34 (br. s., 1 H) 4.77 (br. s., 1 H) 5.77 (d, J=7.28 Hz, 1 H) 7.81 (d, J=6.78 Hz, 1 H) 8.23 - 8.39 (m, 1 H) 9.05 (s, 1 H) 9.78 (s, 1 H) 14.37 (s, 1 H).

Example 96

(-)-A-((1R,2S,4R,5S)-4-((5-fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)amino)bicyclo[3.1.0]hexan-2-yl)benzamide

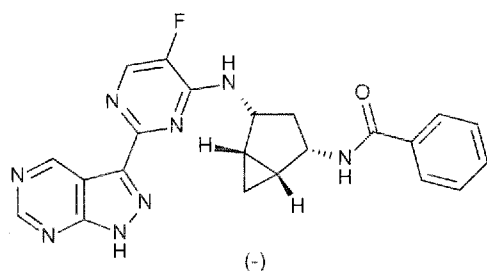


[A] (-)-A-((1R,2S,4R,5S)-4-((5-fluoro-2-(1-tetrahydro-2H-pyran-2-yl)pyrazolo[3,4-d]pyrimidin-3-yl)amino)bicyclo[3.1.0]hexan-2-yl)benzamide



In analogy to the synthesis of Example 90/Step A, 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (Intermediate D-1, 359 mg, 1.27 mmol) was used to afford the title compound (100 mg, 31% yield) as a white solid after silica gel flash chromatography purification. MS: 515.2 [M+Hf.

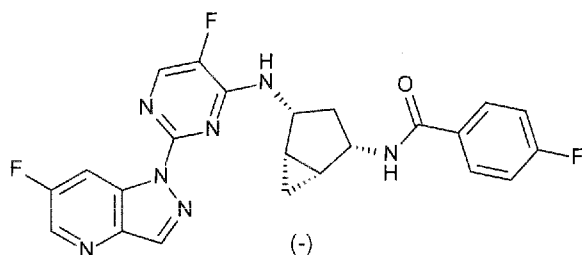
[B] (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-phenylpyrazolo[3,4-d]pyrimidin-3-yl)]amino]-2-bicyclo[3.1.0]hexan-2-yl]benzamide



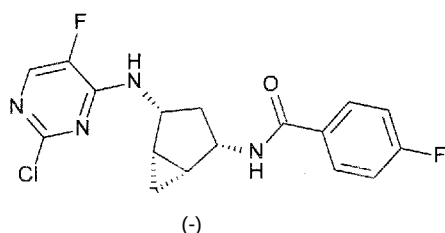
In analogy to the synthesis of Example 90/Step B, (-)-N-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydropyran-2-yl)pyrazolo[3,4-d]pyrimidin-3-yl)]amino]-2-bicyclo[3.1.0]hexan-2-yl]benzamide (100mg, 194 μmol) was used to afford the title compound (30 mg, 36% yield) as a white solid after Prep-HPLC purification. MS: 431.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 0.35 - 0.45 (m, 1 H) 1.03 - 1.11 (m, 1 H) 1.41 - 1.51 (m, 1 H) 1.64 - 1.73 (m, 1 H) 1.77 - 1.86 (m, 1 H) 2.23 (dt, J=12.86, 7.62 Hz, 1 H) 4.61 - 4.72 (m, 1 H) 4.87 (br. s., 1 H) 7.43 - 7.50 (m, 2 H) 7.51 - 7.56 (m, 1 H) 7.85 - 7.91 (m, 2 H) 7.93 (d, J=6.78 Hz, 1 H) 8.36 (d, J=3.76 Hz, 1 H) 8.42 (d, J=7.28 Hz, 1 H) 9.06 (s, 1 H) 9.80 (s, 1 H) 14.39 (br. s., 1 H).

Example 97

(-)-4-Fluoro-N-[(1R,2S,4R,5S)-4-[(5-fluoro-2-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl)]amino]-2-bicyclo[3.1.0]hexan-2-yl]benzamide



1a1 (-)-N-((1R,2S,4R,5S)-4-(2-chloro-5-fluoropyrimidin-4-yl)bicyclo[3.1.0]hexan-2-yl)-4-fluorobenzamide

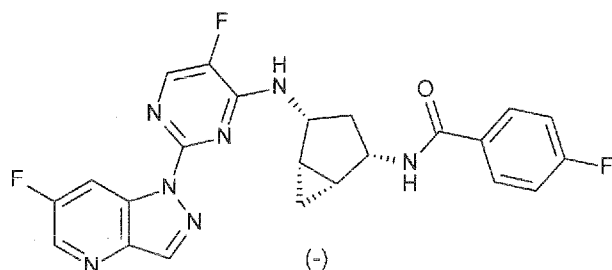


5 To a stirred solution of (-)-(1S,2R,4S,5R)-4-(2-chloro-5-fluoropyrimidin-4-yl)bicyclo[3.1.0]hexane-2,4-diamine 2,2,2-trifluoroacetate (260 mg, 729 μ mol) in DCM (10 mL) was added DIPEA (471 mg, 3.64 mmol), HATU (416 mg, 1.09 mmol) and 4-fluorobenzoic acid (153 mg, 1.09 mmol) and the resulting mixture solution was stirred at room temperature for 12 h. Afterwards, the reaction mixture was poured into water (20 mL)

10 and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (200 mg, 75.2% yield) as a light yellow solid. MS: 365.1 $[\text{M}+\text{H}]^+$.

15

1b1 (-)-4-Fluoro-N-((1R,2S,4R,5S)-4-(5-fluoro-2-(6-fluoro-1H-pyrazolo[4.3-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)benzamide



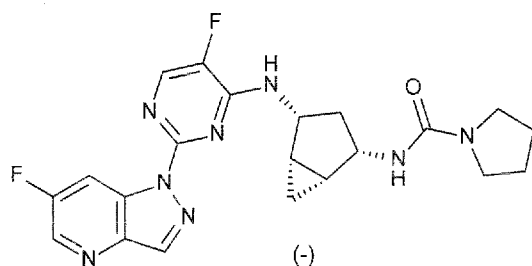
To a stirred mixture solution of (-)-N-((1R,2S,4R,5S)-4-(2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-4-fluorobenzamide (100 mg, 274 μ mol) and 6-fluoro-1H-pyrazolo[4.3-b]pyridine (Intermediate F-2, 154 mg, 1.12 mmol) in dioxane (6 mL) was added copper (I) iodide (20.9 mg, 110 μ mol), (1R,2S)-cyclohexane-1,2-diamine (25 mg, 31.3 μ L,

20

219 pmol) and potassium hydrogenphosphate (71.6 mg, 411 μmol) and the resulting reaction mixture solution was stirred at 120°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (40 mg, 31.3% yield) as white foam. MS: 466.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.74 - 8.79 (m, 1 H) 8.62 - 8.65 (m, 1 H) 8.49 - 8.52 (m, 1 H) 8.11 - 8.15 (m, 1 H) 7.88 - 7.94 (m, 2 H) 7.21 (s, 2 H) 4.95 - 5.04 (m, 1 H) 4.73 - 4.81 (m, 1 H) 2.49 - 2.59 (m, 1 H) 1.90 - 1.97 (m, 1 H) 1.81 - 1.89 (m, 1 H) 1.29 - 1.43 (m, 1 H) 1.04 - 1.10 (m, 1 H) 0.55 - 0.61 (m, 1 H).

Example 98

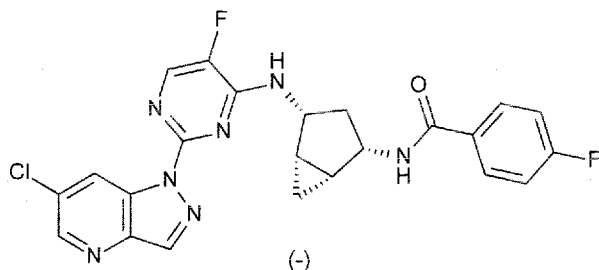
(-)-Al-[(1R,2S,4R,5S)-4-[[5-Fluoro-2-{6-fluoropyrazolo[4,3-b]pyridin-1-yl}pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]pyrrolidine-1-carboxamide



To a stirred mixture solution of (-)-yV-((1R,2S,4R,5S)-4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide (Example 6/Step A, 100 mg, 294 μmol) and 6-fluoro-1H-pyrazolo[4,3-b]pyridine (Intermediate F-2, 154 mg, 1.12 mmol) in dioxane (6 mL) was added copper (I) iodide (22.4 mg, 118 μmol), (1R,2S)-cyclohexane-1,2-diamine (26.9 mg, 235 μmol) and potassium phosphate tribasic (130 mg, 588 μmol) and the resulting reaction mixture solution was stirred at 125°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (20 mg, 15% yield) as white foam. MS: 441.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{MeOH}-d_4$) δ 0.45 - 0.54 (m, 1 H) 0.94 - 1.03 (m, 1 H) 1.20 - 1.34 (m, 1 H) 1.72 - 1.80 (m, 1 H) 1.82 - 1.90 (m, 1 H) 1.90 - 1.99 (m, 4 H) 2.34 - 2.48 (m, 1 H) 3.34 - 3.41 (m, 4 H) 4.45 - 4.57 (m, 1 H) 8.13 (br. s., 1 H) 8.51 (br. s., 1 H) 8.65 (br. s., 1 H) 8.74 (d, J=9.03 Hz, 1 H).

Example 99

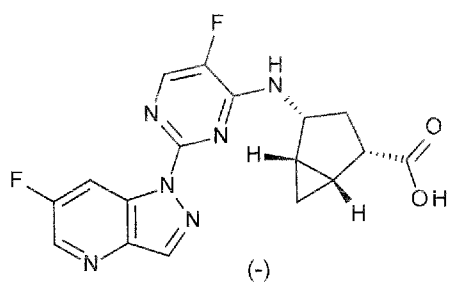
(-)-/V-((1R,2S,4R,5S)-4-((2-(6-Chloro-1H-pyrazolo[4,3-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)-4-fluorobenzamide



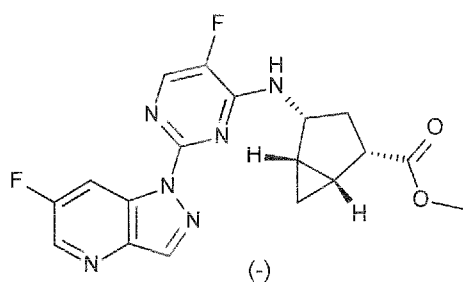
- 5 In analogy to the synthesis of Example 97/Step D, 6-chloro-1H-pyrazolo[4,3-b]pyridine (Intermediate F-3, 154 mg, 1 mmol) was used to afford the title compound (30 mg, 22.7% yield) as a white solid after Prep-HPLC separation. MS: 482.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.11 (d, J=2.01 Hz, 1 H) 8.64 - 8.66 (m, 1 H) 8.49 - 8.52 (m, 1 H) 8.12 - 8.15 (m, 1 H) 7.89 - 7.94 (m, 2 H) 7.18 - 7.24 (m, 2 H) 4.60 - 4.62 (m, 1 H) 2.51 - 2.59 (m, 1 H)
- 10 1.91 - 1.97 (m, 1 H) 1.83 - 1.90 (m, 1 H) 1.30 - 1.43 (m, 2 H) 1.06 - 1.10 (m, 1 H) 0.56 - 0.63 (m, 1 H).

Example 100

- 15 **(-)-(1R,2S,4R,5S)-4-((5-fluoro-2-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid**

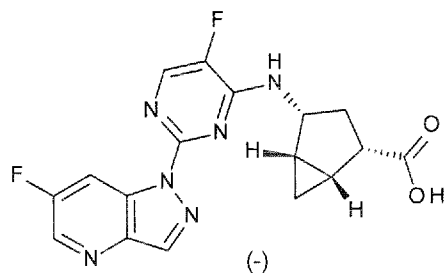


16 (-)-(1R,2S,4R,5S)-methyl 4-((5-fluoro-2-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylate



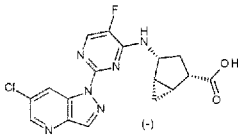
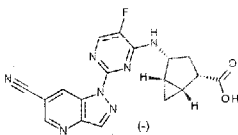
To a stirred mixture solution of (-)-(1R,2S,4R,5S)-methyl 4-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylate (intermediate B-7/step B, 200 mg, 700 μ mol) and 6-fluoro-1H-pyrazolo[4,3-b]pyridine (Intermediate F-2, 173 mg, 1.26 mmol) in dioxane (6 mL) was added copper (I) iodide (53.3 mg, 280 μ mol), (1R,2S)-cyclohexane-1,2-diamine (63.9 mg, 560 μ mol) and potassium hydrogenphosphate (183 mg, 1.05 mmol) and the resulting reaction mixture solution was stirred at 120°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-50% EtOAc-hexane gradient) to yield the title compound (150 mg, 55.5% yield) as a yellow solid. MS: 387.1 [M+H]⁺

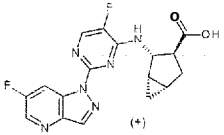
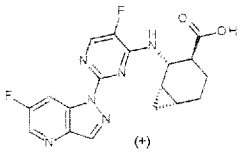
[B1] (-)-(1R,2S,4R,5S)-4-((5-fluoro-2-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylic acid

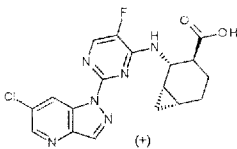
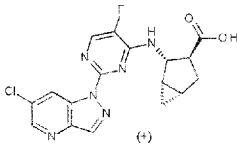


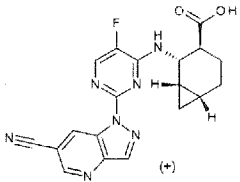
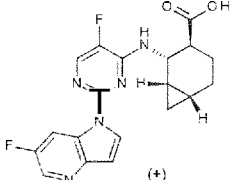
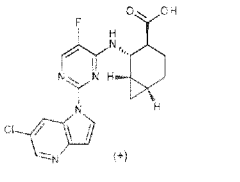
To a stirred mixture solution of (-)-(1R,2S,4R,5S)-methyl 4-((5-fluoro-2-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-2-carboxylate (150 mg, 388 μ mol) in THF (4 mL) and MeOH (2 mL) was added lithium hydroxide (46.5 mg, 1.94 mmol) pre-dissolved in water (1 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (35 mg, 24.2% yield) as white foam. MS: 373.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.78 (d, J=9.54 Hz, 1 H) 8.63 (dd, J=2.51, 1.25 Hz, 1 H) 8.50 (d, J=0.75 Hz, 1 H) 8.12 (d, J=3.51 Hz, 1 H) 4.97 - 5.04 (m, 1 H) 3.14 - 3.22 (m, 1 H) 2.20 - 2.28 (m, 1 H) 1.83 - 1.89 (m, 1 H) 1.74 - 1.80 (m, 1 H) 1.61 - 1.71 (m, 1 H) 0.90 - 0.96 (m, 1 H) 0.46 - 0.53 (m, 1 H).

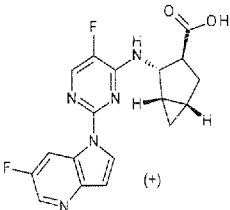
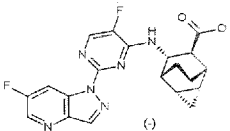
In analogy to the synthesis of Example 100, the following compounds were prepared by using appropriate reagents.

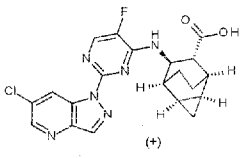
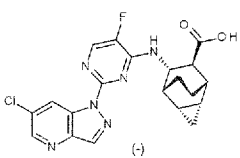
Ex	Compound name	Compound Structure	Starting Materials	MS [M+H]⁺, ¹H NMR and Aspect
101	(-)- (1R,2S,4R,5S)- 4-((2-(6-chloro- 1 <i>H</i> -pyrazolo[4,3- b]pyridin-1-yl)-5- fluoropyrimidin- 4- yl)amino)bicyclo [3.1.0]hexane-2- carboxylic acid		(-)- (1R,2S,4R,5S)- -methyl 4-((2- chloro-5- fluoropyrimidin -4- yl)amino)bicycl o[3.1.0]hexane -2-carboxylate and 6-chloro-1 <i>H</i> - pyrazolo[4,3- b]pyridine (Intermediate F-3)	MS: 389.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 9.08 (d, J=1.51 Hz, 1 H) 8.64 (d, J=2.26 Hz, 1 H) 8.49 (s, 1 H) 8.09 - 8.13 (m, 1 H) 4.93 - 5.00 (m, 1 H) 3.16 - 3.24 (m, 1 H) 2.23 - 2.31 (m, 1 H) 1.84 - 1.90 (m, 1 H) 1.74 - 1.81 (m, 1 H) 1.61 - 1.71 (m, 1 H) 0.91 - 0.97 (m, 1 H) 0.47 - 0.56 (m, 1 H). White foam
102	(-)- (1R,2S,4R,5S)- 4-((2-(6-cyano- 1 <i>H</i> -pyrazolo[4,3- b]pyridin-1-yl)-5- fluoropyrimidin- 4- yl)amino)bicyclo [3.1.0]hexane-2- carboxylic acid		(-)- (1R,2S,4R,5S)- -methyl 4-((2- chloro-5- fluoropyrimidin -4- yl)amino)bicycl o[3.1.0]hexane -2-carboxylate and 1 <i>H</i> - pyrazolo[4,3- b]pyridine-6- carbonitrile (Intermediate	MS: 380.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 9.47 (s, 1 H) 8.94 (d, J=1.76 Hz, 1 H) 8.64 (s, 1 H) 8.15 - 8.17 (m, 1 H) 4.96 - 5.04 (m, 1 H) 3.14 - 3.23 (m, 1 H) 2.21 - 2.30 (m, 1 H) 1.76 - 1.89 (m, 2 H) 1.60 - 1.72 (m, 1 H) 0.91 - 0.97 (m, 1 H) 0.46 - 0.54 (m, 1 H). White foam

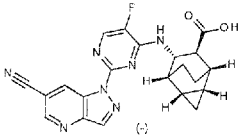
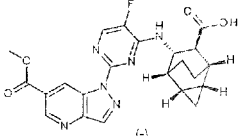
			F-4)	
103	(+)- (1S,2S,3S, 5S)- 2-[[5-Fluoro-2-(6-fluoropyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl]amino]bicyclo[3.1.0]hexane-3-carboxylic acid		(+)- (1S,2S,3S,5S)-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylate and 6-fluoro-1H-pyrazolo[4,3-b]pyridine (intermediate F-2)	MS: 373.2 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 0.40 - 0.52 (m, 1 H) 0.72 (d, J=5.02 Hz, 1 H) 1.54 (br. s., 1 H) 1.85 (br. s., 1 H) 2.24 (d, J=6.78 Hz, 2 H) 2.68 (br. s., 1 H) 5.32 (br. s., 1 H) 8.12 (br. s., 1 H) 8.49 (s, 1 H) 8.63 (s, 1 H) 8.90 (d, J=9.29 Hz, 1 H). white foam
104	(+)- (1S,2S,3S,6R) - 2-((5-Fluoro-2-(6-fluoro-1H-pyrazolo[4,3-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate acid		(+). (1S,2S,3S,6R) -methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate and 6-fluoro-1H-pyrazolo[4,3-b]pyridine (intermediate F-2)	MS: 401.2 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 0.46 (q, J=5.27 Hz, 1 H) 0.73 (td, J=8.78, 5.02 Hz, 1 H) 1.23 - 1.35 (m, 1 H) 1.44 - 1.68 (m, 3 H) 1.79 - 1.88 (m, 1 H) 2.15 - 2.27 (m, 1 H) 2.30 - 2.42 (m, 1 H) 5.21 (dd, J=10.67, 5.65 Hz, 1 H) 8.10 (d, J=3.26 Hz, 1 H) 8.48 (s, 1 H) 8.62 (dd, J=2.38, 1.13 Hz, 1 H) 8.92 (dd, J=9.66, 2.13 Hz, 1 H). White foam

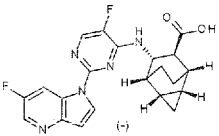
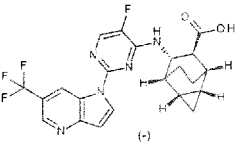
105	(+)- (1S,2S,3S,6R)- 2-[[2-(6- Chloropyrazolo[4,3-b]pyridin-1- yl)-5-fluoro- pyrimidin-4- yl]amino]norcar- ane-3-carboxylic acid		(+)- (1S,2S,3S,6R)- -methyl 2-((2- chloro-5- fluoropyrimidin -4- yl)amino)bicycl o[4.1.0]heptan e-3- carboxylate and 6-chloro-1 <i>H</i> - pyrazolo[4,3- b]pyridine (Intermediate F-3)	MS: 403.2 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOHL- <i>d</i> 4) δ 0.46 (q, J=5.35 Hz, 1 H) 0.73 (td, J=8.78, 5.02 Hz, 1 H) 1.23 - 1.35 (m, 1 H) 1.45 - 1.70 (m, 3 H) 1.79 - 1.89 (m, 1 H) 2.15 - 2.27 (m, 1 H) 2.36 (t, J=10.67 Hz, 1 H) 5.22 (dd, J=10.79, 5.52 Hz, 1 H) 8.10 (d, J=3.51 Hz, 1 H) 8.47 (s, 1 H) 8.63 (d, J=2.01 Hz, 1 H) 9.28 (d, J=1.76 Hz, 1 H). White foam
106	(+)- (1S,2S,3S,5S)- 2-[[2-(6- Chloropyrazolo[4,3-b]pyridin-1- yl)-5-fluoro- pyrimidin-4- yl]amino]bicyclo[3.1.0]hexane-3- carboxylic acid		(+)- (1S,2S,3S,5S)- -methyl 2-((2- chloro-5- fluoropyrimidin -4- yl)amino)bicycl o[3.1.0]hexane -3-carboxylate and 6-chloro-1 <i>H</i> - pyrazolo[4,3- b]pyridine (Intermediate F-3)	MS: 389.2 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- <i>d</i> 4) δ 0.43 - 0.51 (m, 1 H) 0.69 - 0.75 (m, 1 H) 1.50 - 1.58 (m, 1 H) 1.83 - 1.91 (m, 1 H) 2.16 - 2.29 (m, 2 H) 2.59 - 2.66 (m, 1 H) 5.31 (dd, J=9.79, 4.27 Hz, 1 H) 8.12 (d, J=3.26 Hz, 1 H) 8.49 (s, 1 H) 8.65 (d, J=2.01 Hz, 1 H) 9.24 (d, J=1.51 Hz, 1 H). White foam
107	(+)- (1S,2S,3S,6R)-		(+)- (1S,2S,3S,6R)	MS: 394.2 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-

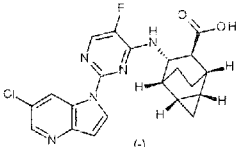
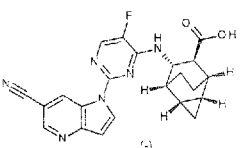
	2-((2-(6-cyano-1H-pyrazolo[4.3-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid		-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate and 1H-pyrazolo[4,3-b]pyridine-6-carbonitrile (Intermediate F-4)	d4) δ 0.48 (q, J=5.27 Hz, 1 H) 0.75 (td, J=8.85, 4.89 Hz, 1 H) 1.25 - 1.36 (m, 1 H) 1.43 - 1.74 (m, 3 H) 2.17 - 2.29 (m, 1 H) 2.37 (t, J=10.67 Hz, 1 H) 5.25 (dd, J=10.79, 5.52 Hz, 1 H) 8.14 (d, J=3.26 Hz, 1 H) 8.62 (s, 1 H) 8.93 (d, J=1.51 Hz, 1 H) 9.68 (s, 1 H). White foam
108	(+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(6-fluoro-1H-pyrrolo[3.2-b]pyridin-1-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid		(+)-(1S,2S,3S,6R)-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate and 6-fluoro-1H-pyrrolo[3,2-b]pyridine	MS: 386.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 8.94 (dd, J=10.42, 2.38 Hz, 1 H) 8.53 - 8.56 (m, 1 H) 8.35 - 8.39 (m, 1 H) 8.07 - 8.10 (m, 1 H) 6.78 - 6.81 (m, 1 H) 5.12 - 5.18 (m, 1 H) 2.27 - 2.36 (m, 1 H) 2.15 - 2.25 (m, 1 H) 1.75 - 1.83 (m, 1 H) 1.46 - 1.68 (m, 3 H) 1.24 - 1.33 (m, 1 H) 0.67 - 0.75 (m, 1 H) 0.39 - 0.46 (m, 1 H). White foam
109	(+)-(1S,2S,3S,6R)-2-((2-(6-chloro-1H-pyrrolo[3,2-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid		(+)-(1S,2S,3S,6R)-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate and 6-chloro-1H-pyrrolo[3,2-b]pyridine	MS: 402.1 [M+H] ⁺ . ¹ H NMR (400 MHz, METHANOL-d ₄) δ 9.23 (d, J=1.76 Hz, 1 H) 8.59 (d, J=3.76 Hz, 1 H)

	fluoropyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid		-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate and 6-chloro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine	8.40 (s, 1 H) 8.07 (d, <i>J</i> =3.51 Hz, 1 H) 6.78 - 6.81 (m, 1 H) 5.12 - 5.18 (m, 1 H) 2.27 - 2.36 (m, 1 H) 2.15 - 2.25 (m, 1 H) 1.75 - 1.83 (m, 1 H) 1.46 - 1.68 (m, 3 H) 1.24 - 1.33 (m, 1 H) 0.67 - 0.75 (m, 1 H) 0.39 - 0.46 (m, 1 H). White foam
110	(+)-(1 <i>S</i> ,2 <i>S</i> ,3 <i>S</i> ,5 <i>S</i>)-2-[[5-fluoro-2-(6-fluoropyrrolo[3,2- <i>b</i>]pyridin-1-yl)pyrimidin-4-yl]amino)bicyclo[3.1.0]hexane-3-carboxylic acid		(+)-(1 <i>S</i> ,2 <i>S</i> ,3 <i>S</i> ,5 <i>S</i>)-methyl 2-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[3.1.0]hexane-3-carboxylate and 6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine	MS: 372.2 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 0.42 - 0.50 (m, 1 H) 0.63 - 0.71 (m, 1 H) 1.52 (br. s., 1 H) 1.78 - 1.87 (m, 1 H) 2.18 - 2.25 (m, 1 H) 2.47 - 2.59 (m, 1 H) 5.23 (dd, <i>J</i> =9.41, 4.39 Hz, 1 H) 6.79 (d, <i>J</i> =3.51 Hz, 1 H) 8.09 (d, <i>J</i> =3.26 Hz, 1 H) 8.36 (s, 1 H) 8.60 (d, <i>J</i> =3.76 Hz, 1 H) 8.92 (dd, <i>J</i> =10.29, 2.51 Hz, 1 H). White foam
111	(-)-(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-7-((5-Fluoro-2-(6-fluoro-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-1-yl)pyrimidin-4-		(-)-(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-3-carboxylate and 6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine	MS: 412.8 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.43 - 12.70 (m, 1 H) 8.72 - 8.77 (m, 1 H) 8.60 - 8.69 (m, 2 H) 8.27 - 8.32 (m, 1 H) 7.75 - 7.82 (m, 1 H) 4.38 - 4.46 (m, 1 H) 2.87 - 2.92 (m, 1 H) 2.57 - 2.62

	yl)amino)tricyclo [3.2.2.0 ^{2,4}]nona ne-6-carboxylic acid		nane-6- carboxylate and 6-fluoro-1 <i>H</i> - pyrazolo[4,3- b]pyridine (Intermediate F-2)	(m, 1 H) 2.53 (d, J=1.76 Hz, 1 H) 2.42 - 2.47 (m, 1 H) 1.65 - 1.72 (m, 1 H) 1.51 - 1.61 (m, 1 H) 1.41 - 1.50 (m, 1 H) 1.08 - 1.14 (m, 1 H) 0.97 - 1.07 (m, 1 H) 0.74 - 0.85 (m, 1 H) 0.26 - 0.35 (m, 1 H). White foam
112	(+)- (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i> ,5 <i>R</i> ,6 R,7 <i>R</i>)-7-((2-(6- chloro-1 <i>H</i> - pyrazolo[4,3- b]pyridin-1-yl)-5- fluoropyrimidin- 4- yl)amino)tricyclo [3.2.2.0 ^{2,4}]nona ne-6-carboxylic acid		(+)- (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i> ,5 <i>R</i> , 6 <i>R</i> ,7 <i>R</i>)-methyl 7-((2-chloro-5- fluoropyrimidin -4- yl)amino)tricycl o[3.2.2.0 ^{2,4}]no nane-6- carboxylate and 6-chloro-1 <i>H</i> - pyrazolo[4,3- b]pyridine (Intermediate F-3)	MS: 429.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- d ₄) δ 9.14 (d, J=1.51 Hz, 1 H) 8.65 (d, J=2.01 Hz, 1 H) 8.50 (d, J=0.75 Hz, 1 H) 8.12 (d, J=3.26 Hz, 1 H) 4.67 - 4.72 (m, 1 H) 2.77 - 2.82 (m, 1 H) 2.59 - 2.65 (m, 1 H) 2.53 - 2.59 (m, 1 H) 1.94 - 2.04 (m, 1 H) 1.76 - 1.87 (m, 1 H) 1.63 - 1.73 (m, 2 H) 1.11 - 1.19 (m, 1 H) 0.98 - 1.05 (m, 1 H) 0.88 - 0.97 (m, 1 H) 0.40 - 0.49 (m, 1 H). White foam
113	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 S,7 <i>S</i>)-7-((2-(6- Chloro-1 <i>H</i> - pyrazolo[4,3- b]pyridin-1-yl)-5- fluoropyrimidin- 4- yl)amino)tricyclo [3.2.2.0 ^{2,4}]nona		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> , 6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-chloro-5- fluoropyrimidin -4- yl)amino)tricycl o[3.2.2.0 ^{2,4}]no nane-6- carboxylate	MS: 429.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- d ₄) δ 9.13 - 9.15 (m, 1 H) 8.65 (d, J=2.01 Hz, 1 H) 8.50 (s, 1 H) 8.08 - 8.14 (m, 1 H) 4.68 - 4.72 (m, 1 H) 2.76 - 2.81 (m, 1 H) 2.60 - 2.65 (m, 1 H) 2.54 - 2.59 (m, 1 H) 1.94 - 2.04 (m, 1 H) 1.76 - 1.86 (m, 1 H) 1.64

	ne-6-carboxylic acid		and 6-chloro- 1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridine (Intermediate F-3)	- 1.74 (m, 2 H) 1.10 - 1.19 (m, 1 H) 0.98 - 1.04 (m, 1 H) 0.88 - 0.96 (m, 1 H) 0.42 - 0.49 (m, 1 H). White foam
114	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> , 5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-7-((2-(6-cyano-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-(6-cyano-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylate and 1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridine-6-carbonitrile (Intermediate F-4)	MS:420. 1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 9.47 (s, 1 H) 8.93 (d, <i>J</i> =1.76 Hz, 1 H) 8.63 (s, 1 H) 8.13 - 8.16 (m, 1 H) 4.67 - 4.72 (m, 1 H) 2.75 - 2.79 (m, 1 H) 2.59 - 2.63 (m, 1 H) 2.53 - 2.57 (m, 1 H) 1.82 - 1.95 (m, 2 H) 1.61 - 1.79 (m, 2 H) 1.12 - 1.20 (m, 1 H) 0.91 - 1.02 (m, 2 H) 0.44 - 0.52 (m, 1 H). White foam
115	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> , 5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-7-((5-fluoro-2-(6-(methoxy carbonyl)-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-1-		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> , 5 <i>S</i> , 6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-(6-cyano-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridin-1-yl)-5-	MS: 453. 1 [M+H] ⁺ . ¹ H NMR (400 MHz, METHANOLS) [δ] ppm 9.63 (s, 1 H) 9.22 (d, <i>J</i> =1.76 Hz, 1 H) 8.57 - 8.59 (m, 1 H) 8.13 - 8.15 (m, 1 H) 4.74 - 4.78 (m, 1 H) 4.04 (s, 3 H) 2.71 - 2.75 (m, 1 H) 2.55 -

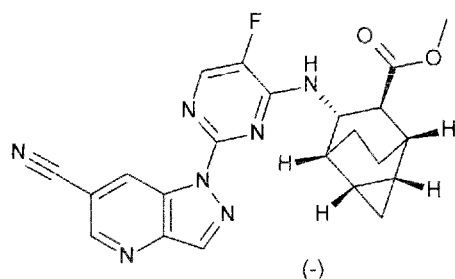
	yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylate and 6-methoxy-1 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridine (Intermediate F-7)	2.60 (m, 1 H) 1.89 - 1.96 (m, 1 H) 1.60 - 1.79 (m, 4 H) 1.08 - 1.16 (m, 1 H) 0.96 - 1.02 (m, 1 H) 0.83 - 0.92 (m, 1 H) 0.39 - 0.47 (m, 1 H). White foam
116	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-7-((5-fluoro-2-(6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridin-1-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylate and 6-fluoro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine	MS: 412.1 [M+H] ⁺ . ¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ ppm 8.88 (dd, <i>J</i> =10.29, 2.01 Hz, 1 H) 8.54 (d, <i>J</i> =3.76 Hz, 1 H) 8.35 (s, 1 H) 8.09 (d, <i>J</i> =3.51 Hz, 1 H) 6.77 (dd, <i>J</i> =3.76, 0.75 Hz, 1 H) 4.43 - 4.48 (m, 1 H) 2.62 (d, <i>J</i> =5.77 Hz, 1 H) 2.49 - 2.53 (m, 1 H) 2.44 - 2.48 (m, 1 H) 1.79 - 1.86 (m, 2 H) 1.67 - 1.76 (m, 1 H) 1.56 - 1.67 (m, 1 H) 1.12 - 1.19 (m, 1 H) 0.93 (s, 2 H) 0.46 - 0.53 (m, 1 H). White foam
117	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-7-((5-fluoro-2-(6-(trifluoromethyl)-		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-chloro-5-fluoropyrimidin	MS: 462.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- <i>d</i> ₄) δ 9.32 (d, <i>J</i> =1.51 Hz, 1 H) 8.69 (d, <i>J</i> =3.76 Hz, 1 H) 8.67 (d, <i>J</i> =1.51 Hz, 1 H)

	1 <i>H</i> -pyrrolo[3,2- b]pyridin-1- yl)pyrimidin-4- yl)amino)tricyclo [3.2.2.0 ^{2,4}]nona ne-6-carboxylic acid		-4- yl)amino)tricycl o[3.2.2.0 ^{2,4}]no nane-6- carboxylate and 6- (trifluoromethyl)-1 <i>H</i> - pyrrolo[3,2- b]pyridine	8.09 (d, J=3.26 Hz, 1 H) 6.85 (d, J=3.76 Hz, 1 H) 4.40 - 4.45 (m, 1 H) 2.55 - 2.59 (m, 1 H) 2.40 - 2.47 (m, 2 H) 1.67 - 1.83 (m, 3 H) 1.53 - 1.65 (m, 1 H) 1.10 - 1.19 (m, 1 H) 0.87 - 1.00 (m, 2 H) 0.45 - 0.53 (m, 1 H). White foam
118	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 S,7 <i>S</i>)-7-((2-(6- chloro-1 <i>H</i> - pyrrolo[3,2- b]pyridin-1-yl)-5- fluoropyrimidin- 4- yl)amino)tricyclo [3.2.2.0 ^{2,4}]nona ne-6-carboxylic acid		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> , 6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-(6-cyano- 1 <i>H</i> -pyrrolo[3,2- b]pyridin-1-yl)- 5- fluoropyrimidin -4- yl)amino)tricycl o[3.2.2.0 ^{2,4}]no nane-6- carboxylate and 6-chloro-1 <i>H</i> - pyrrolo[3,2- b]pyridine	
119	(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,6 S,7 <i>S</i>)-7-((2-(6- cyano-1 <i>H</i> - pyrrolo[3,2- b]pyridin-1-yl)-5- fluoropyrimidin-		(-)- (1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> , 6 <i>S</i> ,7 <i>S</i>)-methyl 7-((2-(6-cyano- 1 <i>H</i> -pyrrolo[3,2- b]pyridin-1-yl)- 5-	MS: 419.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH- d ₄) δ 9.37 - 9.40 (m, 1 H) 8.75 (d, J=3.76 Hz, 1 H) 8.70 (d, J=1.76 Hz, 1 H) 8.11 (d, J=3.26 Hz, 1 H) 6.89 (d, J=3.76 Hz, 1 H)

	4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylate and 1H-pyrrolo[3.2-b]pyridine-6-carbonitrile	4.43 - 4.48 (m, 1 H) 2.59 - 2.64 (m, 1 H) 2.43 - 2.51 (m, 2 H) 1.80 - 1.87 (m, 2 H) 1.68 - 1.78 (m, 1 H) 1.58 - 1.66 (m, 1 H) 1.12 - 1.20 (m, 1 H) 0.89 - 1.01 (m, 2 H) 0.46 - 0.54 (m, 1 H). White foam

Example 120

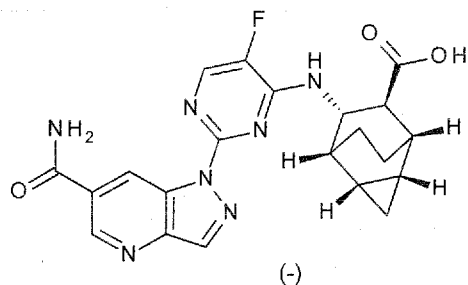
(-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(6-cyano-1H-pyrazolo[4,3-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Example 74/Step A, (-) enantiomer, 325 mg, 998 μ mol), and 1H-pyrazolo[4.3-b]pyridine-6-carbonitrile (Intermediate F-4, 187 mg, 1.3 mmol) in dioxane (6 mL) was added copper (I) iodide (76 mg, 399 μ mol), (1R,2S)-cyclohexane-1,2-diamine (91.1 mg, 798 μ mol) and potassium hydrogenphosphate (261 mg, 1.5 mmol) and the resulting reaction mixture solution was stirred at 120°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-70% EtOAc-hexane gradient) to afford the title compound (100 mg, 23.1% yield) as white foam. MS; 434.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.42 - 9.44 (m, 1 H) 8.93 (d, J=1.76 Hz, 1 H) 8.62 (s, 1 H) 8.15 (d, J=3.01 Hz, 1 H) 4.64 - 4.68 (m, 1 H) 3.63 (s, 3 H) 2.76 - 2.80 (m, 1 H) 2.55 - 2.60 (m, 1 H) 2.45 - 2.49 (m, 1 H) 1.84 - 1.91 (m, 2 H) 1.64 (br. s., 2 H) 1.12 - 1.22 (m, 2 H) 0.92 - 1.00 (m, 1 H) 0.46 - 0.53 (m, 1 H).

Example 121

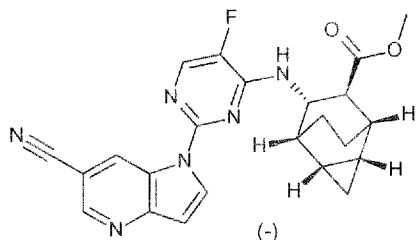
(-)-(1 R,2S,4R,5S,6S,7S)-7-((2-(6-carbamoyl-1 H-pyrazolo[4,3-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred solution of (-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-(6-cyano-1 H-pyrazolo[4,3-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Example 120, 100 mg, 231 μ mol) in THF (4mL) and MeOH (2 mL) was added LiOH (27.6 mg, 1.15 mmol) pre-dissolved in water (1mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL), and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over to give a crude product, which was then purified by Prep-HPLC to afford the title compound (9.6 mg, 9.5% yield) as white foam. MS: 438.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-*d*₄) δ 9.55 (d, J=1.00 Hz, 1 H) 9.10 (d, J=1.76 Hz, 1 H) 8.55 (s, 1 H) 8.12 - 8.16 (m, 1 H) 4.84 - 4.87 (m, 1 H) 2.60 - 2.64 (m, 1 H) 2.44 - 2.51 (m, 2 H) 1.55 - 1.89 (m, 4 H) 1.10 - 1.17 (m, 1 H) 0.89 - 0.98 (m, 2 H) 0.44 - 0.52 (m, 1 H).

Example 122

(-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-(6-cyano-1 H-pyrrolo[3,2-b]pyridin-1-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

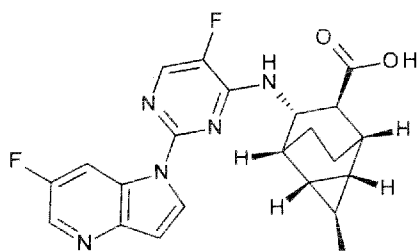


To a stirred mixture solution of (-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Example 74/Step A, (-) enantiomer, 200 mg, 614 μ mol) and 1H-pyrrolo[3,2-b]pyridine-6-carbonitrile (158 mg, 1.11 mmol) in dioxane (6 mL) was added copper(I) iodide (46.8 mg, 246 μ mol), (1R,2S)-

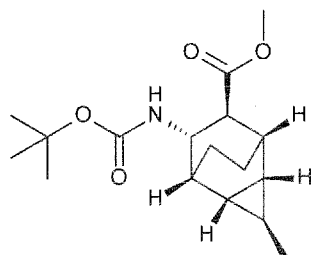
cyclohexane-1,2-diamine (56.1 mg, 70.1 μ L, 491 μ mol) and potassium hydrogenphosphate (160 mg, 921 μ mol) and the resulting reaction mixture solution was stirred at 120°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-50% EtOAc-hexane gradient) to afford the title compound (200mg, 75.3% yield) as white foam. MS: 433.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 9.40 - 9.41 (m, 1 H) 8.71 - 8.74 (m, 2 H) 8.13 - 8.15 (m, 1 H) 6.92 - 6.94 (m, 1 H) 4.49 - 4.52 (m, 1 H) 3.64 (s, 3 H) 2.63 - 2.66 (m, 1 H) 2.48 - 2.52 (m, 1 H) 2.38 - 2.42 (m, 1 H) 1.81 - 1.87 (m, 2 H) 1.58 - 1.68 (m, 2 H) 1.11 - 1.20 (m, 1 H) 0.95 - 1.01 (m, 1 H) 0.88 - 0.94 (m, 1 H) 0.46 - 0.55 (m, 1 H).

Example 123

(rac)-(1R,2S,3R,4S,5S,6S,7S)-7-((5-fluoro-2-(6-fluoro-1H-pyrrolo[3,2-b]pyridin-1-yl)pyrimidin-4-yl)amino)-3-methyltricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



[AT] (rac)-(1R,2S,4S,5S,6S,7S)-methyl 7-((tert-butoxycarbonyl)amino)-3-methyltricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

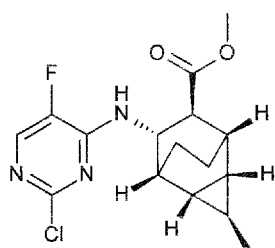


To a stirred mixture solution of (rac)-(1S,2S,3S,4R)-methyl 3-((tert-butoxycarbonyl)amino)bicyclo[2.2.2]oct-5-ene-2-carboxylate (Intermediate 12/step C, 562 mg, 2 mmol) in DCM (10 mL) was added diethylzinc (3 mL, 3 mmol) at 0°C. After stirred for 5 min, 1,1-diiodoethane (1.69 g, 5.99 mmol) was added slowly at 0°C. The resulting mixture solution was stirred at 0°C for 10 min before the 2nd batch of diethylzinc (3 mL, 3 mmol) and 1,1-diiodoethane (1.69 g, 5.99 mmol) were added sequentially. The reaction mixture was stirred at 0°C for additional 2 h and then allowed to warm up to room temperature. The

mixture solution was then diluted with water (20 mL) and extracted with DCM (140 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude title compound. MS: 310.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

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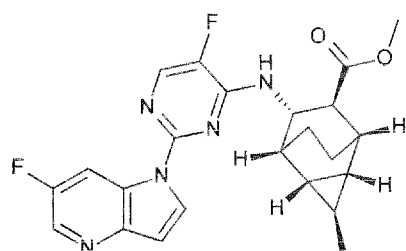
FBI (rac)-(1R,2S,4S,5S,6S,7S)-Methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methyltricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of (rac)-(1R,2S,4S,5S,6S,7S)-methyl 7-((tert-butoxycarbonyl)amino)-3-methyltricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (600 mg, 1.94 mmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol) and the resulting mixture solution was stirred at room temperature for 12 h. Afterwards, the reaction mixture was concentrated under reduced pressure. The residue was re-dissolved in THF (10 mL) followed by the addition of DIPEA (2.51 g, 19.4 mmol) and 2,4-dichloro-5-fluoropyrimidine (648 mg, 3.88 mmol) and the resulting mixture solution was stirred at 65°C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-40% EtOAc-hexane gradient) to afford the title compound (170 mg, 9% yield) as yellow oil. MS: 340.1 $[\text{M}+\text{H}]^+$.

20

[CI (rac)-(1R,2S,4S,5S,6S,7S)-methyl 7-((5-fluoro-2-(6-fluoro-1H-pyrrclo[3.2-b]pyridin-1-yl)pyrimidin-4-yl)amino)-3-methyltricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

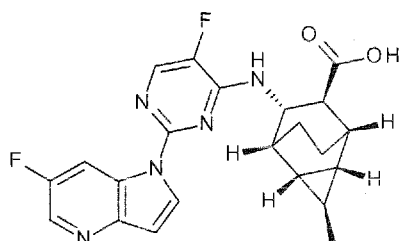


To a stirred mixture solution of (rac)-(1R,2S,4S,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)-3-methyltricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (170 mg, 175

25

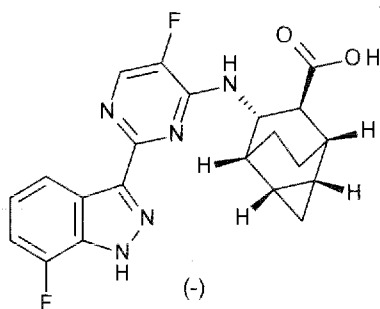
μmol), and 6-fluoro-1H-pyrrolo[3,2-b]pyridine (154 mg, 1.13 mmol) in dioxane (6 mL) was added copper(I) iodide (13.3 mg, 70 μmol), (1R,2S)-cyclohexane-1,2-diamine (16 mg, 140 μmol) and potassium hydrogenphosphate (45.7 mg, 263 μmol) at room temperature and the resulting reaction mixture solution was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-50% EtOAc-hexane gradient) to afford the title compound (30 mg, 39% yield) as a white solid. MS: 440.1 [M+H]⁺.

ID] (rac)-d R.2S.3R.4S.5S.6S.7S)-7-((5-fluoro-2-(6-fluoro-1 H-pyrrolo[3.2-b]Pvridin-1 - vl)pyrimidin-4-vi)amino)-^methyitricycloi3.2.- .02,4]nonane-6-carboxyiic acid

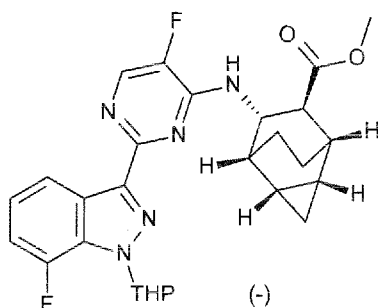


To a stirred solution of (rac)-(1 R,2S,4S.5S.6S,7S)-methyi 7-((5-fluoro-2-(6-fluoro-1 H-pyrrolo[3.2-b]pyridin-1-yl)pyrimidin-4-yl)amino)-3-methyltricyclo[3.2.2.02,4]nonane-6-carboxylate (30 mg, 68.3 μmol) in THF (4mL) and MeOH (2 mL) was added LiOH (8.17 mg, 341 μmol) pre-dissolved in water (1mL). The reaction mixture solution was stirred at room temperature for 2 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded, and the aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by Prep-HPLC to afford the title compound (3 mg, 10.3% yield) as white foam. MS;426.1 [M+H]⁺ ¹H NMR (400 MHz, MeOH-c/4) δ 8.94 (dd, J=10.42, 2.38 Hz, 1 H) 8.65 - 8.68 (m, 1 H) 8.33 - 8.36 (m, 1 H) 8.04 (d, J=3.26 Hz, 1 H) 6.76 - 6.81 (m, 1 H) 4.62 - 4.66 (m, 1 H) 2.57 - 2.62 (m, 1 H) 2.51 - 2.56 (m, 1 H) 2.44 - 2.49 (m, 1 H) 1.86 - 1.94 (m, 1 H) 1.64 - 1.81 (m, 2 H) 1.45 - 1.54 (m, 1 H) 1.27 - 1.34 (m, 1 H) 1.03 (d, J=5.77 Hz, 3 H) 0.71 - 0.77 (m, 1 H) 0.52 - 0.59 (m, 1 H).

Example 124-(H1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid



1A1 (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate

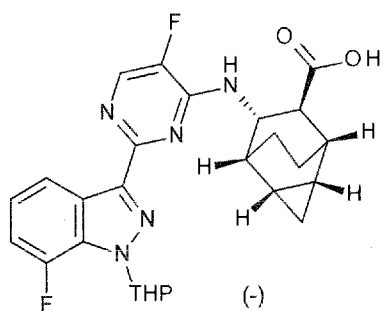


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To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (Example 74/Step A, (-) enantiomer, 660 mg, 2.03 mmol) and Pd(PPh₃)₄ (234 mg, 203 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (1.76 g, 1.6 mL, 3.04 mmol) at room temperature. The reaction mixture solution was stirred at 125°C for 2 h before it was cooled back to room temperature and re-dissolved in dioxane (16 mL). To the above solution was then added 7-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-1a, 1.05 g, 3.04 mmol) and Pd(PPh₃)₄ (234 mg, 203 μmol) and the resulting reaction mixture solution was stirred at 145°C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (200mg, 19.4% yield) as yellow oil. MS: 510.1 [M+H]⁺

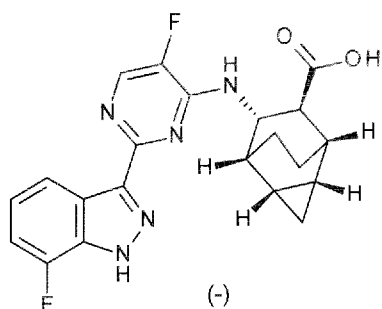
20

1B1 (-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid



To a stirred solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (200 mg, 393 μmol) in THF (4 mL) and MeOH (2 mL) was added LiOH (47 mg, 1.96 mmol) pre-dissolved in water (1 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The separated aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to afford a crude title compound (194 mg, 99.7% yield) as yellow oil. MS: 496.1 $[\text{M}+\text{H}]^+$. It was used directly in the next step reaction without further purification.

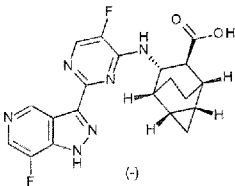
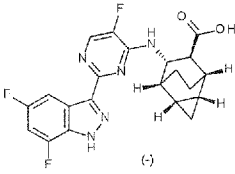
[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid

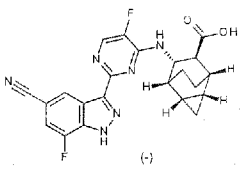
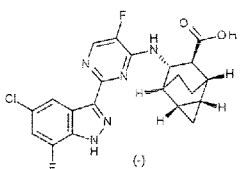
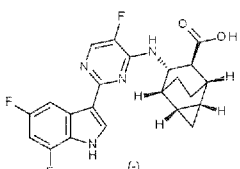


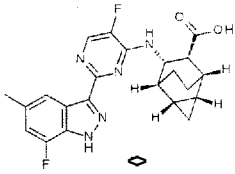
To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (194 mg, 392 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) at room temperature. The reaction mixture solution was stirred at room temperature for 12 h before it was concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (34 mg, 21.1% yield) as white foam. MS: 412.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 - 8.32 (m, 2 H) 7.39 - 7.45 (m, 1 H) 7.14 - 7.25 (m, 2 H) 4.44 - 4.51 (m, 1 H) 2.80 - 2.86 (m, 1 H) 2.60 - 2.65 (m, 1 H)

2.40 - 2.47 (m, 1 H) 1.59 - 1.79 (m, 2 H) 1.45 - 1.58 (m, 2 H) 1.07 - 1.14 (m, 1 H) 0.95 - 1.05 (m, 1 H) 0.72 - 0.81 (m, 1 H) 0.24 - 0.32 (m, 1 H).

In analogy to the synthesis of Example 124, the following compounds were prepared by using appropriate reagents in step A.

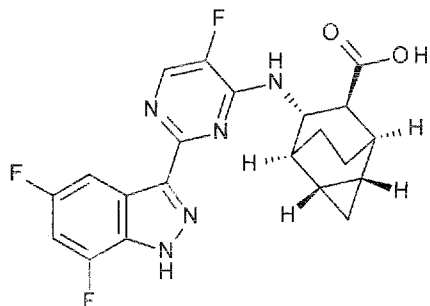
Ex	Compound name	Compound Structure	Starting Materials	MS [M+H] ⁺ , ¹ H NMR and Aspect
125	(-)- (1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-1H-pyrazolo[4,3-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		7-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridine (Intermediate G-5)	MS: 413.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 9.69 (s, 1 H) 8.29 (s, 1 H) 8.16 (s, 1 H) 4.73 - 4.78 (m, 1 H) 2.73 - 2.77 (m, 1 H) 2.60 - 2.64 (m, 1 H) 2.51 - 2.56 (m, 1 H) 1.57 - 1.93 (m, 4 H) 1.11 - 1.18 (m, 1 H) 0.97 - 1.03 (m, 1 H) 0.88 - 0.96 (m, 1 H) 0.43 - 0.50 (m, 1 H). White foam
126	(-)- (1R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		5,7-Difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-2)	MS: 430.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 8.07 - 8.15 (m, 2 H) 7.07 - 7.14 (m, 1 H) 4.67 - 4.72 (m, 1 H) 2.73 - 2.78 (m, 1 H) 2.63 - 2.69 (m, 1 H) 2.52 - 2.58 (m, 1 H) 1.90 - 1.99 (m, 1 H) 1.61 - 1.85 (m, 3 H) 1.11 - 1.18 (m, 1 H) 0.99 (br. s., 1 H) 0.88 - 0.96 (m, 1 H) 0.42 - 0.50 (m, 1 H). White foam

127	(-)- (1R,2S,4R,5S,6S,7S)-7-((2-(5-Cyano-7-fluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		7-Fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-5-carbonitrile (Intermediate G-4)	MS:437.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 8.76-9.02 (m, 1H), 8.06-8.32 (m, 1H), 7.35-7.67 (m, 1H), 4.62-4.78 (m, 1H), 2.69-2.83 (m, 1H), 2.59-2.69 (m, 1H), 2.43-2.57 (m, 1H), 1.40-2.09 (m, 5H), 1.04-1.20 (m, 2H), 0.86-1.00 (m, 1H). White foam
128	(-)- (1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-7-fluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		5-Chloro-7-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-3)	MS:446.1 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO-d ₆) δ 8.18-8.42 (m, 2H), 7.29-7.56 (m, 2H), 4.36-4.58 (m, 1H), 2.73-2.93 (m, 1H), 2.56-2.62 (m, 1H), 2.41-2.48 (m, 1H), 1.42-1.93 (m, 4H), 0.96-1.16 (m, 2H), 0.68-0.88 (m, 1H), 0.20-0.38 (m, 1H). White foam
129	(-)- (1R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1H-indol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		5,7-Difluoro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole (Intermediate G-6)	MS:429.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOH-d ₄) δ 8.89 (d, J=2.51 Hz, 1H) 8.24 (s, 1H) 8.21 - 8.23 (m, 1H) 8.05 (d, J=4.02 Hz, 1H) 4.53 - 4.57 (m, 1H) 2.64 - 2.68 (m, 1H) 2.54 - 2.59 (m, 1H) 2.45 - 2.50 (m, 1H) 1.90 - 1.98 (m, 1H) 1.69 - 1.87 (m, 3H) 1.59 - 1.68 (m, 1H) 1.11 - 1.18

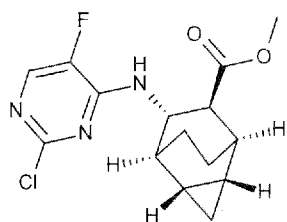
				(m, 1 H) 0.90 - 0.99 (m, 1 H) 0.43 - 0.51 (m, 1 H). White foam
130	(-)- (1R,2S,4R,5S, 6S,7S)-7-((5-Fluoro-2-(7-fluoro-5-methyl-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0 ^{2,4}]nonane-6-carboxylic acid		7-fluoro-3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (intermediate G-7)	MS: 426.1 [M+H] ⁺ ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.86 (br s, 1H), 12.49 (br s, 1H), 8.29 (d, J=3.79 Hz, 1H), 8.08 (br s, 1H), 7.41 (br s, 1H), 7.08 (br d, J=10.39 Hz, 1H), 4.53 (br s, 1H), 2.87 (br d, J=6.24 Hz, 1H), 2.59 (br s, 1H), 2.44 (s, 4H), 1.60-1.80 (m, 2H), 1.42-1.59 (m, 2H), 1.09-1.19 (m, 1H), 0.95-1.07 (m, 1H), 0.78 (br s, 1H), 0.28 (q, J=7.30 Hz, 1H). White foam

Example 131

(rac)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

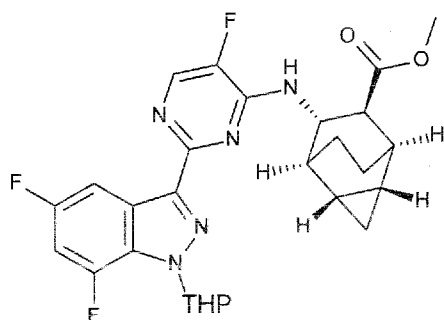


(rac)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A mixture solution of (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate B-18, 1.1 g, 5.63 mmol), 2,4-dichloro-5-fluoropyrimidine (2 g, 12 mmol) and *N,N*-diisopropylethylamine (2.91 g, 22.5 mmol) in THF (40 mL) was stirred at 65°C for 14 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether:EtOAc = 0 to 40%) to afford the title compound (1.6 g, 87.2 % yield) as yellow oil.

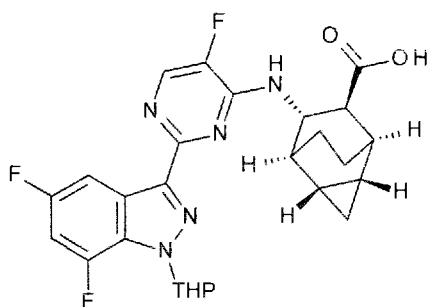
10 rac-(1R,2R,4S,5S,6S,7S)-Methyl 7-((2-(5,7-difluoro-1-tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (220 mg, 675 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexafluoroethane (588 mg, 1.01 mmol) at room temperature. The reaction mixture solution was stirred at 125°C for 2 h before being cooled to room temperature and redissolved in dioxane (16 mL). To the above mixture solution was then added 5,7-difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-2, 320 mg, 878 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) and the resulting reaction mixture solution was stirred at 145°C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash

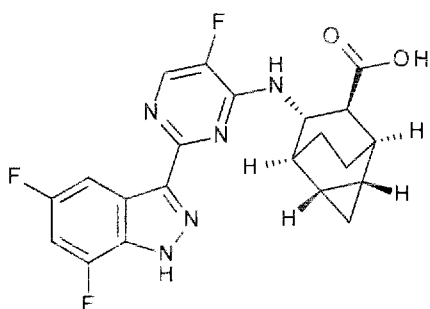
chromatography (0-80% EtOAc-hexane gradient) to afford the title compound as yellow oil. (100 mg, 28.1 % yield). MS: 528.2 [M+H]⁺.

5 [c] (rac)-(1 R,2R,4S,5S,6R,7R)-7-((2-(5,7-Difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A mixture solution of (rac)-(1 R,2R,4S,5S,6S,7S)-methyl 7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (100 mg, 190 μmol) and lithium hydroxide monohydrate (79.5 mg, 1.9 mmol) in water (5 mL) and tetrahydrofuran (5 mL) was stirred at room temperature for 2 h. Afterwards, the reaction mixture solution was concentrated in vacuo to give a crude title compound (100 mg, 100% yield) as a yellow solid. MS: 514.2 [M+H]⁺. It was used directly in the next step reaction without further purification.

15 [P] (rac)-f1R,2R,4S,5S,6S,7S)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-vi)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

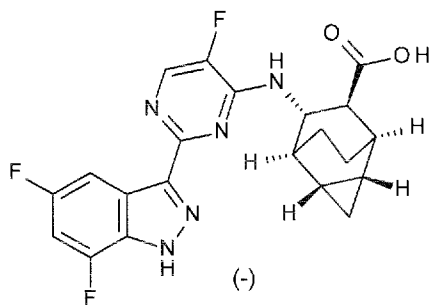


A solution of (rac)-(1 R,2R,4S,5S,6R,7R)-7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (100mg, 195 μmol) in TFA (10 mL) was stirred at room temperature for 14 h before the solvent was evaporated under reduced pressure to give a crude product, which was then purified by Prep-HPLC to afford the title compound (25 mg, 29.9 % yield) as a white solid. MS: 430.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 7.96-8.15 (m, 2H), 6.99 (br t, J=9.72

Hz, 1H), 5.01 (br s, 1H), 2.24-2.45 (m, 2H), 1.34-1.55 (m, 4H), 1.19 (br s, 2H), 1.00 (br s, 1H), 0.70-0.79 (m, 1H), 0.38-0.50 (m, 1H).

Example 132

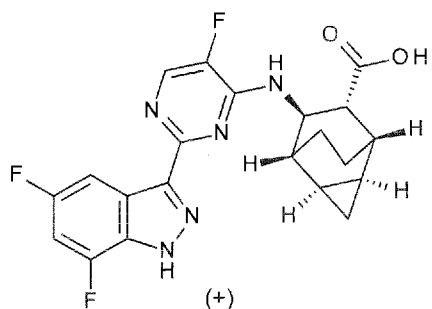
- 5 **(-)-(1R,2R,4S,5S,6S,7S)-7-((2-{5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid**



The title compound was obtained after SFC chiral separation (AD, 250 x 20 mm I.D., mobile phase A/C0₂, B/IPA, 30% gradient B) of Example 131 with a negative sign of optical rotation value. MS: 430.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD-d₄) δ 7.96-8.15 (m, 2H), 6.99 (br t, J=9.72 Hz, 1H), 5.01 (br s, 1H), 2.24-2.45 (m, 2H), 1.34-1.55 (m, 4H), 1.19 (br s, 2H), 1.00 (br s, 1H), 0.70-0.79 (m, 1H), 0.38-0.50 (m, 1H).

Example 133

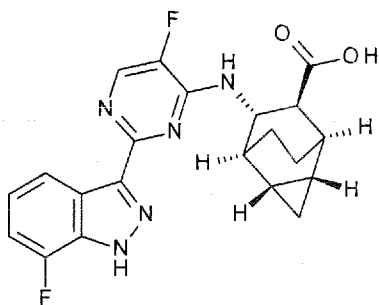
- 15 **(+M1S,2S,4R,5R,6R,7R)-7-((2-{5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid**



The title compound was obtained after SFC chiral separation (AD, 250 x 20 mm I.D., mobile phase A/C0₂, B/IPA, 30% gradient B) of Example 131 with a positive sign of optical rotation value. MS: 430.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-c₄) δ 7.96-8.15 (m, 2H), 6.99 (br t, J=9.72 Hz, 1H), 5.01 (br s, 1H), 2.24-2.45 (m, 2H), 1.34-1.55 (m, 4H), 1.19 (br s, 2H), 1.00 (br s, 1H), 0.70-0.79 (m, 1H), 0.38-0.50 (m, 1H).

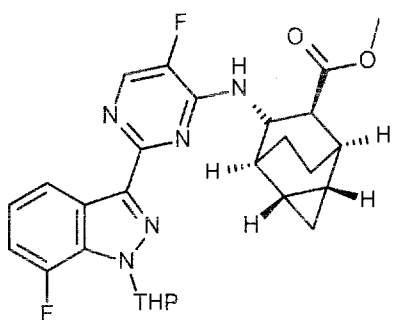
Example 134 - ELN025012-030-P1- RW08-2015-099

(rac)-(1S,2S,4R,5R,6S,7S)-7-((5-Fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



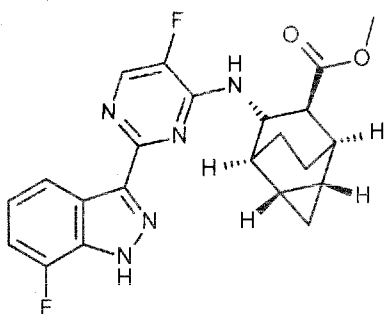
FAI (rac)-(1S,2S,4R,5R,6S,7S)-Methyl 7-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-

5 1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



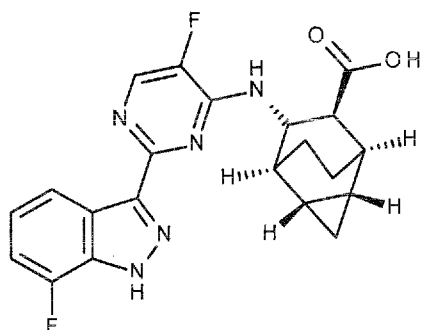
To a stirred solution of 7-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (400 mg, 1.06 mmol, Intermediate G-1a) in THF (30 mL) was added (rac)-(1S,2S,4R,5R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (intermediate EMS, 227.7 mg, 1.17 mmol) and DIPEA (137 mg, 1.06 mmol) at room temperature and the resulting reaction mixture was stirred at 70 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by Prep-TLC (petroleum ether:EtOAc = 1:1) to afford the title compound (330 mg, 61.3% yield) as a yellow solid. MS: 510.2 [M+H]⁺

[6] (1S,2S,4R,5R,6S,7S)-Methyl 7-((5-fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a solution of (rac)-(1S,2S,4R,5R,6S,7S)-methyl-7-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (330 mg, 0.647 mmol) in DCM (10 mL) was added TFA (10 mL) at room temperature and stirred for 12 h. After TLC (petroleum ether:EtOAc = 1:1) showed that the reaction was completed, the reaction mixture was concentrated in vacuo to give a crude title compound (250 mg, 90.7% yield) as a red solid. MS: 426.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

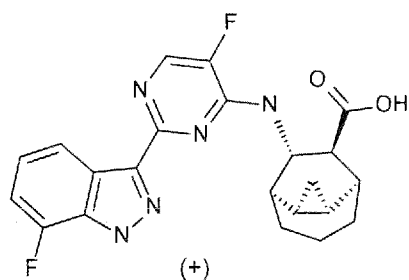
[C] (rac)-(1S,2S,4R,5R,6S,7S)-7-((5-fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



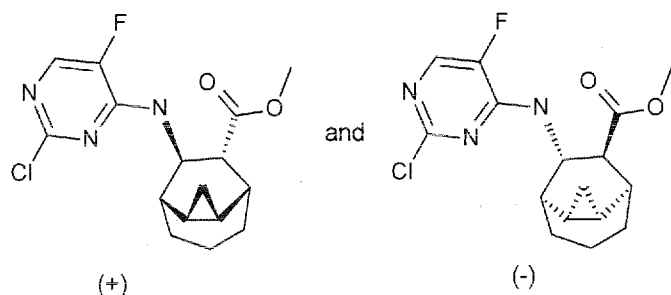
To a solution of (rac)-(1S,2S,4R,5R,6S,7S)-methyl-7-((5-fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 0.587 mmol) in MeOH (10 mL) was added 4 N NaOH solution (10 mL) at room temperature and stirred for 3 h. After TLC (petroleum ether:EtOAc = 1:1) showed that the reaction was completed, the reaction mixture was concentrated to remove MeOH, and the residue solution was acidified with 4 N HCl to adjust pH = 6-7. The reaction mixture was then extracted with DCM (20 mL three times) and the organic extracts were concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (10 mg, 10% yield) as a yellow solid. MS: 412.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.38 (d, J=8.03 Hz, 1 H), 8.31 (br. s., 1 H), 7.31-7.39 (m, 1 H), 7.21-7.30 (m, 1 H), 5.32 (br. s., 1 H), 2.91 (d, J=4.77 Hz, 1 H), 2.58 (br. s., 1 H), 2.47 (br. s., 1 H), 1.50-1.66 (m, 3 H), 1.21-1.39 (m, 2 H), 1.15 (d, J=3.51 Hz, 1 H), 0.84-0.94 (m, 1 H), 0.63 (q, J=7.28 Hz, 1 H).

Example 135

(+)-{1S,2R,4S,5R,9S,10S}-10-((5-Fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid

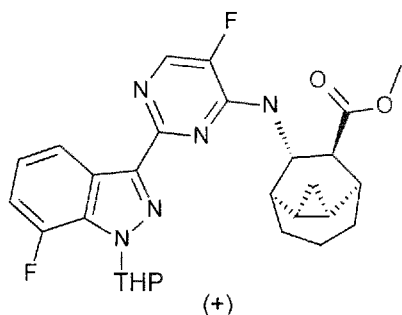


1A1 (+)-(1R,2S,4R,5S,9R,10R)-Methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-
tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate and (-)-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-
 5 chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



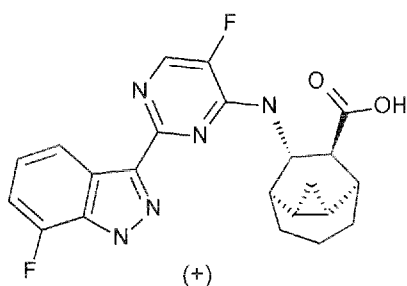
A mixture solution of (rac)-(1S,2R,4S,5R,9S,10S)-methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (Intermediate B-17, 11.2 g, 66.9 mmol), 2,4-dichloro-5-fluoropyrimidine (11.2 g, 66.9 mmol), and *N,N*-diisopropylethylamine (8.65 g, 66.9 mmol) in THF (150 mL) was heated at 60°C for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was purified first by silica gel flash chromatography (petroleum ether:EtOAc = 0 to 30%) and then SFC chiral separation (IC, 250 x 30 mm I.D., mobile phase A/C02, B/MeOH, 50% gradient B) to afford the title compound (+)-(1R,2S,4R,5S,9R,10R)-methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (2 g, 31% yield) and (-)-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (2 g, 31% yield) as white solids. MS: 340.2 [M+H]⁺.

FBI (+)-(1S,2R,4S,5R,9S,10S)-Methyl 10-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



To a stirred mixture solution of (-)-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (250 mg, 736 μ mol) and Pd(PPh₃)₄ (85 mg, 73.6 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (512 mg, 883 μ mol) and the reaction mixture was stirred at 125°C for 2 h before it was cooled back to room temperature. To the above stirred mixture solution was added 7-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-1a, 382 mg, 1.1 mmol) and Pd(PPh₃)₄ (85 mg, 73.6 μ mol) in dioxane (16 mL). The resulting reaction mixture was re-heated at 145°C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (50 mg, 13.4% yield) as a yellow solid. MS: 524.2 [M+Hf].

[C] (+)-(1S,2R,4S,5R,9S,10S)-methyl 10-((5-fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid

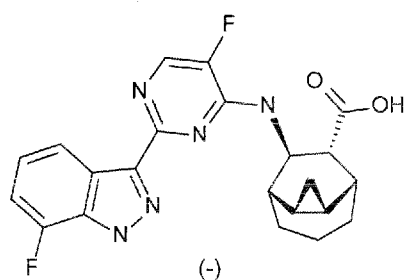


To a stirred mixture solution of (+)-(1S,2R,4S,5R,9S,10S)-methyl 10-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (600 mg, 1.15 mmol) in THF (6 mL) and MeOH (3 mL) was added LiOH (200 mg, 8.35 mmol) pre-dissolved in water (3 mL). The reaction mixture solution was stirred at 55°C for 12 h, and after cooling to room temperature, the solvent was removed under reduced pressure. The residue was re-suspended in DCM (10 mL) and TFA (10 mL) and stirred at room temperature for 16 h. After solvent was removed under reduced pressure,

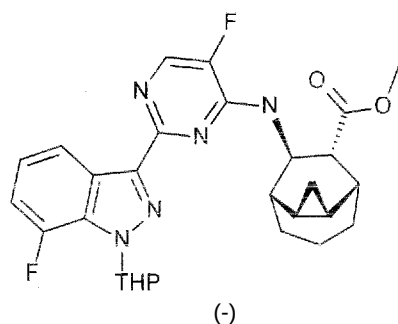
the residue was purified by Prep-HPLC to afford the title compound (240 mg, 42.1 % yield) as white foam. MS: 426.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 8.36-8.54 (m, 1H), 8.13 (d, $J=3.91$ Hz, 1H), 7.04-7.29 (m, 2H), 5.17 (br d, $J=6.72$ Hz, 1H), 2.76-2.93 (m, 2H), 2.54 (br s, 1H), 2.21 (br dd, $J=4.71, 12.65$ Hz, 1H), 1.92-2.03 (m, 1H), 1.68-1.92 (m, 4H), 1.11-1.27 (m, 2H), 0.90-1.07 (m, 1H), 0.50-0.71 (m, 1H).

Example 136

(-H1R,2S,4R,5S,9R,10R)-10-((5-Fluoro-2-{7-fluoro-1H-indazol-3-yl})pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid

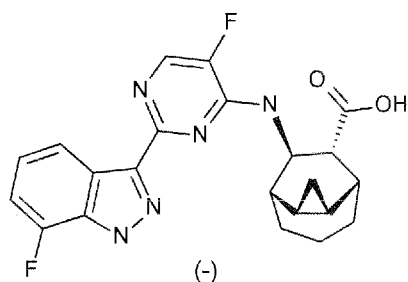


fAl (-)-(1R,2S,4R,5S,9R,10R)-methyl 10-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



In analogy to the synthesis of Example 135/step B, (+)-(1R,2S,4R,5S,9R,10R)-methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (250 mg, 736 μ mol) was used to afford the title compound (100 mg, 26% yield) as a yellow solid after silica gel flash chromatography (0-80% EtOAc-hexane gradient) purification. MS: 524.2 $[M+H]^+$.

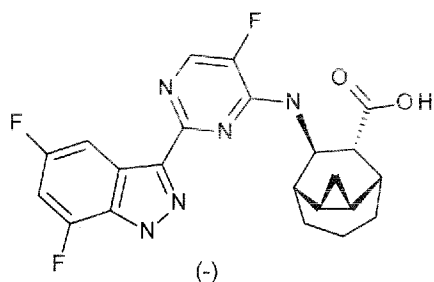
(-H1R,2S,4R,5S,9R,10R)-10-((5-Fluoro-2-(7-fluoro-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



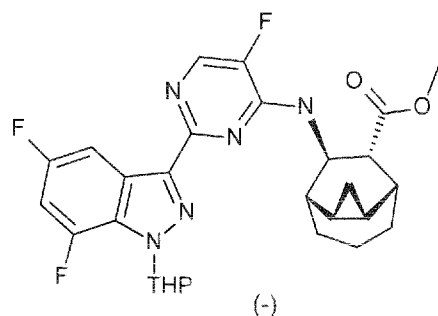
In analogy to the synthesis of Example 135/step C, (-)-(1R,2S,4R,5S,9R,10R)-methyl 10-((5-fluoro-2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylate (100 mg, 191 μ mol) was used to afford the title compound (20 mg, 24.6% yield) as white foam after Prep-HPLC purification. MS: 426.3 [M+H]⁺. ¹HNMR (400 MHz, MeOH-d₄) δ 8.36-8.54 (m, 1H), 8.13 (d, J=3.91 Hz, 1H), 7.04-7.29 (m, 2H), 5.17 (br d, J=6.72 Hz, 1H), 2.76-2.93 (m, 2H), 2.54 (br s, 1H), 2.21 (br dd, J=4.71, 12.65 Hz, 1H), 1.92-2.03 (m, 1H), 1.68-1.92 (m, 4H), 1.11-1.27 (m, 2H), 0.90-1.07 (m, 1H), 0.50-0.71 (m, 1H).

Example 137

(-)-(1S,2R,4S,5R,9S,10S)-10-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylic acid



[A] (-)-(1R,2S,4R,5S,9R,10R)-Methyl 10-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylate

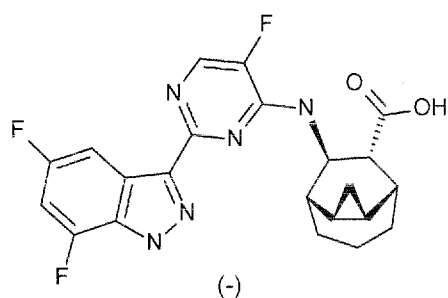


In analogy to the synthesis of Example 135/step B, (+)-(1R,2S,4R,5S,9R,10R)-methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)-tricyclo[3.3.2.0.2,4]decane-9-carboxylate (250 mg,

736 mmol) and 5,7-difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (289 mg, 795 μmol) were used to afford the title compound (60 mg, 21.6% yield) as a yellow solid after silica gel flash chromatography (0-80% EtOAc-hexane gradient) purification. MS: 542.2 $[\text{M}+\text{H}]^+$.

5

137 (-)-(1S,2R,4S,5R,9S,10S)-10-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



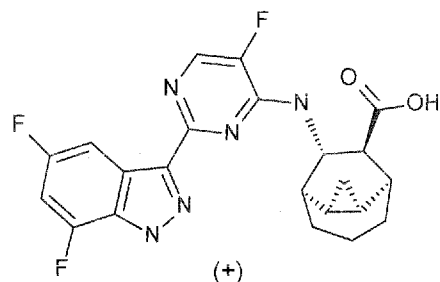
10

In analogy to the synthesis of Example 135/Step C, (-)-(1R,2S,4R,5S,9R,10R)-methyl 10-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (60 mg, 115 μmol) was used to afford the title compound (20 mg, 24.4 % yield) as a white solid after Prep-HPLC purification. MS: 444.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 7.94-8.16 (m, 2H), 6.86-7.11 (m, 1H), 5.04 (br d, $J=6.24$ Hz, 1H), 2.15-2.71 (m, 2H), 2.40 (br s, 1H), 2.12 (br rid, $J=5.32, 12.41$ Hz, 1H), 1.78-1.91 (m, 1H), 1.57-1.78 (m, 4H), 0.96-1.17 (m, 2H), 0.80-0.93 (m, 1H), 0.42-0.61 (m, 1H).

15

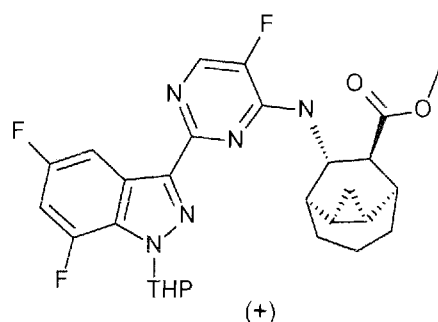
20 **Example 138**

(+)-(1S,2R,4S,5R,9S,10S)-10-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



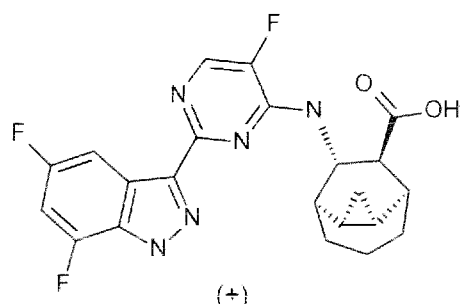
138 (+)-(1S,2R,4S,5R,9S,10S)-Methyl 10-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate

25



in analogy to the synthesis of Example 135/step B, (-)-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0(2,4)]decane-9-carboxylate (250 mg, 736 μ mol) and 5,7-difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (289 mg, 795 μ mol) were used to afford the title compound (60 mg, 20.9% yield) as a yellow solid after silica gel flash chromatography (0-80% EtOAc-hexane gradient) purification. MS: 542.2 [M+H]⁺.

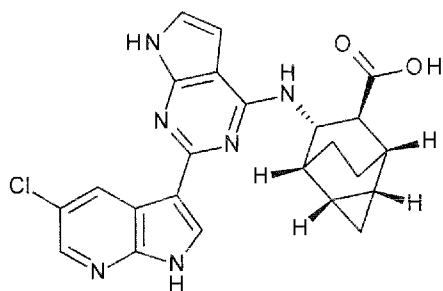
[B] (+)-(1S,2R,4S,5R,9S,10S)-10-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0(2,4)]decane-9-carboxylic acid



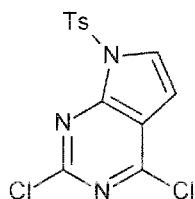
In analogy to the synthesis of Example 135/step C, (+)-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0(2,4)]decane-9-carboxylate (60 mg, 115 μ mol) was used to afford the title compound (10 mg, 11.9% yield) as a white solid after Prep-HPLC purification. MS: 444.2 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 7.90-8.21 (m, 2H), 6.84-7.08 (m, 1H), 5.04 (br d, J=5.62 Hz, 1H), 2.66-2.78 (m, 2H), 2.41 (br s, 1H), 2.12 (br dd, J=5.07, 12.04 Hz, 1H), 1.80-1.89 (m, 1H), 1.56-1.77 (m, 4H), 1.01-1.14 (m, 2H), 0.87 (td, J=4.22, 7.95 Hz, 1H), 0.43-0.57 (m, 1H).

Example 139

(rac)-{1R,2S,4R,5S,6S,7S}-7-((2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid

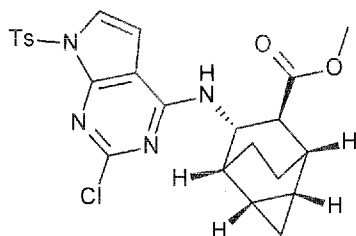


[A] 2,4-Dichloro-7-(p-tolylsulfonyl)pyrrolo[2,3-d]pyrimidine



A mixture solution of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (24 g, 127.6 mmol), TsCl (26.8 g, 140.4 mmol), and tetrabutylammonium hydrogen sulfate (2.1 g, 6.38 mmol) in DCM (400 mL) was treated with 50% aq. NaOH solution (25 mL) at room temperature and stirred for 30 min. After TLC showed the completion of the reaction (petroleum ether:EtOAc 5:1), the reaction mixture was partitioned between H₂O (100 mL) and DCM (100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography to afford the title compound (41 g, 94% yield) as a white solid. MS: 342.1 [M+H]⁺. ¹H NMR (400 MHz, CHCl₃-d₁) δ 8.16 - 8.07 (m, 2H), 7.76 (d, J=4.0 Hz, 1H), 7.37 (d, J=8.2 Hz, 2H), 6.68 (d, J=4.0 Hz, 1H), 2.47 - 2.39 (m, 3H).

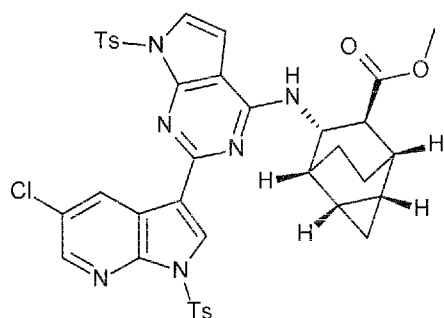
[B] (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1.5 g, 7.65 mmol) in THF (20 mL) was added 2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (3.08 g, 9 mmol) and DIPEA (1.06 g, 8.19 mmol) and the resulting reaction mixture solution was stirred at 75°C for 12 h. After cooling to room temperature, the

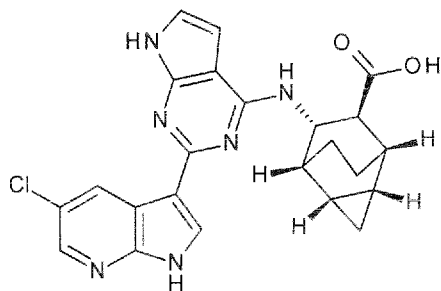
reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude title compound (**3** g, 78% yield) as white foam. MS: 501.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

[c] (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



10 A stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250mg, 499 μmol), 1,1,1,2,2,2-hexabutyldistannane (347 mg, 599 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in dioxane (10 mL) was heated at 125°C for 3 h before it was cooled back to room temperature. To the above stirred solution was then added 5-chloro-3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (281 mg, 649 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in dioxane (10 mL) and the resulting mixture was re-heated at 145°C for 50 min. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was purified by silica gel flash chromatography (0 to 80% EtOAc-petroleum ether gradient) to afford the title compound (100 mg, 26% yield) as yellow oil. MS: 772.1 $(\text{M}+1)^+$.

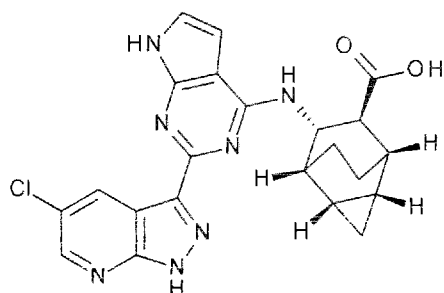
[D] (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



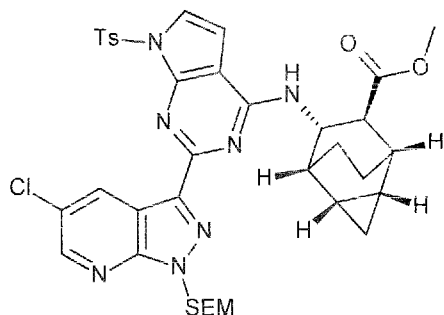
A mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (200 mg, 259 μ mol) and lithium hydroxide monohydrate (109 mg, 2.59 mmol) in THF (5 mL) and water (5 mL) was stirred at room temperature for 16 h before the reaction mixture was neutralized with TFA. Afterwards, the solvent was evaporated under reduced pressure to give a crude product, which was purified by Prep-HPLC to afford the title compound (20 mg, 17.2% yield) as white foam. MS: 449.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-*d*₄) δ ppm 8.87-8.93 (m, 1H), 8.65-8.73 (m, 1H), 8.19-8.25 (m, 1H), 7.17-7.21 (m, 1H), 6.91-6.96 (m, 1H), 4.40-4.52 (m, 1H), 2.63-2.71 (m, 1H), 2.54-2.60 (m, 1H), 2.48-2.54 (m, 1H), 1.76-1.91 (m, 2H), 1.61-1.76 (m, 2H), 1.14-1.24 (m, 1H), 0.96-1.06 (m, 1H), 0.78-0.89 (m, 1H), 0.54-0.65 (m, 1H).

Example 140

(rac)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1 H-pyrazolo[3 ,4-b]pyridin-3-yl)-7 H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



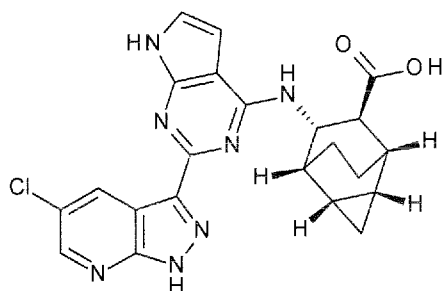
[A] (rac)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1-((2-trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3.4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



In analogy to the synthesis of Example 139/step C, 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3.4-b]pyridine (Intermediate A-3, 266 mg, 649 μ mol) was used to afford the title compound (100 mg, 26.8% yield) as yellow oil after silica

gel flash chromatography (0-80% EtOAc-petroleum ether gradient) purification. MS: 749.1 (M+1)⁺.

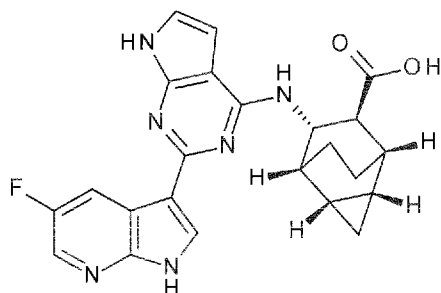
[B] (rac)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (200 mg, 267 μ mol) and lithium hydroxide monohydrate (112 mg, 2.67 mmol) in THF (5 mL) and water (5 mL) was stirred at room temperature for 16 h. Afterwards, the solvent was removed under reduced pressure and the residue was re-dissolved in TFA (10 mL) and stirred at room temperature for another 16 h. The volatile was evaporated under reduced pressure to give a crude product, which was then purified by Prep-HPLC to afford the title compound (10 mg, 8.32% yield) as white foam. MS: 450.1 (M+1)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.97-9.03 (m, 1H), 8.38-8.46 (m, 1H), 6.99-7.07 (m, 1H), 6.59-6.68 (m, 1H), 4.64-4.73 (m, 1H), 2.59-2.64 (m, 1H), 2.50-2.58 (m, 1H), 2.38-2.47 (m, 1H), 1.80-1.92 (m, 1H), 1.50-1.76 (m, 3H), 0.99-1.09 (m, 1H), 0.92-0.99 (m, 1H), 0.77-0.88 (m, 1H), 0.31-0.43 (m, 1H).

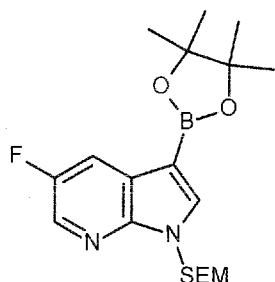
Example 141

(rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



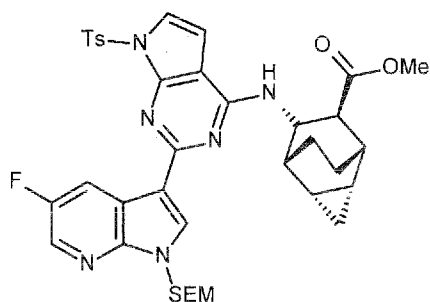
IA 1 5-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine



To a stirred solution of 5-fluoro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate A-2, 6 g, 15 mmol) in THF (100 mL) was added *i*-PrMgCl·LiCl (23 mL, 30 mmol) slowly at -20 °C. After the addition, the reaction mixture was stirred at 0 °C for 1 hr before bis(pinacol)diborane (4.2 g, 27.0 mmol) was added and the resulting reaction mixture was stirred at 0 °C for additional 3 h. After TLC (petroleum ether:EtOAc = 10:1) showed that the reaction was completed, the reaction was quenched with satd. aq. NH₄Cl solution (100 mL), poured into water and extracted with EtOAc (200 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (petroleum ether:EtOAc = 20:1 to 5:1) to afford the title compound (3.5 g, 60.3% yield as yellow oil. MS: 393.2 [M+H]⁺).

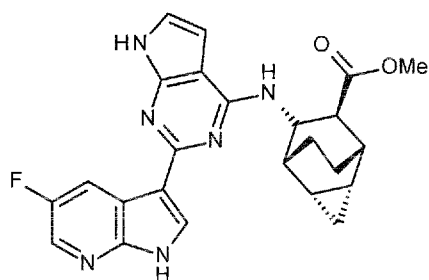
15 (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of 5-fluoro-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (1 g, 2.54 mmol) and (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1 g, 2 mmol) in THF (20 mL) was added X-phos biphenyl (156 mg, 0.2 mmol), K₃PO₄ (840 mg, 4.0 mmol) and H₂O (4.0 mL) and the resulting mixture was stirred at 60 °C for 12 h. After LC-MS showed that the reaction was

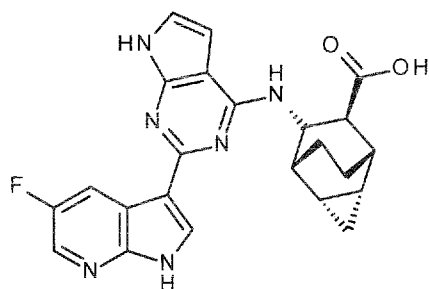
completed, the reaction mixture was cooled to room temperature and extracted with EtOAc (200 mL three times). Combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (DCM:MeOH = 100:1 to 30:1) to afford the title compound (1.2 g, 82.2% yield) as a white solid. MS: 731.3 $[\text{M}+\text{H}]^+$.

[C] (rac)-d R.2S.4R.5S.6S.7S)-Methyl 7-((2-(5-fluoro-1 H-pyrrolo[2.3-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



10 A solution of (rac)-(1 R.2S.4R.5S.6S.7S)-methyl 7-((2-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (730 mg, 1 mmol) in 2 M TBAF/THF solution (10 mL, 20 mmol) was stirred at 80°C for 4 h. After cooling to room temperature, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL three times). Combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified by silica gel flash chromatography (DCM:MeOH=100:1~20:1) to afford the title compound (300 mg, 67.2% yield) as a yellow solid. MS: 446.2 $[\text{M}+\text{H}]^+$.

20 ID1 (rac)-(1 R.2S.4R.5S.6S.7S)-7-((2-(5-fluoro-1H-pyrrolo[2.3-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



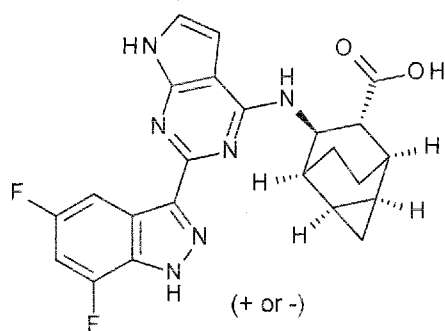
To a stirred solution of (rac)-(1 R.2S.4R.5S.6S.7S)-methyl 7-((2-(5-fluoro-1 H-pyrrolo[2.3-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-

carboxylate (270 mg, 0.60 mmol) in THF/H₂O (20 mL, 1:1) was added LiOH (43.0 mg, 1.8 mmol) and the reaction mixture was stirred at room temperature for 12 h. After LC-MS showed that the reaction was completed, the mixture was neutralized with 1N aq. HCl solution and concentrated in vacuo to give a crude product, which was then purified by
 5 Prep-HPLC to afford the title compound (93 mg, 85.9% yield) as a white solid. MS: 433.2 [M+H]⁺. ¹H NMR(400MHz, CHCl₃-d₁) δ 8.85-8.81 (m, 1H), 8.49(s, 1H), 8.20-8.19 (m, 2H), 7.10-7.09 (m, 1H), 6.77-6.76 (m, 1H), 5.02(m, 1H), 2.68-2.67 (m, 1H), 2.56 (m, 1H), 2.47 (m, 1H), 1.77 (m, 1H), 1.55 (m, 2H), 1.35-1.26 (m, 1H), 1.15-1.14 (m, 1H), 0.88-0.87 (m, 1H), 0.59-0.54 (m, 1H).

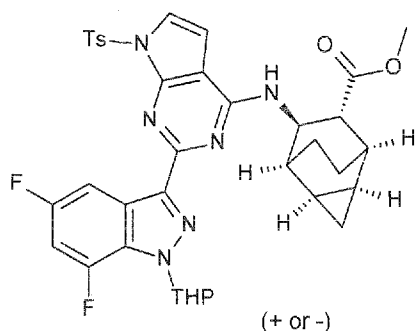
10

Example 142

(+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



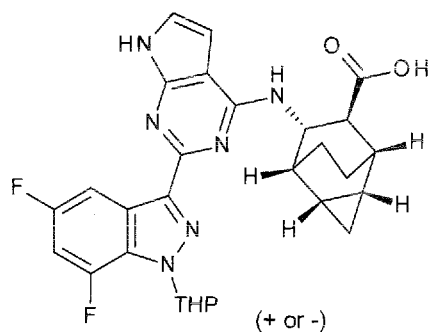
15 (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Example
 20 139/Step B, 400 mg, 798 μmol) and Pd(PPh₃)₄ (92.3 mg, 79.8 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (695 mg, 1.2 mmol) and the resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature.

To the above stirred mixture solution was added 5,7-difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (436 mg, 1.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (92.3 mg, 79.8 μmol) in dioxane (16 mL) and the resulting reaction mixture was re-heated at 145 °C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (130 mg, 23.2% yield) as yellow oil. MS: 703.1 $[\text{M}+\text{H}]^+$

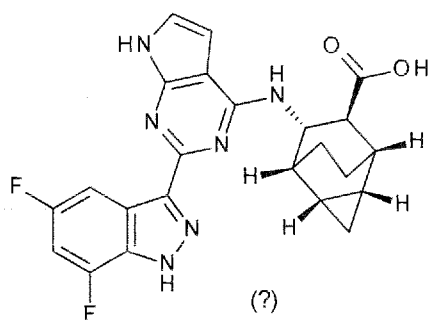
10 1b1 (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-

15 yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (130 mg, 185 μmol) in THF (15 mL) and MeOH (4 mL) was added LiOH (44.3 mg, 1.85 mmol) pre-dissolved in water (4 mL). The reaction mixture solution was stirred at room temperature for 12 h before it was diluted with water (10 mL) and extracted with diethyl ether (20 mL). The separated aqueous layer was acidified with concentrated HCl to pH = 4 and extracted with EtOAc (40 mL three times).
 20 The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude title compound (99 mg, 100% yield) as yellow oil. MS: 535.1 $[\text{M}+\text{H}]^+$. This crude product was used directly in the next step without further purification.

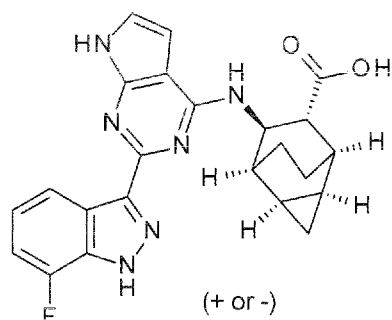
25 1c1 (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



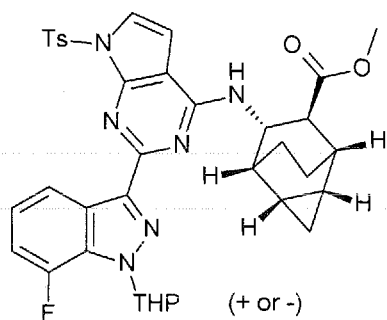
To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0]nonane-6-carboxylic acid (99 mg, 185 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol) at room temperature. The reaction mixture solution was stirred at room temperature for 12 h before being concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (5 mg, 6% yield) as white foam. MS: 451.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 7.86-8.13 (m, 1H), 6.98-7.24 (m, 2H), 6.62-6.88 (m, 1H), 4.49-4.67 (m, 1H), 2.40-2.64 (m, 3H), 1.43-1.57 (m, 4H), 0.99-1.17 (m, 1H), 0.73-0.93 (m, 2H), 0.27-0.55 (m, 1H).

Example 143

(+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(7-Fluoro-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0]nonane-6-carboxylic acid

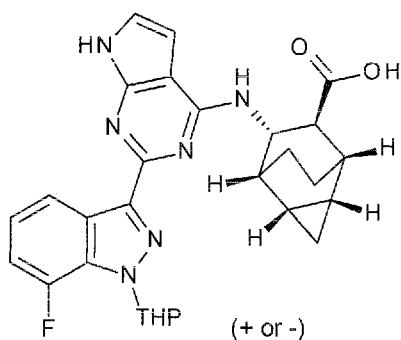


[Al (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0]nonane-6-carboxylate



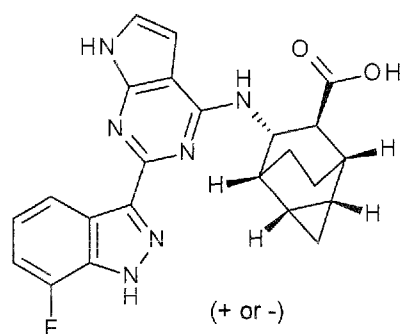
In analogy to the synthesis of Example 142/step A, 7-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-1a, 415 mg, 1.2 mmol) was used to afford the title compound (120 mg, 21.9% yield) as yellow oil after silica gel flash chromatography (0-80% EtOAc-hexane gradient) purification. MS: 685.1 [M+H]⁺

IB] (+ or -)-[(1R,2S,4R,5S,6S,7S)-7-((2-(7-Fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



10 in analogy to the synthesis of Example 142/step B, (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (120 mg, 175 μmol) was used to give a crude title compound (91 mg, 100% yield) as yellow oil. MS: 517.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

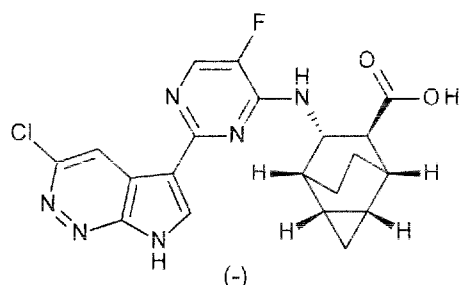
IC] (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(7-Fluoro-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



In analogy to the synthesis of Example 142/step C, (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(7-Fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylic acid (90 mmg, 174 μ mol) was used to afford the title compound (5 mg, 6.2% yield) as white foam after Prep-HPLC purification. MS: 433.1 [M+H]⁺. ¹HNMR (400 MHz, MeOH-c/4) δ 8.17-8.37 (m, 1H), 6.98-7.26 (m, 3H), 6.66-6.84 (m, 1H), 4.53-4.65 (m, 1H), 2.42-2.68 (m, 3H), 1.47-1.83 (m, 4H), 0.93-1.15 (m, 1H), 0.73-0.89 (m, 2H), 0.29-0.61 (m, 1H).

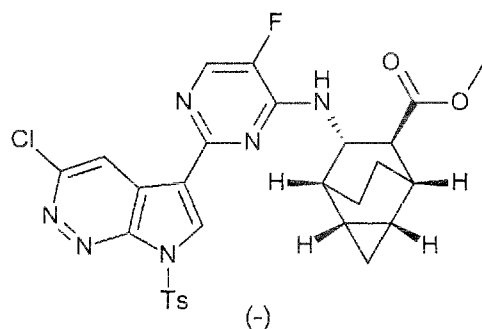
10 **Example 144**

(-)-(1R,2S,4R,5S,6S,7S)-7-((2-(3-Chloro-7H-pyrrolo[2,3-c]pyridazin-5-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylic acid



[A] (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(3-chloro-7H-pyrrolo[2,3-c]pyridazin-5-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate

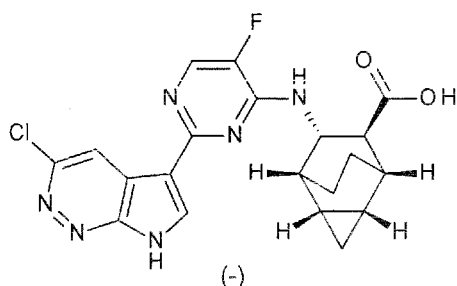
15 5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate (Example 74/Step A, (-)

enantiomer, 250 mg, 767 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (442 mg, 762 μmol) and the reaction mixture was stirred at 145°C under microwave conditions for 1 h. After cooling down, to the above mixture solution was added 5-bromo-3-chloro-7-tosyl-7H-pyrrolo[2,3-c]pyridazine (Intermediate E-2, 445 mg, 1.15 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol). The reaction mixture solution was then re-heated at 145°C for additional 1 hour under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (200 mg, 43.6% yield) as yellow oil. MS: 597.1 ($\text{M}+1$)⁺.

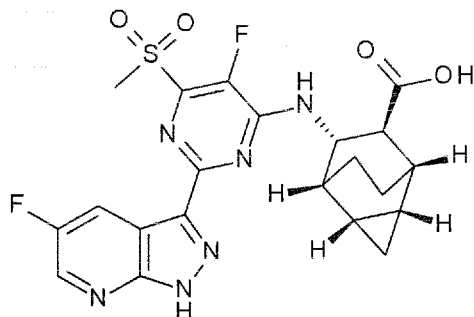
IB 1 (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(3-chloro-7H-pyrrolo[2,3-c]pyridazin-5-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(3-chloro-7H-pyrrolo[2,3-c]pyridazin-5-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (200 mg, 335 μmol) in THF (5 mL) and MeOH (5 mL) was added LiOH (80.2 mg, 3.35 mmol) pre-dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL), and extracted with diethyl ether (20 mL). The organic layer was discarded, and the aqueous layer was acidified with concentrated HCl to pH = 4 and then extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (10 mg, 7% yield) as white foam. MS: 429.1 [$\text{M}+1$]⁺. ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.54 (s, 1H), 8.49 (s, 1H), 7.96 (d, *J*=3.91 Hz, 1H), 4.35-4.41 (m, 1H), 2.46-2.51 (m, 1H), 2.37-2.42 (m, 1H), 2.29-2.35 (m, 1H), 1.58-1.79 (m, 3H), 1.47-1.56 (m, 1H), 0.96-1.08 (m, 1H), 0.77-0.88 (m, 2H), 0.32-0.42 (m, 1H).

Example 145

(rac)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-(methylsulfonyl)pyrimidin-4-yl)amino)tricyclo [3.2.2.0^{2,4}]nonane-6-carboxylic acid



- 5 To a stirred solution of (rac)-(6S,7S)-7-((5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)-6-(methylthio)pyrimidin-4-yl)arnino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (150 mg, 327 μ mol) in DCM (20 mL) was added 3-chlorobenzoperoxoic acid (67.7 mg, 393 μ mol) in an ice-bath. The reaction mixture was stirred at room temperature for 16 h before being poured into an aqueous saturated NaHCO₃ solution (20 ml) and extracted with DCM (20 mL
- 10 three times). Combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound, which was purified by prep-HPLC to afford the title compound (5 mg, 3.1% yield) as a white solid. MS: 491.3 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.40-8.51 (m, 2H). 4.58 (d, J=6.11 Hz, 1H), 3.36 (s, 3H), 2.69 (d, J=6.72 Hz, 1H), 2.55 (s, 1H). 2.43 (d, J=2.08 Hz, 1H). 1.67-1.81 (m, 2H),
- 15 1.53-1.62 (m, 2H). 1.03 (tt, J=4.10, 8.31 Hz, 1H), 0.78-0.91 (m, 2H). 0.35 (q, J=7.66 Hz, 1H).

Example 146

- 20 **(-)-(1R,2S,4R,5S,6S,7S)-7-((2-{5-Fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7 H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid**

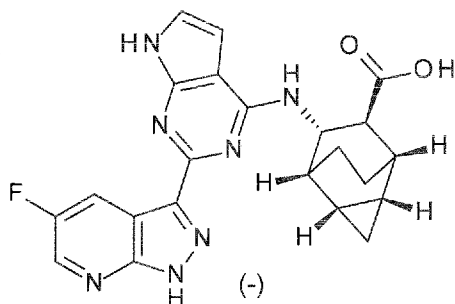
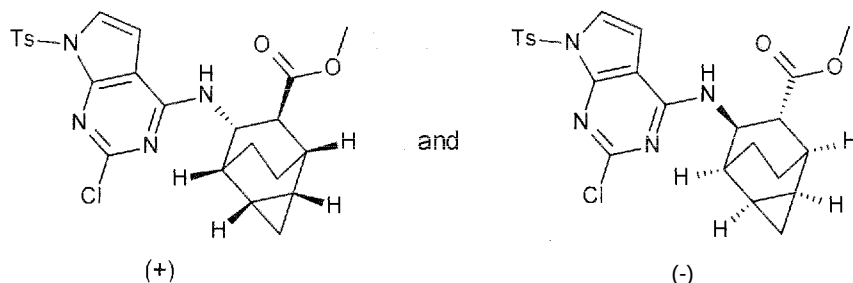


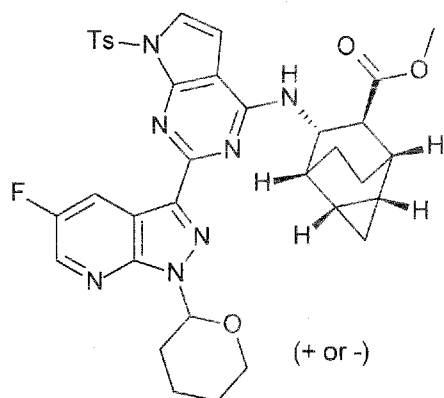
Table 1 (+)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (-)-(1S,2R,4S,5R,6R,7R)-methyl 7-

((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



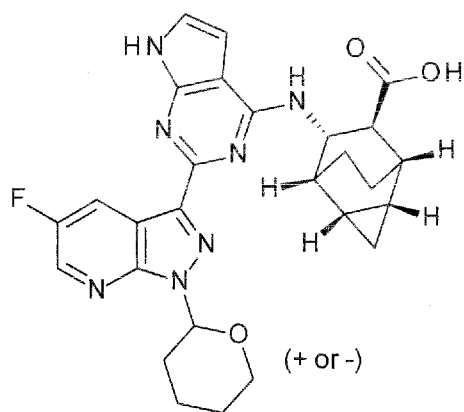
To a stirred solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1.5 g, 7.65 mmol) in THF (20 mL) were added 2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (3.08 g, 9 mmol) and DIPEA (1.06 g, 8.19 mmol) and the resulting reaction mixture solution was stirred at 75 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (3 g, 78% yield) as a white foam. Subsequent SFC chiral separation (DAICEL, IC, 250 x 30 mm, 5 μm column, 40% MeOH in CO₂) then afforded the title compound (+)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1.38 g, 92% yield), MS: 501.1 (M+H)⁺ and (-)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1.41 g, 94% yield), MS: 501.1 (M+H)⁺, both as light yellow solids.

1B1 (+or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (+)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (300 mg, 599 μ mol) and Pd(PPh₃)₄ (69.2 mg, 59.9 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (521 mg, 472 μ L, 898 μ mol) at room temperature and the resulting reaction mixture solution was heated and stirred at 125 °C for 2 h before being cooled back to room temperature. After dilution with dioxane (16 mL), to the above stirred mixture solution were added 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 312 mg, 898 μ mol) and Pd(PPh₃)₄ (69.2 mg, 59.9 μ mol). The reaction mixture solution was then stirred at 145 °C for an additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL x2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (100 mg, 24.4% yield) as a yellow oil. MS: 686.1 (M+H)⁺.

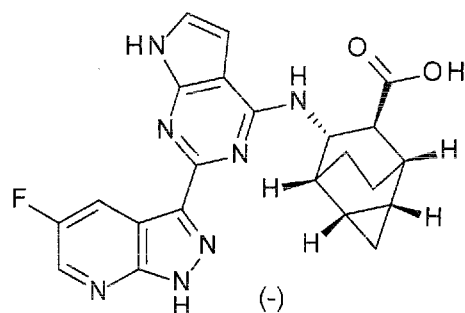
[C] (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (100 mg, 146 μ mol) in THF (6 mL) and MeOH (3 mL) was added LiOH (17.5 mg, 729 μ mol) dissolved in water (3 mL). The reaction mixture solution was then stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over

anhydrous Na_2SO_4 , filtered, and evaporated in vacuo to afford the crude title compound (77mg, 100% yield) as a yellow solid. MS: 518.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

5 1D1 (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

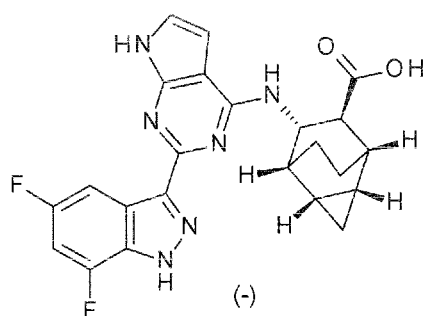


To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-fluoro-1H-pyrrolo[2,3-d]pyrimidin-4-

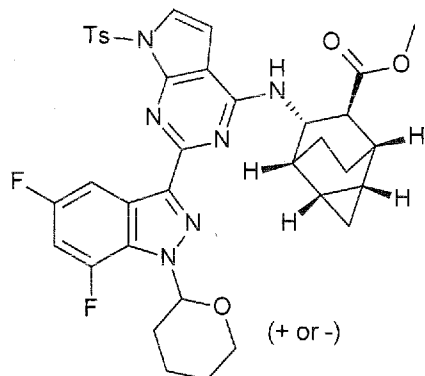
10 yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (100 mg, 193 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) at room temperature and stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title compound (12 mg, 14.3% yield) as a white foam. MS: 434.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.59-8.71 (m, 1H), 8.37-8.46 (m, 1H), 6.98-7.11 (m, 1H), 6.53-6.69 (m, 1H), 4.57-4.69 (m, 1H), 2.57-2.63 (m, 1H), 2.49-2.55 (m, 1H), 2.40-2.47 (m, 1H), 1.47-1.86 (m, 4H), 0.99-1.09 (m, 1H), 0.88-0.98 (m, 1H), 0.78-0.88 (m, 1H), 0.34-0.45 (m, 1H).

Example 147

20 (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

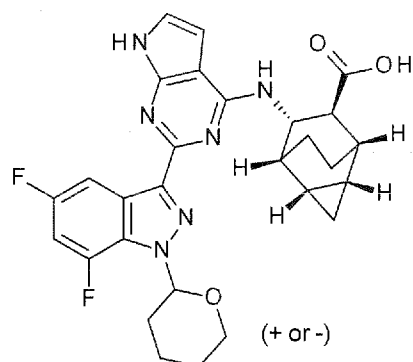


[A] (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl))-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



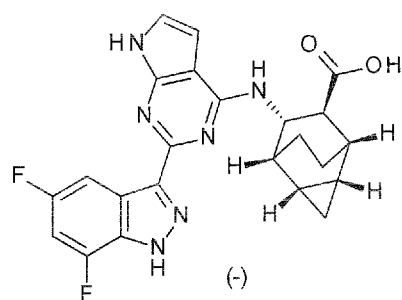
- 5 To a stirred mixture solution of (+)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate 146/step A, 300 mg, 599 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (69.2 mg, 59.9 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (521 mg, 472 μL , 898 μmol) at room temperature. The resulting reaction mixture solution was stirred at 125 °C for 2 h before being cooled to
- 10 room temperature. To the above stirred mixture solution in dioxane (16 mL) was then added 5,7-difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-2, 327 mg, 898 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (69.2 mg, 59.9 μmol) and the reaction mixture was stirred at 145 °C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice).
- 15 The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (100 mg, 23.8% yield) as a yellow oil. MS: 703.1 (M+H)⁺

- 20 [B] (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1-(tetrahydro-2H-pyran-2-yl))-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyi 7-((2-(5,7-difluoro-i-
(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-
yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (100 mg, 142 pmol) in THF (6 mL) and
5 MeOH (3 mL) was added LiOH (17 mg, 711 pmol) dissolved in water (3 mL). The resulting
reaction mixture solution was stirred at room temperature for 12 h before being diluted with
water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded
and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and
extracted with EtOAc (40 mL three times). The combined organics were dried over
10 anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford a crude title compound (77
mg, 100% yield) as a yellow solid. MS: 535.1 (M+H)⁺. This crude product was used directly
in the next step without further purification.

[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid



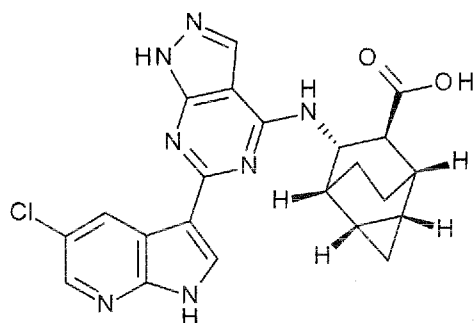
To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1-
(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-
yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (100 mg, 187 pmol) in DCM (3 mL)
20 was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) at room temperature. The
reaction mixture solution was stirred at room temperature for 12 h before being
concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford

the title compound (14 mg, 16.6% yield) as a white foam. MS: 451.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 7.89-7.96 (m, 1H), 7.09-7.21 (m, 1H), 6.97-7.07 (m, 1H), 6.74-6.83 (m, 1H), 4.54-4.61 (m, 1H), 2.56-2.64 (m, 1H), 2.45-2.53 (m, 2H), 1.68-1.82 (m, 2H), 1.51-1.66 (m, 2H), 1.03-1.13 (m, 1H), 0.76-0.94 (m, 2H), 0.40-0.52 (m, 1H).

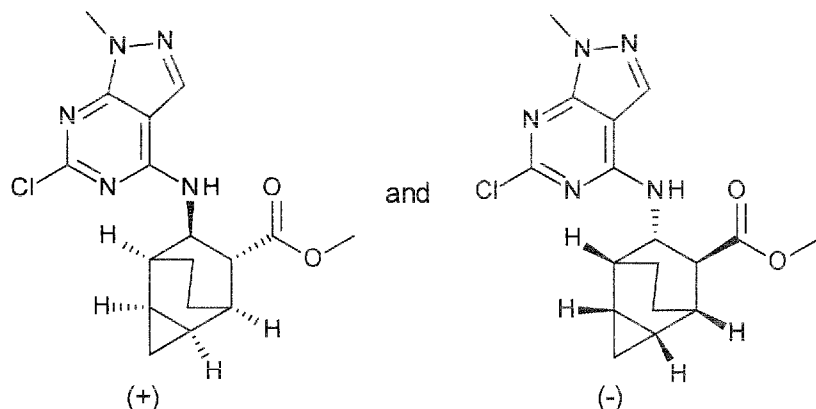
5

Example 148

(rac)-(1R,2S,4R,5S,7S)-7-((6-(S-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



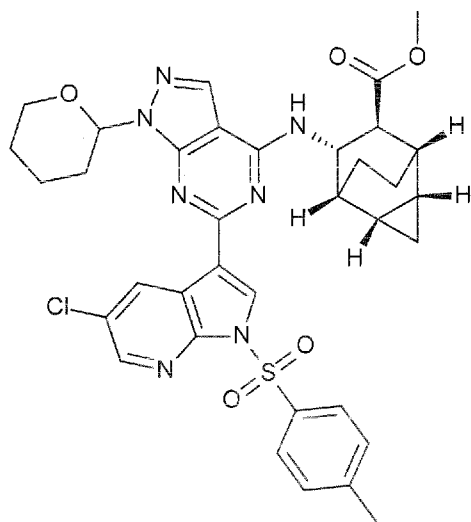
10 1A1 (+)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



15 To a stirred solution of (rac)-(2S,4R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (3.4 g, 17.4 mmol) in THF (150 mL) was added 4,6-dichloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (Intermediate A-4c, 4.24 g, 20.9 mmol) and N-ethyl-N-isopropylpropan-2-amine (3.38 g, 4.52 mL, 26.1 mmol) at room temperature and the resulting reaction mixture solution was stirred at 60 °C for 16 h. After cooling to room
20 temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organics were washed with brine, dried over anhydrous

Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to give a racemic mixture of the product (4.1 g, 65.1% yield) as a white solid. MS: 362.0 [M+H]⁺. Subsequent SFC chiral separation (Chiral Pak, IC-H, 250 x 30 mm, 5 μm column, 40% Methanol in CO₂) then afforded both enantiomers (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate as white solids.

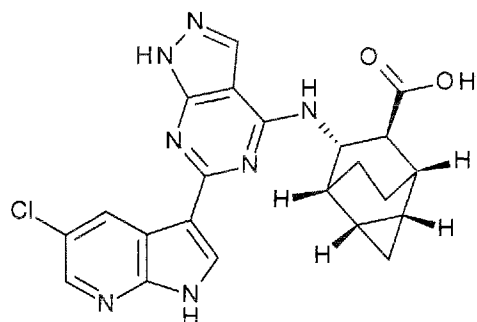
10 [B1] (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((6-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (rac)-(2S,4R,6S,7S)-methyl 7-((6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 579 μmol) and Pd(PPh₃)₄ (66.9 mg, 57.9 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (403 mg, 365 μL, 695 μmol) and the resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above mixture, were then added 5-chloro-3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (376 mg, 868 μmol) and Pd(PPh₃)₄ (66.9 mg, 57.9 μmol) in dioxane (10 mL). The resulting reaction mixture was stirred at 145 °C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product,

which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (80 mg, 19.7% yield) as a yellow oil. MS: 702.2 [M+H]⁺.

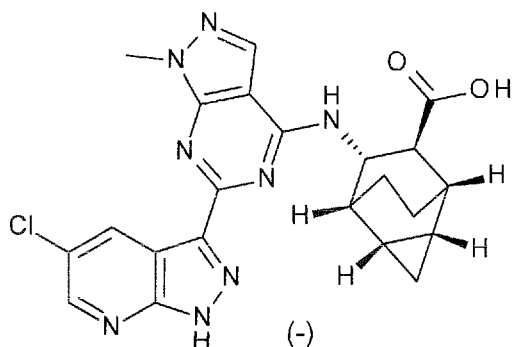
[C] (rac)-(1R,2S,4R,5S,6S,7S)-7-((6-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



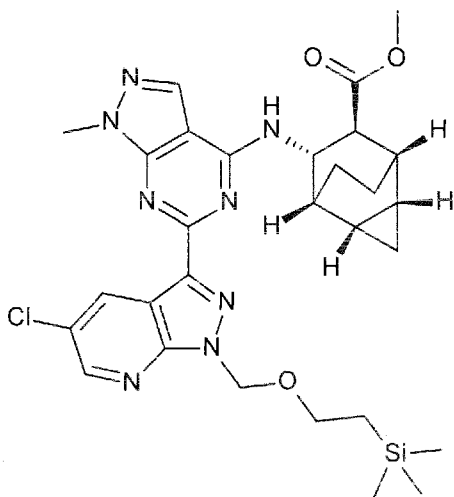
A mixture of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (160 mg, 228 μmol) and lithium hydroxide hydrate (95.6 mg, 2.28 mmol) in THF/H₂O (20 mL, 1:1) was stirred at room temperature for 16 h. After solvent was evaporated in vacuo, the residue was re-dissolved in TFA (10 mL) and stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the solvent was evaporated and the residue was purified by prep-HPLC to afford the title compound (25 mg, 24.4% yield) as a white solid. MS: 450.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.21 (s, 1H), 12.31 (s, 1H), 8.92 (d, J=2.20 Hz, 1H), 8.26-8.31 (m, 2H), 8.16 (s, 1H), 7.70 (d, J=4.89 Hz, 1H), 4.51 (s, 1H), 2.62 (d, J=9.66 Hz, 2H), 2.41 (s, 1H), 1.82 (s, 1H), 1.70 (s, 1H), 1.56 (s, 2H), 1.04 (s, 2H), 0.84 (d, J=7.09 Hz, 2H), 0.32-0.41 (m, 1H).

Example 149

(-)-(1R,2S,4R,5S,6S,7S)-7-((6-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



1A 1 (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((6-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyrimidin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

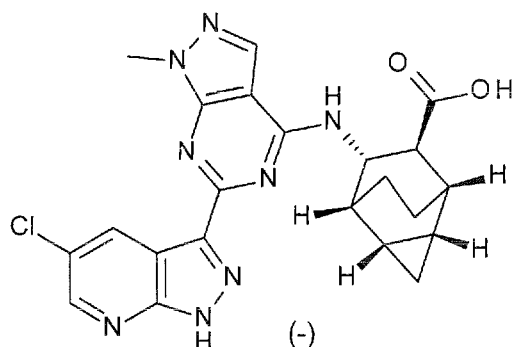


5

To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 691 μmol) and Pd(PPh₃)₄ (79.8 mg, 69.1 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (481 mg, 435 μL, 829 μmol) and the resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above mixture, were then added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (425 mg, 1.04 mmol) and Pd(PPh₃)₄ (79.8 mg, 69.1 μmol) in dioxane (10 mL). The resulting reaction mixture was stirred at 145 °C for 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (55 mg, 13% yield) as a yellow oil. MS: 609.1 [M+H]⁺.

15

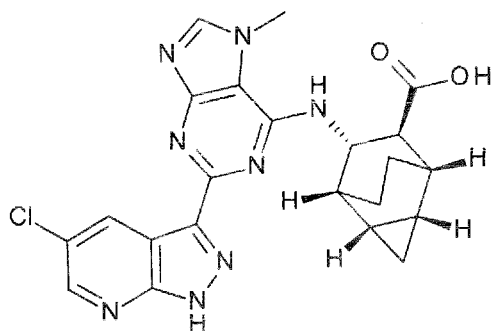
FBI (-)-(1R,2S,4R,5S,6S,7S)-7-((6-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



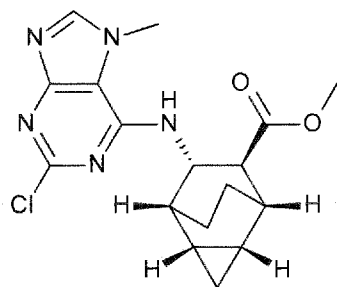
A mixture of (1R,2S,4R,5S,6S,7S)-methyl 7-((6-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (220 mg, 361 μmol) and lithium hydroxide hydrate (30.3 mg, 722 μmol) in THF/H₂O (20 mL, 1:1) was stirred at room temperature for 16 h. After solvent was removed under reduced pressure, the residue was re-dissolved in TFA (10 mL) and stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the solvent was evaporated and the residue was purified by prep-HPLC to afford the title compound (35 mg, 20.4% yield) as a white solid. MS: 465.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.91 (s, 1H), 8.43 (d, J=2.08 Hz, 1H), 8.08 (s, 1H), 3.97 (s, 3H), 2.61 (d, J=6.11 Hz, 1H), 2.56 (d, J=4.40 Hz, 1H), 2.45 (s, 1H), 1.89 (s, 1H), 1.68-1.77 (m, 1H), 1.52-1.66 (m, 2H), 1.05 (s, 1H), 0.79-0.93 (m, 3H), 0.39 (d, J=6.60 Hz, 1H).

Example 150

(rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

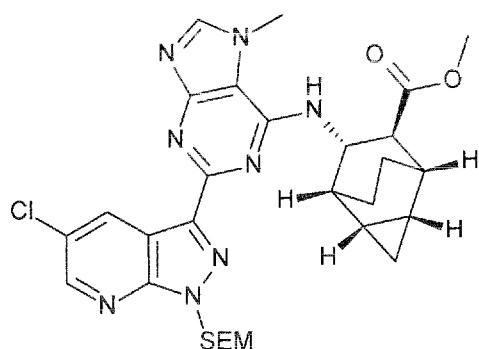


{A} (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-7-methyl-7H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of 2,6-dichloro-7-methyl-7H-purine (780 mg, 3.84 mmol) in THF (35 mL) was added (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0.2,4]nonane-6-carboxylate (500mg, 2.56 mmol) and DIPEA (993 mg, 134 mL, 7.68 mmol) at room temperature and the resulting reaction mixture solution was stirred at 92 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-40% EtOAc-hexane gradient) to afford the title compound (600 mg, 64.8% yield) as a white solid. MS: 362.1 (M+H)⁺.

IB 1 (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-purin-6-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate



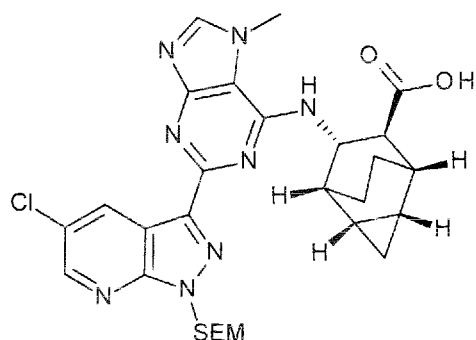
15

To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-methyl-7H-purin-6-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (250 mg, 691 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (481 mg, 435 μL, 829 μmol) at room temperature. Then the reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were then added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-3, 425 mg, 1.04 mmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol). Then reaction mixture

solution was stirred at 145 °C for an additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was

5 purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient, then 0-20% DCM-MeOH gradient) to afford the title compound (60 mg, 14.3% yield) as a yellow oil. MS: 608.9 (M+1)⁺.

[C] (raci-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,2}.0^{2,4}]nonane-6-carboxylic acid

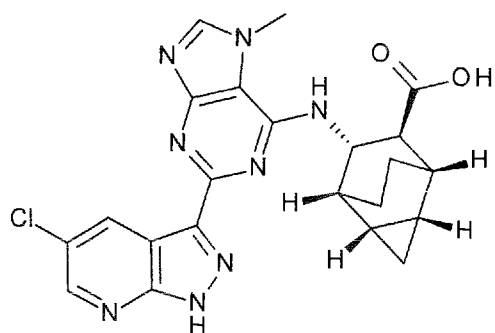


To a stirred mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-purin-6-

15 yl)amino)tricyclo[3.2.2.0^{2,2}.0^{2,4}]nonane-6-carboxylate (60 mg, 98.5 μmol) in THF (5 mL) and MeOH (5 mL) was added LiOH (23.6 mg, 985 μmol) dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before it was diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with

20 EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product (59 mg, 100% yield) as a yellow solid. MS: 595.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

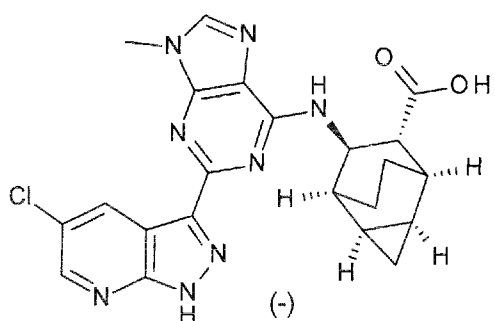
[D] (rac)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1 H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-purin-6-yl)amino)tricyclo[3,2,2.0^{2,2}.0^{2,4}]nonane-6-carboxylic acid



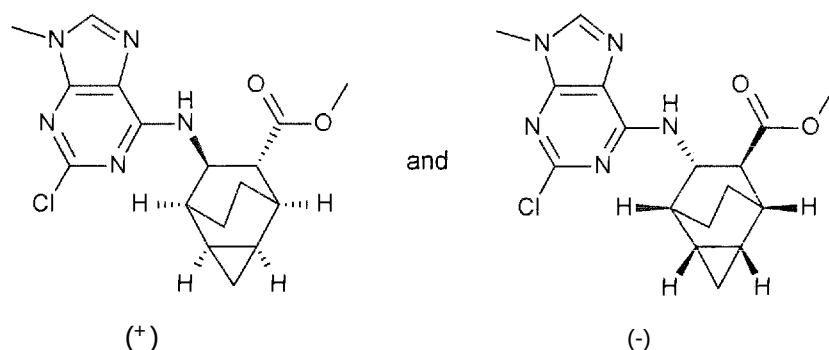
To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (52 mg, 87.4 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) at room temperature and stirred at room temperature for 12 h. Solvent was removed under reduced pressure and the crude product was purified by prep-HPLC to afford the title compound (4.5 mg, 9.8% yield) as a white foam. MS: 465.1 (M+H)⁺. ¹H NMR (400 MHz, METHANOL-d₄) δ 9.07-9.10 (m, 1H), 8.61-8.67 (m, 1H), 8.37-8.41 (m, 1H), 5.20-5.27 (m, 1H), 4.26 (s, 3H), 2.56-2.64 (m, 1H), 2.45-2.53 (m, 2H), 1.68-1.82 (m, 2H), 1.51-1.66 (m, 2H), 1.03-1.13 (m, 1H), 0.76-0.94 (m, 2H), 0.40-0.52 (m, 1H).

Example 151

(-)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

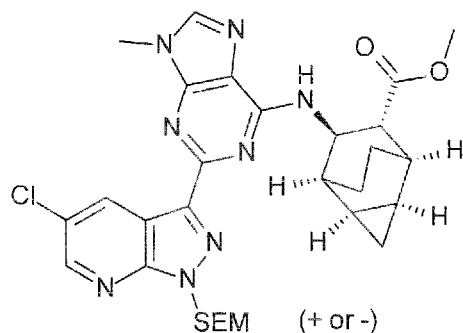


[A] (+)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



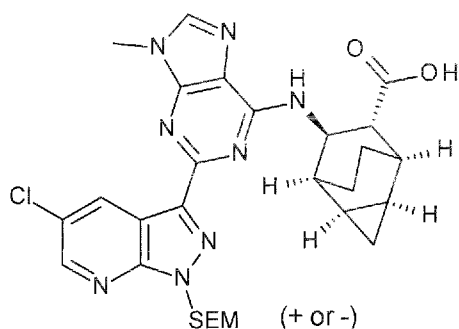
To a stirred mixture solution of 2,6-dichloro-9-methyl-9H-purine (7.8 g, 38.4 mmol) in THF (35 ml) were added (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0.2,4]nonane-6-carboxylate (5 g, 25.6 mmol) and DIPEA (9.93 g, 13.4 ml, 76.8 mmol) at room temperature and the resulting reaction mixture solution was heated at 92 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 ml) and extracted with EtOAc (150 ml twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to give a racemic mixture of title compound (7.3 g, 78.8% yield). Subsequent SFC chiral separation (DAICEL, IC, 250 x 30 mm, 5 μm column, 40% MeOH in CO₂) then afforded the title compound (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (3.4 g), MS: 362.1 (M+H)⁺ and (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (3.5 g), MS: 362.1 (M+H)⁺, both as yellow solids. MS: 362.1 (M+H)⁺.

1b] (+ or -)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate



To a stirred mixture solution of (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 691 μ mol) and Pd(PPh₃)₄ (100 mg, 86.5 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (481 mg, 435 μ L, 829 μ mol) at room temperature and the resulting reaction mixture solution was stirred at 125 °C for 2 h before being cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3.4-b]pyridine (intermediate A-3, 425 mg, 1.04 mmol) and Pd(PPh₃)₄ (100 mg, 86.5 μ mol). Then the reaction mixture solution was stirred at 145 °C for an additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient, then 0-5% DCM-MeOH gradient) to afford the title compound (80 mg, 19% yield) as a yellow oil. MS: 608.9 (M+1)⁺.

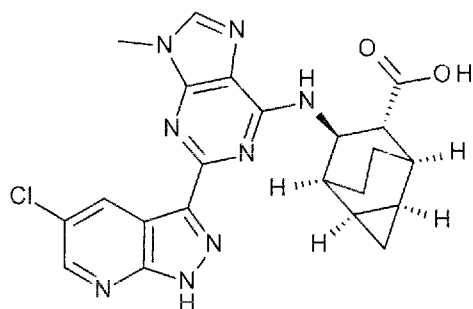
[C] (+ or -)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3.4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (+ or -)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3.4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (320 mg, 525 μ mol) in THF (5 mL) and MeOH (5 mL) was added LiOH (126 mg, 5.25 mmol) dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before it was diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give the crude product (314 mg,

100% yield) as a yellow solid. MS: 595.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

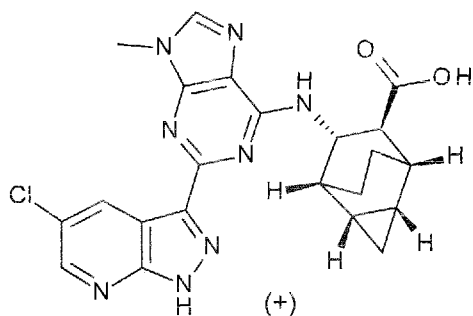
Ex 1 (-)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



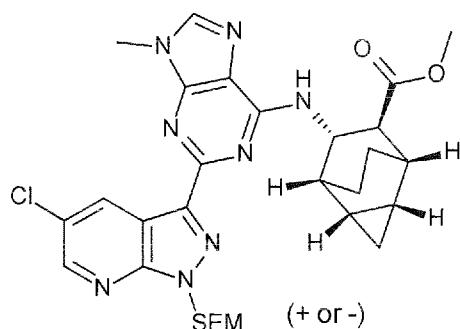
To a stirred mixture solution of (+ or -)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (300 mg, 504 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the crude product was purified by prep-HPLC to afford the title compound (90 mg, 38.4% yield) as a white foam. MS: 465.1 (M+H)⁺. ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.71-8.81 (m, 1H), 8.41-8.52 (m, 1H), 7.85-7.98 (m, 1H), 4.34-4.47 (m, 1H), 3.89 (s, 3H), 2.57-2.63 (m, 1H), 2.49-2.55 (m, 1H), 2.40-2.47 (m, 1H), 1.47-1.86 (m, 4H), 0.99-1.09 (m, 1H), 0.88-0.98 (m, 1H), 0.78-0.88 (m, 1H), 0.34-0.45 (m, 1H).

Example 152

(+)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

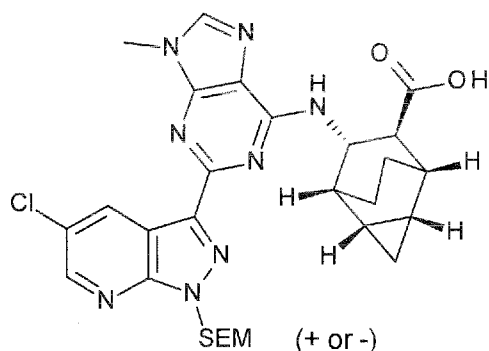


1A1 (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate



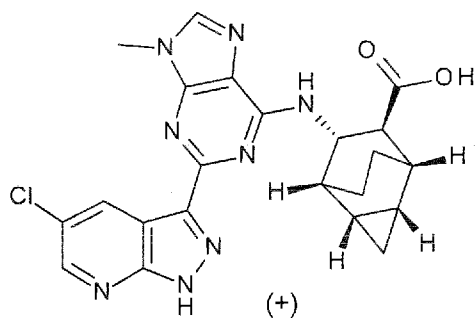
- 5 Similar to the synthesis of example 151/step B, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (250 mg, 691 μmol) was used to afford title compound (50 mg, 11.9% yield) as yellow oil. MS: 608.9 (M+1)⁺.

- 10 1B1 (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid



- 15 Similar to the synthesis of example 151/step C, (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (300 mg, 492 μmol) was used to afford title compound (294 mg, 100% yield) as a crude product. MS: 595.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

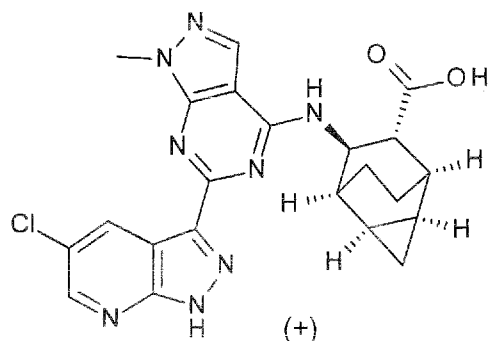
- 20 [C] (+)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-Pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid



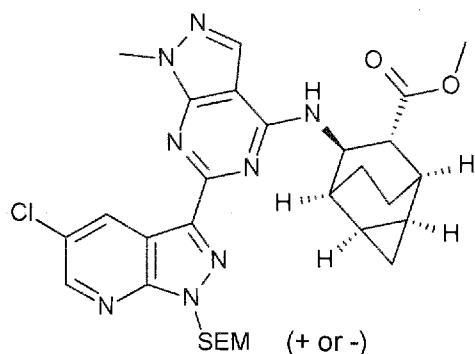
To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (300 mg, 504 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. After solvent was removed under reduced pressure, the crude product was purified by prep-HPLC to afford the title compound (45 mg, 19.1 % yield) as a white foam. MS: 465.1 (M+H)⁺. ¹H NMR (400 MHz, CHCl₃-d) δ 8.83-8.96 (m, 1H), 8.50-8.62 (m, 1H), 7.83-8.03 (m, 1H), 4.35-4.56 (m, 1H), 4.10 (s, 3H), 2.57-2.63 (m, 1H), 2.49-2.55 (m, 1H), 2.40-2.47 (m, 1H), 1.47-1.86 (m, 4H), 0.99-1.09 (m, 1H), 0.88-0.98 (m, 1H), 0.78-0.88 (m, 1H), 0.34-0.45 (m, 1H).

Example 153

(+)-(1S,2R,4S,5R,6R,7R)-7-((6-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid

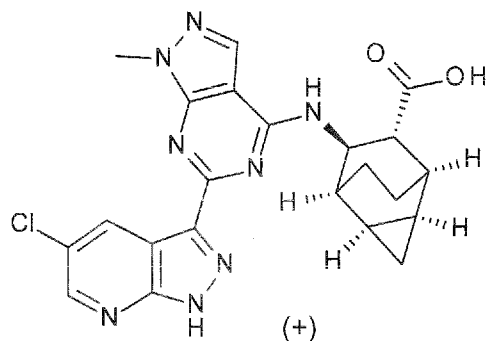


153] (+ or -)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((6-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate



To a stirred mixture solution of (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 691 pmol) and Pd(PPh₃)₄ (79.8 mg, 69.1 pmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (481 mg, 435 pL, 829 pmol) and the resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above mixture, were then added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (425 mg, 1.04 mmol) and Pd(PPh₃)₄ (79.8 mg, 69.1 μmol) in dioxane (10 mL). The resulting reaction mixture was stirred at 145 °C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (90 mg, 21% yield) as an off-white oil. MS: 609.2 [M+H]⁺.

IB 1 (+)-(1S,2R,4S,5R,6R,7R)-7-((6-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



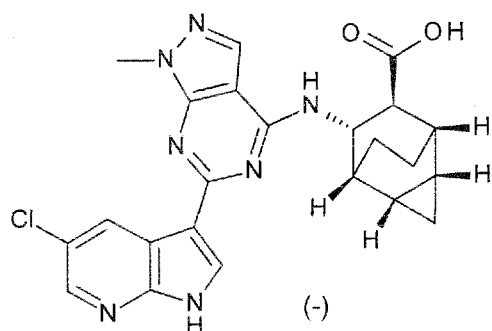
A mixture of (+ or -)-(1S,2R,4S,5R,6R,7R)-methyl 7-((6-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (360 mg, 591 pmol) and

lithium hydroxide hydrate (49.6 mg, 1.18 mmol) in THF/H₂O (20 mL, 1:1) was stirred at room temperature for 16 h. After the solvent was removed under reduced pressure, the residue was dissolved in TFA (10 mL) and stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the solvent was evaporated and the residue was purified by prep-HPLC to afford the title compound (40 mg, 14.3% yield) as a white solid. MS: 465.0 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.91 (s, 1H), 8.43 (d, J=2.20 Hz, 1H), 8.08 (s, 1H), 3.97 (s, 3H), 2.62 (d, J=5.99 Hz, 1H), 2.56 (d, J=4.52 Hz, 1H), 2.45 (s, 1H), 1.89 (s, 1H), 1.72 (s, 1H), 1.53-1.64 (m, 2H), 1.05 (s, 1H), 0.90 (s, 1H), 0.83 (s, 2H), 0.39 (d, J=6.97 Hz, 1H).

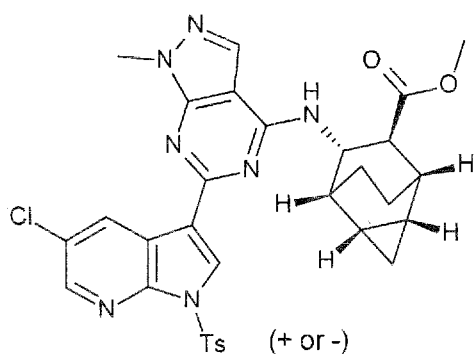
^n
i0

Example 154

(-)-(1R,2S,4R,5S,6S,7S)-7-((6-{5-Chloro-1 H-pyrrolo[2,3-b]pyridin-3-yl)-1-methyl-1 H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



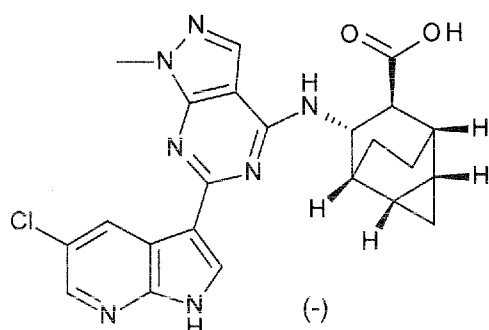
15 1 (+ or -H₂S,4R,6S,7S)-Methyl 7-((6-(5-chloro-1 -tosyl- 1H-pyrrolo[2,3-b]pyridin-3-yl)- 1-methyl- 1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S, 7S)-methyl 7-((6-chloro-1 -methyl-1 H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 691 μmol) and Pd(PPh₃)₄ (79.8 mg, 69.1 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (481 mg, 435 μL, 829 μmol) and the resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above mixture, were then added 5-chloro-3-iodo-1 -tosyl-1 H-pyrrolo[2, 3-b]pyridine (448 mg, 1.04

mmol) and $\text{Pd}(\text{PPh}_3)_4$ (79.8 mg, 69.1 μmol) in dioxane (10 mL). The resulting reaction mixture was stirred at 145 °C for an additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (13 mg, 2.98% yield) as an off-white oil. MS: 632.1 $[\text{M}+\text{H}]^+$.

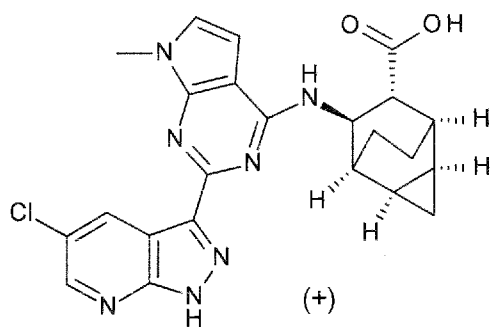
[B] (-)-(1R,2S,4R,5S,6S,7S)-7-((6-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



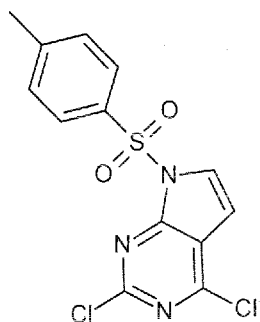
A mixture of (+ or -)-(2S,4R,6S,7S)-methyl 7-((6-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (60 mg, 94.9 μmol) and lithium hydroxide hydrate (7.97 mg, 190 μmol) in THF/H₂O (20 mL, 1:1) was stirred at room temperature for 16 h. After solvent was removed under reduced pressure, the residue was dissolved in TEA (10 mL) and stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the solvent was evaporated and the residue was purified by prep-HPLC to afford the title compound (28 mg, 62.3% yield) as a white solid. MS: 464.2 $[\text{M}+\text{H}]^+$. ¹H NMR (400 MHz, MeOH-d₄) δ 8.92 (d, J=2.32 Hz, 1H), 8.34 (s, 1H), 8.10 (d, J=2.20 Hz, 1H), 8.02 (s, 1H), 4.45 (d, J=4.16 Hz, 1H), 3.93 (s, 3H), 2.46 (d, J=11.13 Hz, 2H), 2.33 (s, 1H), 1.61-1.82 (m, 3H), 1.51 (d, J=11.98 Hz, 1H), 1.00-1.09 (m, 1H), 0.82-0.90 (m, 2H), 0.40 (q, J=8.27 Hz, 1H).

Example 155

(+)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

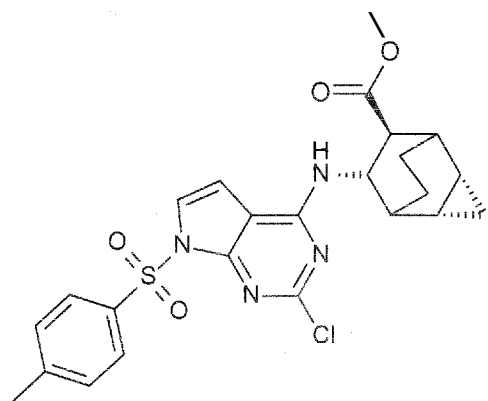


[A1] 2,4-Dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine



A mixture of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (20 g, 106 mmol), Cs_2CO_3 (52 g, 160 mmol) and 4-toluenesulfonyl chloride (26.3 g, 138 mmol) in DMF (80 mL) was stirred at room temperature for 4 h. The reaction mixture was poured into water and the suspension was collected by filtration to afford a crude product (32 g, 79.5 mmol, 74.7 % yield) as a white solid. MS: 342.2 [M+Hf].

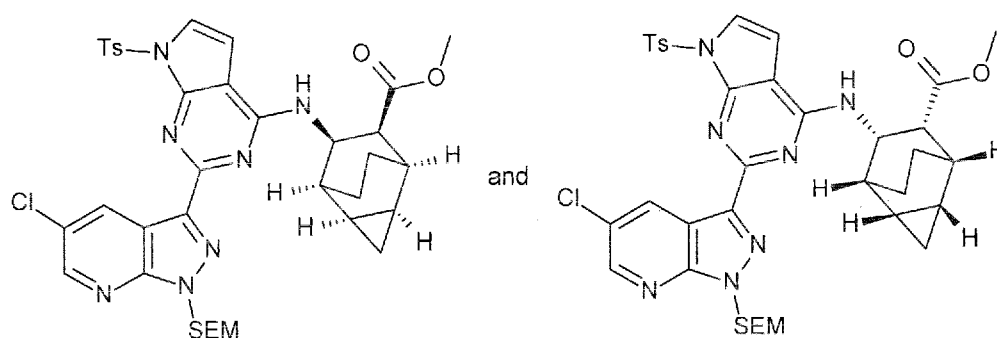
10 [B1] (rac)-(2S,4R,6S,7S)-Methyl 7-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)thicyclo[3.2.2]nonane-6-carboxylate



A mixture of 2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (13.5 g, 39.4 mmol), rac-(2S,4R,6S,7S)-methyl 7-aminotricyclo[3.2.2]nonane-6-carboxylate (7 g, 35.8 mmol) and N-ethyl-N-isopropylpropan-2-amine (5.56 g, 43 mmol) in THF (250 mL) was stirred at

60 °C for 16 h. After solvent was evaporated, the crude product was purified by silica-gel chromatography (EA:PE=0 to 30%) to afford the title compound (8.9 g, 49.6 % yield) as a white solid. MS: 501.1 [M+H]⁺.

- 5 [C] (+ or -) (1S,2S,4R,5R,6S,7S)-Methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (- or +)-(1R,2R,4S,5S,6R,7R)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



10

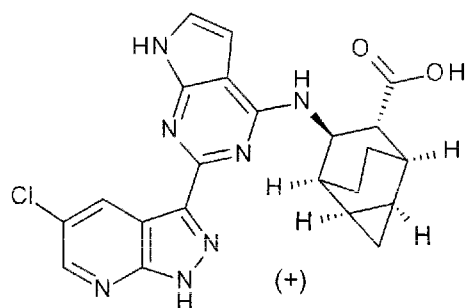
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To a stirred mixture solution of rac-(1S,2S,4R,5R,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (400 mg, 798 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (556 mg, 958 μmol) and the resulting reaction mixture was stirred at 125 °C for 2 h before being cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (491 mg, 1.2 mmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) and the reaction mixture solution was stirred at 145 °C for another 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford a racemic mixture of the product (50 mg, 13.4% yield) as a yellow oil. MS: 478.2 [M+H]⁺. Subsequent chiral separation by SFC afforded two enantiomeric title compounds as white solids.

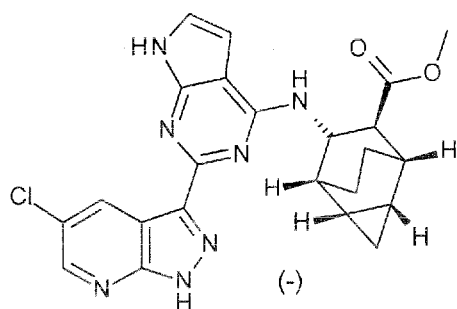
- [D] (+)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A mixture solution of (+ or -)-(1R,2R,4S,5S,6R,7R)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (488 mg, 652 μmol) and
 5 LiOH.H₂O (274 mg, 6.52 mmol) in THF/MeOH (1:1, 10 mL) was stirred at 50 °C for 10 h. After solvent was evaporated, the residue was re-dissolved in TFA (15 mL) and the mixture was stirred at room temperature for 24 h. The solvent was evaporated and the crude product was purified by silica-gel chromatography to afford the title compound (50 mg, 17 % yield) as a white solid. MS: 450.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.00 (s, 1H),
 10 8.62 (d, J=2.08 Hz, 1H), 7.18-7.54 (m, 1H), 6.95 (br d, J=3.18 Hz, 1H), 4.77 (br d, J=4.52 Hz, 1H), 2.76 (br s, 1H), 2.54-2.70 (m, 2H), 1.79-2.04 (m, 2H), 1.71 (br d, J=6.11 Hz, 2H), 1.20 (br s, 1H), 0.99 (br d, J=5.14 Hz, 2H), 0.58 (br d, J=6.60 Hz, 1H).

Example 156

15 (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid

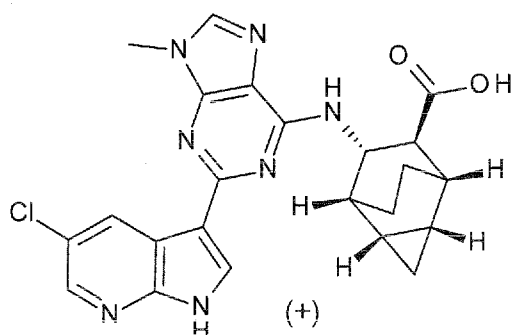


A mixture solution of (+ or -) (1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (488mg, 652 μmol) and
 20 LiOH.H₂O (274 mg, 6.52 mmol) in THF/MeOH (1:1, 10 mL) was stirred at 50 °C for 10 h. After solvent was evaporated, the residue was re-dissolved in TFA (15 mL) and the mixture was stirred at room temperature for 24 h. The solvent was evaporated and the crude

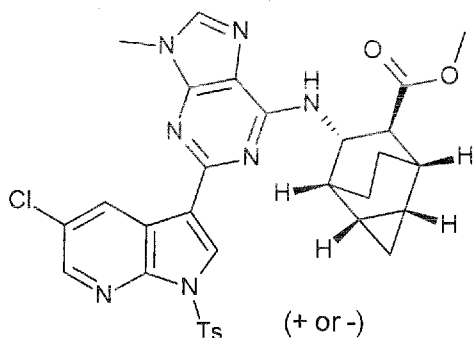
product was purified by silica-gel chromatography to afford the title compound (60 mg, 20.5 % yield) as a white solid. MS: 450.1. $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 9.00 (s, 1H), 8.62 (d, $J=2.08$ Hz, 1H), 7.18-7.54 (m, 1H), 6.95 (br d, $J=3.18$ Hz, 1H), 4.77 (br d, $J=4.52$ Hz, 1H), 2.76 (br s, 1H), 2.54-2.70 (m, 2H), 1.79-2.04 (m, 2H), 1.71 (br d, $J=6.11$ Hz, 2H), 1.20 (br s, 1H), 0.99 (br d, $J=5.14$ Hz, 2H), 0.58 (br d, $J=6.60$ Hz, 1H).

Example 157

(+)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



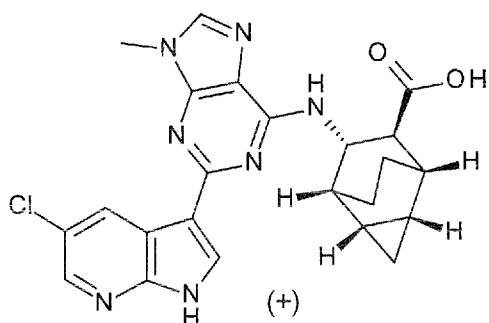
(+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate 151/stepA, 250 mg, 691 μ mol) and $Pd(PPh_3)_4$ (100 mg, 86.5 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (442 mg, 400 μ L, 762 μ mol) at room temperature and the resulting reaction mixture solution was stirred at 145 °C for 1 h under microwave heating. After cooling to room temperature, to the above stirred mixture solution in dioxane (16 mL) were added 5-chloro-3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (448 mg, 1.04 mmol) and $Pd(PPh_3)_4$ (100 mg, 86.5 μ mol), and the reaction mixture solution was stirred at 125 °C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was

poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient, then 0-5% DCM-MeOH gradient) to afford the title compound (80 mg, 18.3% yield) as a yellow oil. MS: 632.1 ($\text{M}+1$).

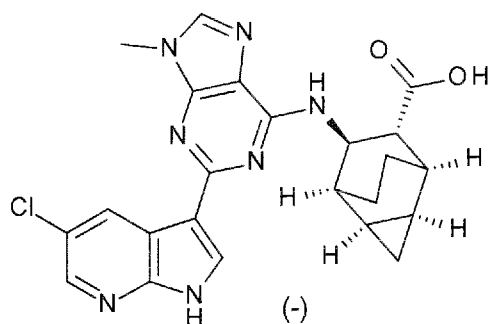
(+)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



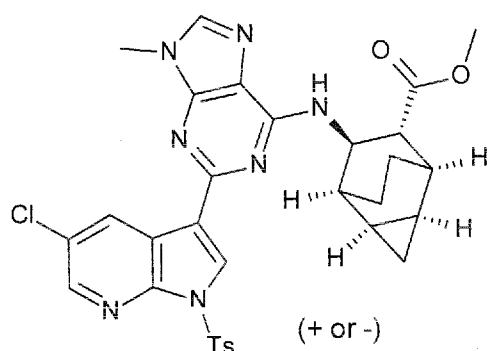
To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (80 mg, 127 μmol) in THF/MeOH (1:1, 10 mL) was added LiOH (30.3 mg, 1.27 mmol) dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with ethyl acetate (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was then purified by prep-HPLC to afford the title compound (23 mg, 39.2% yield) as a white foam. MS: 464.1 ($\text{M}+\text{Hf}$). ^1H NMR (400 MHz, MeOH-d_4) δ 8.85-8.89 (m, 1H), 8.52-8.57 (m, 1H), 8.33-8.40 (m, 1H), 8.23-8.28 (m, 1H), 4.48-4.55 (m, 1H), 3.96 (s, 3H), 2.62-2.67 (m, 1H), 2.56-2.61 (m, 1H), 2.46-2.53 (m, 1H), 1.82-1.92 (m, 2H), 1.62-1.74 (m, 2H), 1.16-1.27 (m, 1H), 0.99-1.10 (m, 1H), 0.82-0.91 (m, 1H), 0.58-0.68 (m, 1H).

Example 158

(-)-(1S,2R,4S,5R,6R,7R)-7-((2-(S-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-S-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

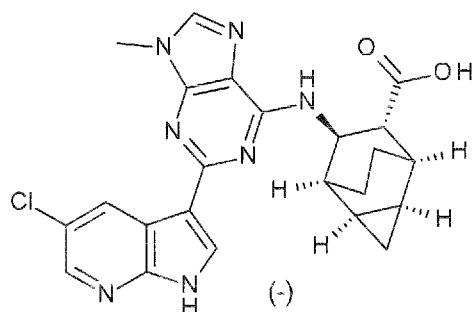


fA] (+ or -)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((2-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



- 5 Similar to the synthesis of example 157/step A, (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate 151/step A, 250 mg, 691 μ mol) was used to afford the title compound (80 mg, 18.3% yield) after silica gel flash chromatography purification as a yellow oil. MS: 632.1 (M+1)⁺.

- 10 IB 1 (-)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



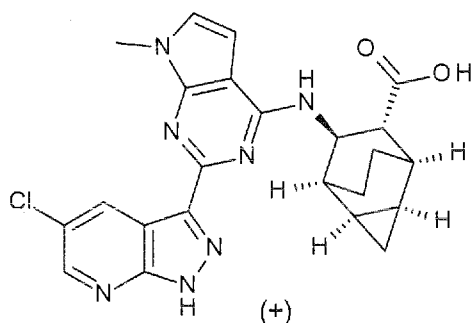
- Similar to the synthesis of example 157/step B, (+ or -)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-9-methyl-9H-purin-6-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (80 mg, 127 μ mol) was used to afford the title compound (23 mg, 39.2% yield) after prep-HPLC purification as a white foam. MS:

464.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.79-8.86 (m, 1H), 8.50-8.58 (m, 1H), 8.34-8.43 (m, 1H), 8.21-8.28 (m, 1H), 4.45-4.54 (m, 1H), 4.00 (s, 3H), 2.61-2.66 (m, 1H), 2.56-2.61 (m, 1H), 2.46-2.53 (m, 1H), 1.80-1.91 (m, 2H), 1.63-1.75 (m, 2H), 1.17-1.25 (m, 1H), 1.00-1.09 (m, 1H), 0.81-0.89 (m, 1H), 0.57-0.68 (m, 1H).

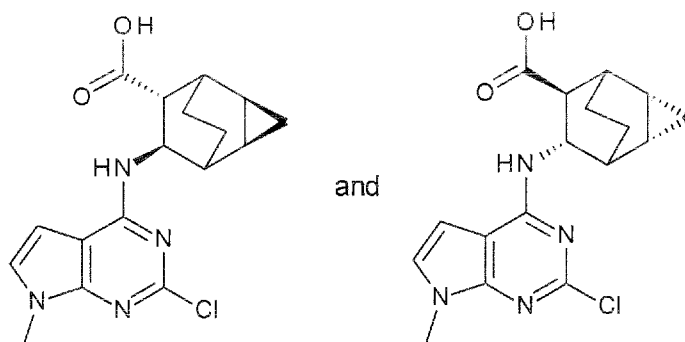
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Example 159

(+)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



10 rac (+ or -) (2S,4R,6S,7S)-Methyl 7-((2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (+ or -) (2R,4S,6R,7R)-methyl 7-((2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



15 (+ or -)

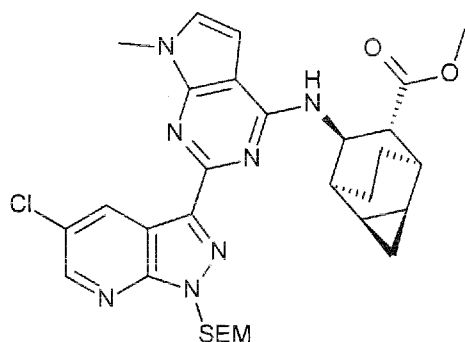
(- or +)

A mixture solution of 2,4-dichloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (5.69 g, 28.2 mmol), rac-(2S,4R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (5 g, 25.6 mmol) and DIPEA (3.97 g, 30.7 mmol) in THF (5mL) was stirred at 60 °C for 16 h. After solvent was evaporated, the residue was purified by silica-gel chromatography (EtOAc: petroleum ether = 0 to 60%) to afford the racemic mixture of the title compound (6 g, 16.6 mmol, 64.9 % yield). MS: 361.2 [M+H]⁺. Second purification by silica-gel chromatography then afforded both (+ or -) (2S,4R,6S,7S)-methyl 7-((2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-

20

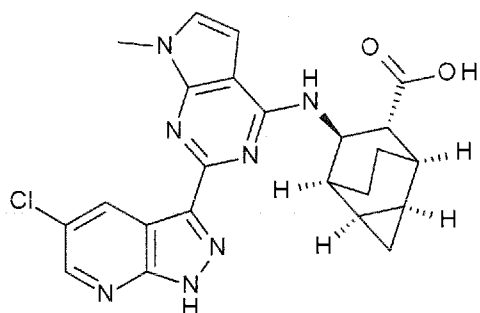
yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate and (+ or -) (2R,4S,6R,7R)-methyl 7-((2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate as single enantiomers. MS: 361.2 [M+H]⁺.

- 5 1B 1 (+ or -) (1S,2R,4S,5R,6R,7R)-Methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



- To a stirred mixture solution of (+ or -) (1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (300 mg, 831 μ mol) and Pd(PPh₃)₄ (100 mg, 86.5 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (579 mg, 998 μ mol) and the resulting reaction mixture solution was stirred at 125 °C for 2 h before being cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) was added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (511 mg, 1.25 mmol) and Pd(PPh₃)₄ (100 mg, 86.5 μ mol) and the reaction mixture solution was stirred at 145 °C for an additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (50 mg, 13.4% yield) as a yellow oil. MS: 609.2 [M+H]⁺.

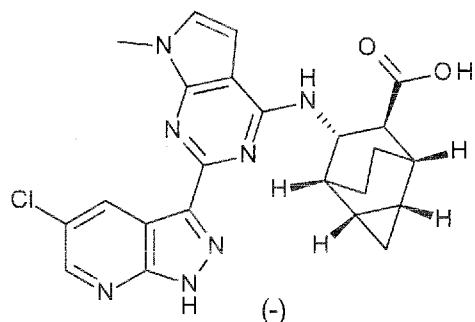
- 25 [C] (+)-(1S,2R,4S,5R,6R,7R)-7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



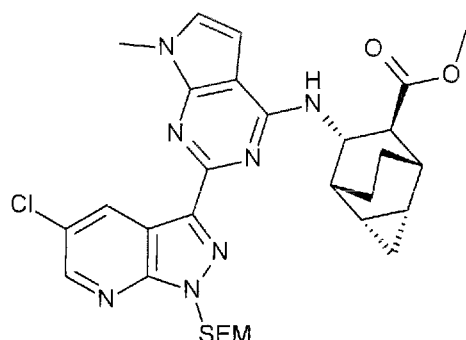
The mixture of (+ or -)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-(5-chloro-1-((2-trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (200mg, 329 μ mol) and
 5 LiOH.H₂O (138 mg, 3.29 mmol) in THF (5 ml) and MeOH (5 mL) was stirred at 50 °C for 10 h. Solvent was then evaporated and the residue was directly used in the next step. The residue was redissolved in TFA (15 mL) and the mixture was stirred at room temperature for 24 h. Solvent was then evaporated and the residue was purified by silica-gel chromatography to afford the title compound (45 mg, 97 μ mol, 29.5 % yield) as a white solid. MS: 464.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.00 (d, J=2.45 Hz, 1H), 8.43 (d, J=2.45 Hz, 1H), 6.98 (d, J=3.42 Hz, 1H), 6.61 (d, J=3.42 Hz, 1H), 4.66 (br d, J=6.36 Hz, 1H), 3.66-3.86 (m, 3H), 2.50-2.59 (m, 2H), 2.42 (br d, J=2.20 Hz, 1H), 1.80-1.93 (m, 1H), 1.58-1.74 (m, 2H), 1.45-1.58 (m, 1H), 0.98-1.07 (m, 1H), 0.89-0.98 (m, 1H), 0.80 (td, J=4.14, 7.98 Hz, 1H), 0.35 (q, J=7.70 Hz, 1H).

Example 160

(-)-{1R,2S,4R,5S,6S,7S)-7-((2-{5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid

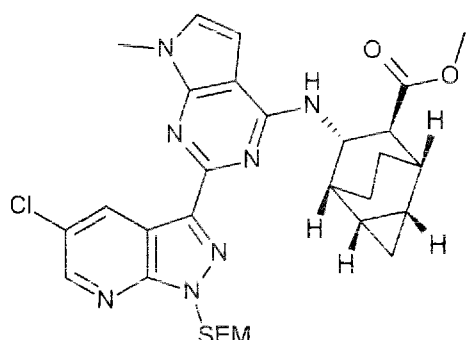


[A] (+ or -) (1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate



Similar to the synthesis of example 159/step B, (+ or -) (1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (300 mg, 831 μ mol) was used to afford the title compound (50 mg, 13.4 yield) after silica gel flash chromatography purification as a yellow oil. MS: 609.2 $[M+H]^+$.

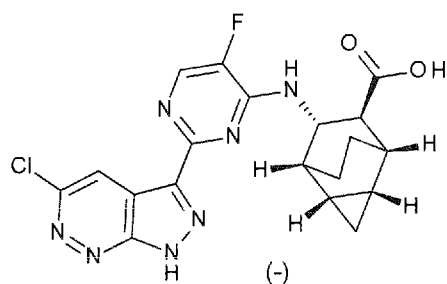
Ex 1 (-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid



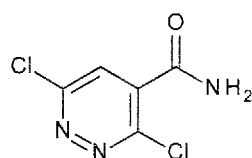
Similar to the synthesis of example 159/step C, (+ or -) (1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (300 mg, 493 μ mol) was used to afford the title compound (60 mg, μ mol, 26.2 % yield) after silica gel flash chromatography purification as a white solid. MS: 464.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 9.00 (d, $J=2.45$ Hz, 1H), 8.43 (d, $J=2.45$ Hz, 1H), 6.98 (d, $J=3.42$ Hz, 1H), 6.61 (d, $J=3.42$ Hz, 1H), 4.66 (br d, $J=6.36$ Hz, 1H), 3.66-3.86 (m, 3H), 2.50-2.59 (m, 2H), 2.42 (br d, $J=2.20$ Hz, 1H), 1.80-1.93 (m, 1H), 1.58-1.74 (m, 2H), 1.45-1.58 (m, 1H), 0.98-1.07 (m, 1H), 0.89-0.98 (m, 1H), 0.80 (td, $J=4.14, 7.98$ Hz, 1H), 0.35 (q, $J=7.70$ Hz, 1H).

Example 161

(-)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid

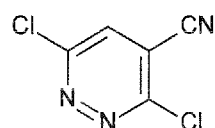


[A] 3,6-Dichloropyridazine-4-carboxamide

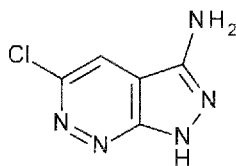


To a stirred solution of 3,6-dichloropyridazine-4-carboxylic acid (10 g, 52 mmol) in DCM (100 mL) was added $(\text{COCl})_2$ (13.2 g, 104 mmol) and DMF (1 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. After solvent was removed under reduced pressure and the residue was re-dissolved in THF (20 mL), to the above mixture was added an aqueous solution of NH_4OH (100 mL) at 0 °C, and the mixture solution was stirred at 0 °C for 0.5 h. After TLC (petroleum ether: EtOAc=1 : 1) showed completion of the reaction, the mixture solution was extracted with EtOAc (100 mL three times). Combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product (6.67 g, 67% yield) as a white solid. This crude product was used directly in the next step without further purification.

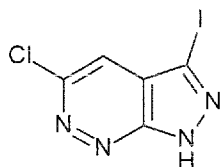
[B] 3,6-Dichloropyridazine-4-carbonitrile



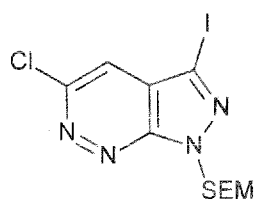
To a stirred solution of 3,6-dichloropyridazine-4-carboxamide (400 mg, 2.08 mmol) in DMF (10 mL) was added cyanuric chloride (231 mg, 1.25 mmol) and the resulting reaction mixture was stirred at room temperature for 15 h. After TLC showed the completion of reaction, the reaction was quenched by the addition of saturated aqueous solution of NaHCO_3 (40 mL). The mixture solution was extracted with EtOAc (50 mL), and the combined organic were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give the crude product (400 mg) as a yellow oil. This crude product was used directly in the next step without further purification.

id 5-Chloro-1 H-pyrazolo[4,3-elf1 ,2.4]triazin-3-amine

To a stirred solution of 3,6-dichloropyridazine-4-carbonitrile (100 mg, 0.651 mmol) in EtOH (10 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (0.5 mL) and the resulting reaction mixture was stirred at 90 °C for 1 h. After TLC showed completion of the reaction, the solvent was removed under reduced pressure. The residue was re-suspended in water (5 mL) and filtered. The solid was collected and washed with additional water (1 mL) and dried under vacuo to give the crude product (100 mg) as a yellow solid. This crude product was used directly in the next step without further purification.

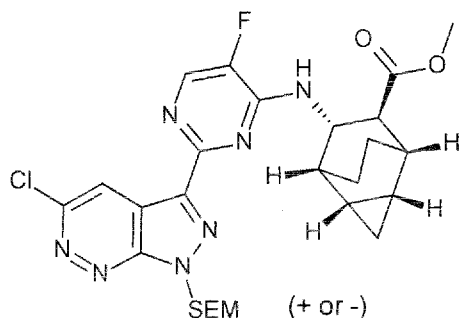
[D] 5-Chloro-1 H-pyrazolo[3,4-clpyridazin-3-amine

To the stirred mixture solution of 5-chloro-1H-pyrazolo[3,4-c]pyridazin-3-amine (100 mg, 0.586 mmol) and I_2 (446 mg, 1.758 mmol) in MeCN (10 mL) was added isopentyl nitrite (192 mg, 1.641 mmol) at 80 °C and the resulting mixture was stirred at 80 °C for 1 h. After TLC (petroleum ether:EtOAc = 3:1) showed completion of the reaction, a saturated aqueous solution of Na_2SO_3 was introduced to quench the reaction. The mixture solution was extracted with EtOAc (20 mL three times), and the combined organic were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give the crude product (100 mg) as a yellow solid. This crude product was used directly in the next step without further purification.

[E] 5-Chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-clpyridazine

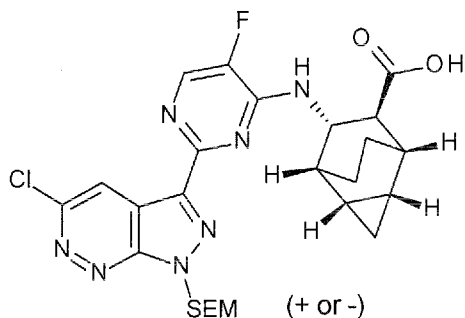
To a stirred solution of 5-chloro-3-iodo-1 H-pyrazolo[3,4-c]pyridazine (2.0 g, 7.13 mmol) in DMF (20 mL) was added NaH (342 mg, 8.56 mmol) at 0 °C and the resulting mixture solution was stirred at 0 °C for 1 h. SEMCI (1.78 g, 10.7 mmol) was added to the reaction mixture dropwise and the mixture solution was stirred at 0 °C for additional 1 h. After TLC (petroleum ether: EtOAc=3: 1) showed the completion of reaction, the reaction was quenched with water (60 mL). The reaction mixture was extracted with EtOAc (50 mL x3). Combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc =50:1 to 30:1) to afford the title compound (2.10 g, 71.7% yield) as a white solid.

FF1 (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (intermediate 74/step A, 250 mg, 767 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (442 mg, 400 μL, 762 μmol) at room temperature. The resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-c]pyridazine (473 mg, 1.15 mmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) and the resulting reaction mixture solution was stirred at 145 °C for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (130 mg, 29.5% yield) as a yellow oil. MS: 574.1 (M+1)⁺.

[G] (+ or -)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-Pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

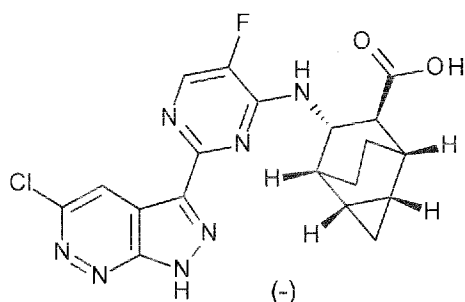


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To a stirred mixture solution of (+ or -)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (130 mg, 226 μ mol) in THF (5 mL) and MeOH (5 mL) was added LiOH (54.2 mg, 2.26 mmol) dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL), and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product. This crude product was used directly in the next step without further purification. MS: 560.1 (M+H)⁺.

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[H] (-)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



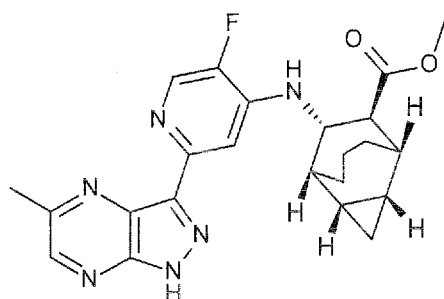
To a stirred mixture solution of (+ or -)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-chloro-1 -((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (130 mg, 232 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. Solvent was removed under reduced

20

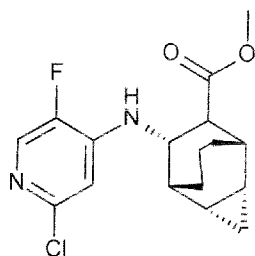
pressure and the residue was purified by prep-HPLC to afford the title compound (25 mg, 25.1% yield) as a white foam. MS: 430.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.79 (s, 1H), 8.15-8.20 (m, 1H), 4.69-4.75 (m, 1H), 2.73-2.80 (m, 1H), 2.61-2.67 (m, 1H), 2.49-2.57 (m, 1H), 1.80-1.98 (m, 2H), 1.61-1.77 (m, 2H), 1.11-1.20 (m, 1H), 0.97-1.05 (m, 1H), 0.88-0.97 (m, 1H), 0.41-0.52 (m, 1H).

Example 162

(rac)-(1S,2R,4S,5R,9S,10S)-10-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid

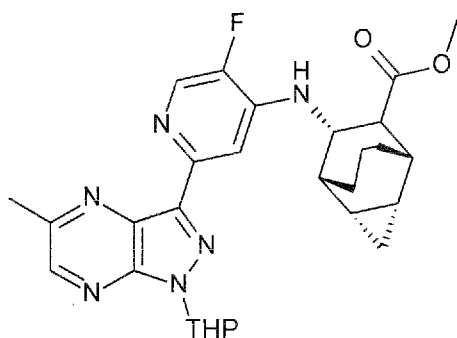


[A] (rac)-(9S,10S)-Methyl 10-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



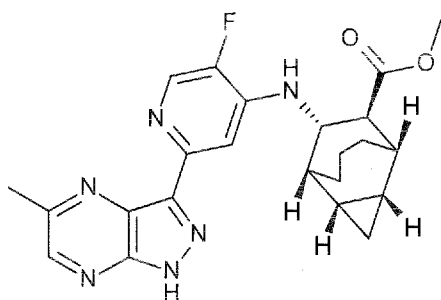
To a mixture solution of rac-(9S,10S)-methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (97.6 mg, 466 μmol) and 2-chloro-5-fluoro-4-iodo-pyridine (120 mg, 466 μmol) in dioxane (5 mL) was added Xantphos (22.5 mg, 38.8 μmol), Pd₂(dba)₃ (35.6 mg, 38.8 μmol) and Cs₂CO₃ (253 mg, 777 μmol) under N₂ and the resulting reaction mixture was stirred at 100 °C for 30 min. After cooling to room temperature, the solvent was removed under reduced pressure. The left over crude product was then purified by silica gel flash chromatography (EtOAc; petroleum ether from 0 to 50%) to afford the title compound as a white solid (110.9 mg, 70.4% yield). MS: 339.1 [M+H]⁺

(rac)-(1S,2R,4S,5R,9S,10S)-Methyl 10-((5-fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



a mixture solution of rac-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylate (250 mg, 738 μmol), 1,1,1,2,2,2-hexabutyldistannane (514 mg, 885 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in dioxane (5 mL) was heated at 125 °C for 3 h. After cooling to room temperature, 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (330 mg, 959 μmol), $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) and dioxane (5 mL) were added to the reaction mixture and heated at 145 °C for additional 50 min. After cooling to room temperature, solvent was removed under reduced pressure and the crude product was purified by silica gel flash chromatography (EtOAc:petroleum ether = 0 to 80%) to afford the title compound (60 mg, 15.6 % yield) as a yellow oil. MS: 521.2 $[\text{M}+\text{H}]^+$.

[c] (rac)-(1S,2R,4S,5R,9S,10S)-10-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylic acid



15

To a stirred solution of rac-(1S,2R,4S,5R,9S,10S)-methyl 10-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylate (60 mg, 115 μmol) in THF (5 mL) and water (5 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (24.2 mg, 576 μmol) and the resulting reaction mixture was stirred at room temperature for 16 h. Solvent was then removed under reduced pressure, and the residue was re-dissolved in TFA (10 mL) and stirred at room temperature for 10 h. After solvent was removed in vacuo, the crude product was purified by prep-HPLC to afford the title compound (5 mg, 10.3 % yield) as a white solid. MS: 423.1 $[\text{M}+\text{H}]^+$. ^1H

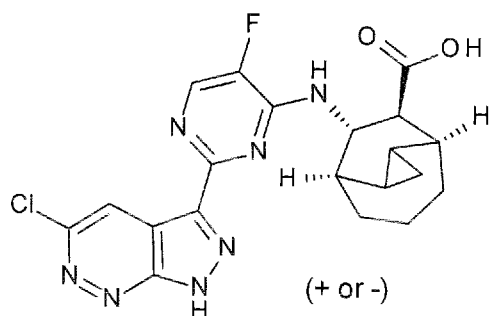
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NMR (400 MHz, MeOH-d₄) δ 8.58 (s, 1H), 8.12-8.37 (m, 2H), 4.51 (br d, J=6.97 Hz, 1H), 2.94 (dd, J=4.40, 6.85 Hz, 1H), 2.83-2.89 (m, 1H), 2.79 (s, 3H), 2.44-2.60 (m, 2H), 1.85-2.02 (m, 3H), 1.78 (br s, 2H), 1.26 (tt, J=3.97, 8.31 Hz, 1H), 1.09-1.18 (m, 1H), 0.97-1.08 (m, 1H), 0.56-0.69 (m, 1H).

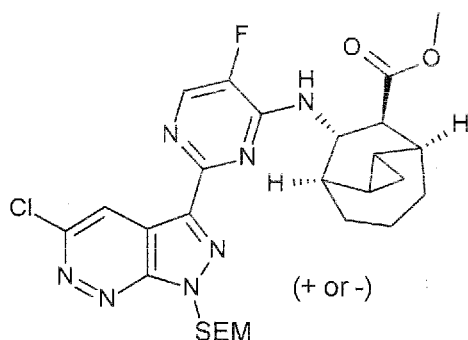
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Example 163

(+ or -)-{1S,5R,9S,10S}-10-[(2-(5-chloro-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino]tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



10 1 (+ or -)-(1S,5R,9S,10S)-Methyl 10-[(2-(5-chloro-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino]tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate

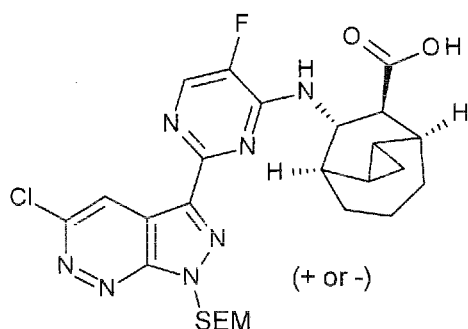


To a stirred mixture solution of (-)-(1S,5R,9S,10S)-methyl 10-[(2-chloro-5-fluoropyrimidin-4-yl)amino]tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (250 mg, 736 μ mol) and Pd(PPh₃)₄ (85 mg, 73.6 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (512 mg, 464 μ mol, 883 μ mol) at room temperature. The resulting reaction mixture solution was then stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) was then added 5-chloro-3-iodo-1-[(2-(trimethylsilyl)ethoxy)methyl]-1H-pyrazolo[3,4-c]pyridazine (intermediate 161/step E, 453 mg, 1.1 mmol) and Pd(PPh₃)₄ (85 mg, 73.6 μ mol). The reaction mixture solution was stirred at 145 °C for another 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice).

The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (150 mg, 34.7% yield) as a yellow oil. MS: 588.1 (M+H)⁺.

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1B] (+ or -)-(1S,5R,9S,10S)-10-((2-(5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid

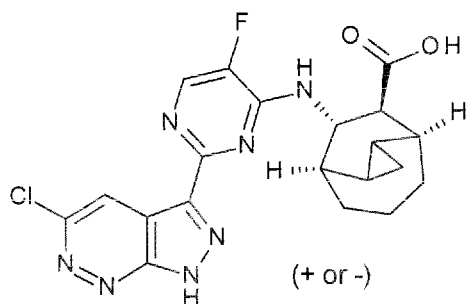


10 To a stirred mixture solution of (+ or -)-(1S,5R,9S,10S)-methyl 10-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (150 mg, 255 pmol) in THF (5 mL) and MeOH (5 mL) was added LiOH (61.1 mg, 2.55 mmol) dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before it was diluted with

15 water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded, and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product. MS: 574.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

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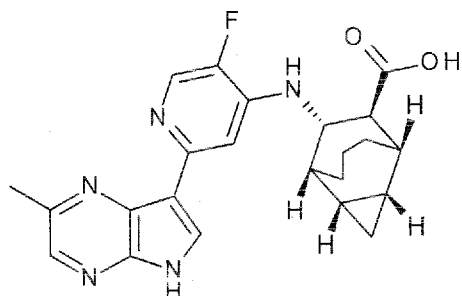
[Cl (+ or -)-(1S,5R,9S,10S)-10-((2-(5-Chloro-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



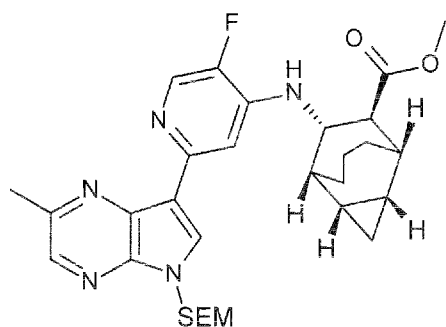
To a stirred mixture solution of (+ or -)-(1S,5R,9S, 10S)-10-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid (123 mg, 214 pmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. Solvent was removed under reduced pressure, and the crude product was purified by prep-HPLC to afford the title compound (30 mg, 31.5% yield) as a white foam. MS: 444.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.50-8.84 (m, 1H), 8.06-8.30 (m, 1H), 5.07-5.24 (m, 1H), 2.80-2.86 (m, 1H), 2.72-2.78 (m, 1H), 2.38-2.47 (m, 1H), 2.01-2.10 (m, 1H), 1.64-1.91 (m, 5H), 1.09-1.19 (m, 1H), 1.02-1.08 (m, 1H), 0.86-0.95 (m, 1H), 0.49-0.63 (m, 1H).

Example 164

(rac)-(1S,2R,4S,5R,9S,10S)-10-((5-Fluoro-2-(2-methyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



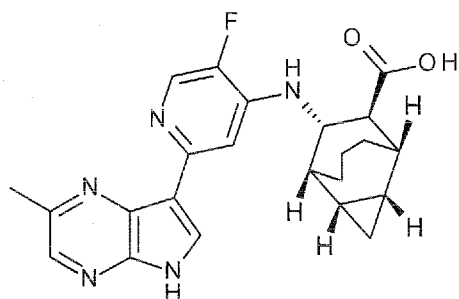
[A] (rac)-(1S,2R,4S,5R,10S)-Methyl 10-((5-fluoro-2-(2-methyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



A stirred mixture solution of rac-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (250 mg, 738 μmol), 1,1,1,2,2,2-hexabutyldistannane (514 mg, 885 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (10 ml) was heated at 125 °C for 3 h. After cooling to room temperature, 7-bromo-2-methyl-5-

((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine (328 mg, 959 μmol), $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) and dioxane (10 mL) was added and the resulting reaction mixture was heated at 145 °C for an additional 80 min. After cooling to room temperature, the solvent was evaporated under reduced pressure. The left over crude product was then purified by silica gel flash chromatography (EtOAc:petroleum ether =0 to 80%) to afford the title compound (50 mg, 12 % yield) as a yellow oil. MS: 566.1 $[\text{M}+\text{H}]^+$.

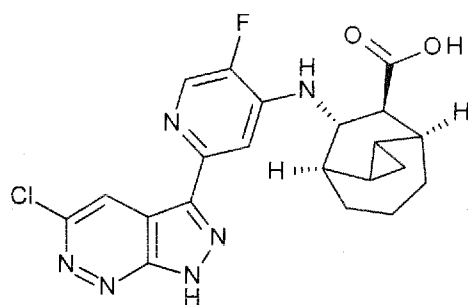
IB1 (rac)-(1S,2R,4S,5R,9S,10S)-10-((5-Fluoro-2-(2-methyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



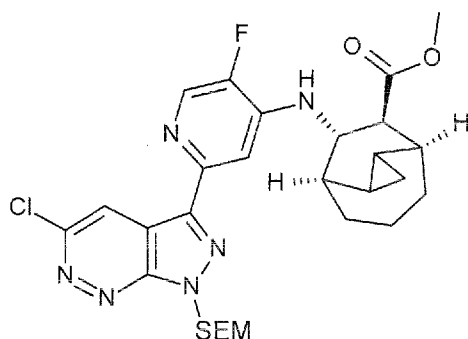
To a stirred mixture solution of rac-(1S,2R,4S,5R,10S)-methyl 10-((5-fluoro-2-(2-methyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (60 mg, 106 μmol) in THF (5 mL) and water (5 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (22.3 mg, 530 μmol) and the resulting reaction mixture solution was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was re-dissolved in TFA (10 mL) and stirred at room temperature for 10 h. After solvent was evaporated in vacuo, the crude product was then purified by prep-HPLC to afford the title compound (10 mg, 22.4% yield) as a white solid. MS: 422.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, MeOH-d_4) δ 8.41 (s, 1H), 8.24 (s, 1H), 8.18 (d, $J=6.1$ Hz, 1H), 7.99 (d, $J=7.82$ Hz, 1H), 4.45 (br d, $J=6.60$ Hz, 1H), 2.84-2.90 (m, 1H), 2.75-2.82 (m, 1H), 2.62 (s, 3H), 2.44 (br s, 1H), 2.24-2.35 (m, 1H), 1.57-1.88 (m, 6H), 1.16 (tt, $J=4.10$, 8.25 Hz, 1H), 0.91-1.00 (m, 2H), 0.54 (dt, $J=6.05$, 7.79 Hz, 1H).

Example 185

(rac)-(1S,5R,9S,10S)-10-((2-(5-Chloro-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



[A] frac-(1S,5R,9S,10S)-Methyl 10-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2.4]decane-9-carboxylate

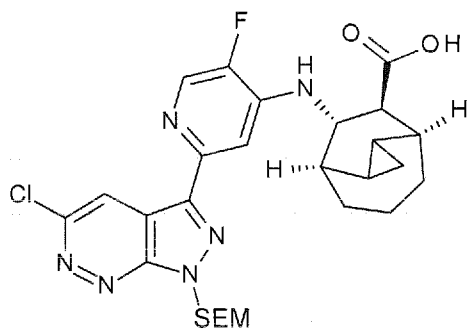


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To a stirred mixture solution of (rac)-(1S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2.4]decane-9-carboxylate (250 mg, 738 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (85.3 mg, 73.8 μmol , Eq: 0.1) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (514 mg, 465 μL , 885 μmol) and the resulting reaction mixture was stirred at 125 $^\circ\text{C}$ for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were added 5-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridazine (intermediate 161/step E, 455 mg, 1.11 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (85.3 mg, 73.8 μmol). The resulting reaction mixture solution was stirred at 145 $^\circ\text{C}$ for additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (70 mg, 16.2% yield) as a yellow oil. MS: 587.1 ($\text{M}+\text{H}$) $^+$

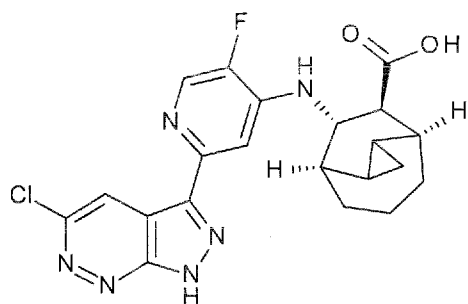
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[B] frac-(1S,5R,9S,10S)-10-((2-(5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2.4]decane-9-carboxylic acid



To a stirred mixture solution of (rac)-(1S,5R,9S,10S)-methyl 10-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (70 mg, 119 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (28.6 mg, 1.19 mmol) dissolved in water (5 mL). The resulting reaction mixture solution was stirred at room temperature for 12 h before was diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product. MS: 573.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

[C] (rac)-(1S,5R,9S,10S)-10-((2-(5-Chloro-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid

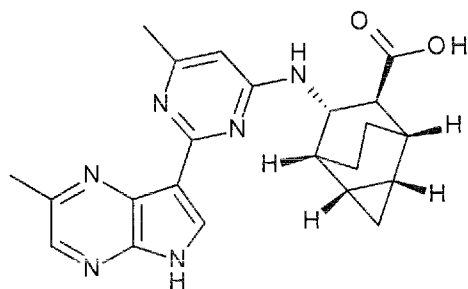


To a stirred mixture solution of (rac)-(1S,5R,9S,10S)-10-((2-(5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid (70 mg, 122 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. After solvent was removed under reduced pressure, the crude product was then purified by prep-HPLC to afford the title compound (18 mg, 33.3% yield) as a white foam. MS: 443.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.73-8.76 (m, 1H), 8.19-8.22 (m, 1H), 7.50-7.55 (m, 1H), 4.34-4.39 (m, 1H), 2.79-2.84 (m,

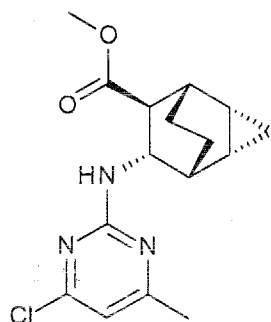
1H), 2.73-2.78 (m, 1H), 2.42-2.49 (m, 1H), 2.08-2.15 (m, 1H), 1.70-1.95 (m, 5H), 1.18-1.26 (m, 1H), 1.08-1.14 (m, 1H), 0.97-1.05 (m, 1H), 0.56-0.66 (m, 1H).

Example 166

- 5 (rac)-(1 R,2S,4R,5S,6S,7S)-7-((6-Methyl-2-(2-methyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

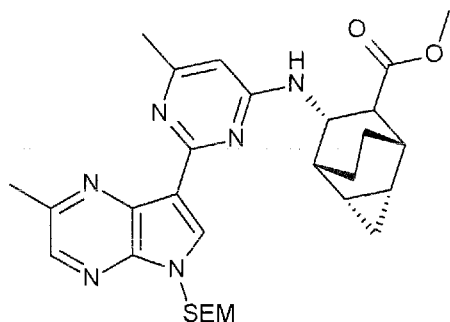


[A] (rac)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((4-chloro-6-methylpyrimidin-2-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



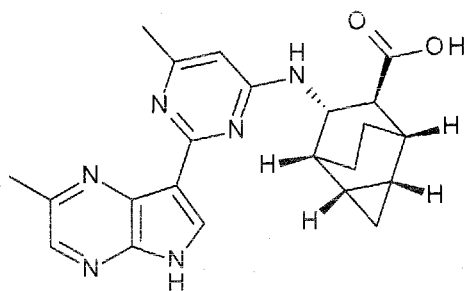
- 10 A mixture solution of rac-(1 R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1 g, 5.12 mmol), 2,4-dichloro-6-methylpyrimidine (1.25 g, 7.68 mmol) and DIPEA (1.99 g, 15.4 mmol) in THF (20 mL) was stirred at 65 °C for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residual crude product was then purified by silica gel flash chromatography (EtOAc/petroleum ether = 0 to 20%) to afford the title compound (300 mg, 18.2 % yield) as a yellow solid. MS: 322.2 [M+Hf].

- 20 [B] (rac)-(1 R,2S,4R,5S,7S)-Methyl 7-((6-methyl-2-(2-methyl-5-(di-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



A mixture solution of (1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (250 mg, 777 μmol), 1,1,1,2,2,2-hexabutyldistannane (541 mg, 932 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in dioxane (10 mL) was heated at 125 $^\circ\text{C}$ for 3 h. After cooling back to room temperature, 7-bromo-2-methyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine (346 mg, 1.01 mmol), $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) and dioxane (10 mL) were added to the above mixture. The resulting reaction mixture was re-heated at 145 $^\circ\text{C}$ for another 80 min. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue crude product was then purified by silica gel flash chromatography (EtOAc/petroleum ether = 0 to 80%) purification to afford the title compound (50 mg, 12 % yield) as a yellow solid. MS: 549.2 $[\text{M}+\text{H}]^+$.

[C] (rac)-(1R,2S,4R,5S,6S,7S)-7-((b-iyiethyi-2-(2-methyl-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylic acid

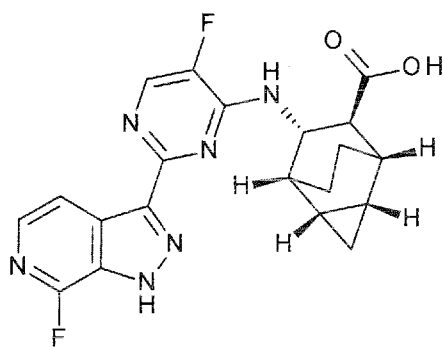


To a stirred mixture solution of rac-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-methyl-2-(2-methyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0.2,4]nonane-6-carboxylate (60 mg, 109 μmol) in THF (5 mL) and water (5 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (22.9 mg, 547 μmol) and the resulting reaction mixture was stirred at room temperature for 16 h. Afterwards, the solvent was evaporated under reduced pressure and the residue was re-dissolved in TFA (10 mL) and stirred at room temperature for an additional 10 h. The solvent was evaporated in vacuo and the residue

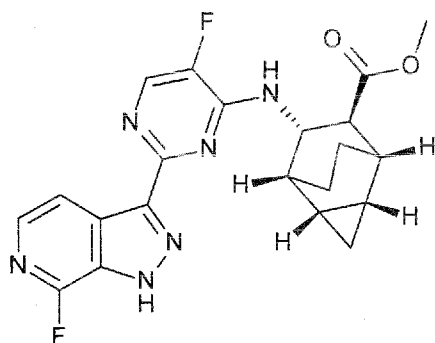
was purified by prep-HPLC to afford the title compound (25 mg, 56.5 % yield) as a white solid. MS: 405.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 9.12 (br s, 1H), 8.36 (s, 1H), 6.42 (s, 1H), 4.39 (br s, 1H), 2.76 (s, 3H), 2.53 (s, 3H), 2.40 (br s, 1H), 2.30 (br s, 2H), 1.70-1.96 (m, 3H), 1.52 (br s, 1H), 1.12 (dt, J=3.91, 8.74 Hz, 1H), 0.94 (br s, 1H), 0.75 (br s, 1H), 0.47 (br d, J=6.85 Hz, 1H).

Example 167

(rac)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-1 H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



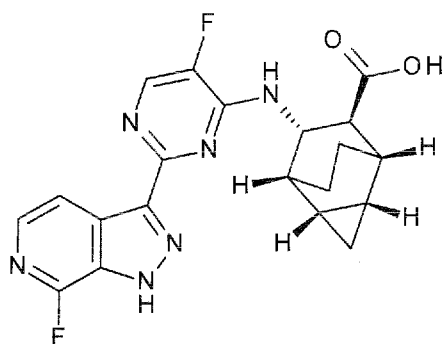
FAI (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(7-fluoro-1 H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of 7-fluoro-3-(5-fluoro-4-(methylsulfinyl)pyrimidin-2-yl)-1H-pyrazolo[3,4-c]pyridine (200 mg, 677 μmol) in THF (35 mL) was added (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (132 mg, 677 μmol) and DIPEA (263 mg, 355 μL, 2.03 mmol) at room temperature and the resulting reaction mixture solution was stirred at 70 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel

flash chromatography (0-40% EtOAc-hexane gradient) to afford the title compound (160 mg, 55.4% yield) as a yellow oil. MS: 427.1 (M+H)⁺.

(rac)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-1H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid



To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(7-fluoro-1H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (150 mg, 352 μmol) in THF (5 mL) and MeOH (5 mL) was added LiOH (84.2 mg, 3.52 mmol) pre-dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by prep-HPLC to afford the title compound (65 mg, 44.8% yield) as a white foam. MS: 413.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.21-8.25 (m, 1H), 8.12-8.17 (m, 1H), 7.83-7.91 (m, 1H), 4.70-4.74 (m, 1H), 2.77-2.82 (m, 1H), 2.58-2.65 (m, 1H), 2.44-2.52 (m, 1H), 1.73-1.81 (m, 2H), 1.55-1.64 (m, 2H), 1.02-1.11 (m, 1H), 0.76-0.90 (m, 2H), 0.33-0.43 (m, 1H).

Example 168

(rac)-(1S,2R,4S,5R,9S,10S)-10-((5-Fluoro-2-(7-fluoro-1H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2]nonane-9-carboxylic acid

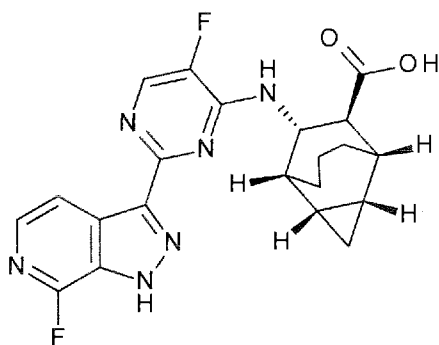
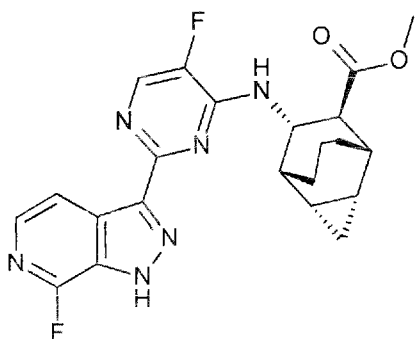


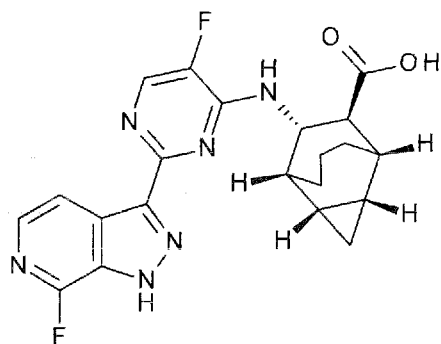
Table 1 (rac)-(1S,2R,4S,5R,9S,10S)-Methyl 10-((5-fluoro-2-(7-fluoro-1H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylate



- 5 To a stirred mixture solution of 7-fluoro-3-(5-fluoro-4-(methanesulfonyl)pyrimidin-2-yl)-1H-pyrazolo[3,4-c]pyridine (150 mg, 508 μ mol) in THF (35 mL) was added (1S,2R,4S,5R,9S,10S)-methyl 10-aminotricyclo[3.3.2.0^{2,4}]decane-9-carboxylate (128 mg, 610 μ mol) and DIPEA (197 mg, 1.52 mmol) at room temperature and the resulting reaction mixture solution was stirred at 70 °C for 12 h. After cooling to room temperature, the
- 10 reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (EtOAc: petroleum ether = 0 to 40%) to afford the title compound (100 mg, 44.7 % yield) as a yellow oil. MS: 441.1 [M+H]⁺.

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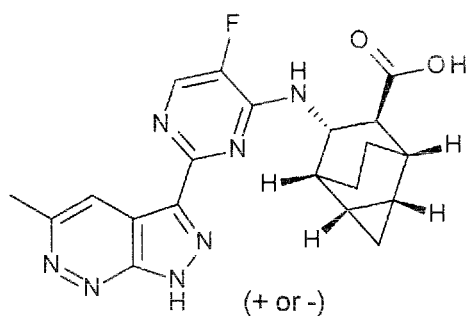
Table 1 (rac)-(1S,2R,4S,5R,9S,10S)-10-((5-Fluoro-2-(7-fluoro-1H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0^{2,4}]decane-9-carboxylic acid



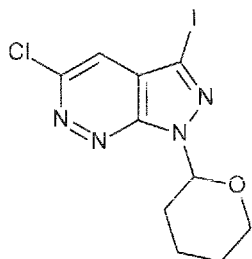
A mixture solution of rac-(1S,2R,4S,5R,9S,10S)-methyl 10-((5-fluoro-2-(7-fluoro-1 H-pyrazolo[3,4-c]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.3.2.0]decane-9-carboxylate (100 mg, 227 μ mol) and LiOH.H₂O (47.6 mg, 31.5 μ I, 1.14 mmol) in THF (10 mL) and water (10 mL) was stirred at room temperature for 16 h. Afterwards, the solvent was evaporated under reduced pressure and the residue crude product was purified by prep-HPLC to afford the title compound (20 mg, 20.7% yield) as a white solid. MS: 427.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.30 (br s, 1H), 8.03 (d, J=3.79 Hz, 1H), 7.70 (br d, J=5.01 Hz, 1H), 5.03 (br s, 1H), 2.66-2.84 (m, 2H), 2.40 (br s, 1H), 1.99-2.13 (m, 1H), 1.61-1.88 (m, 5H), 0.99-1.15 (m, 2H), 0.88 (td, J=4.29, 8.16 Hz, 1H), 0.46-0.56 (m, 1H).

Example 169

(+ or -)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-methyl-1 H-pyrazolo[3,4-c]pyridazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0]nonane-6-carboxylic acid

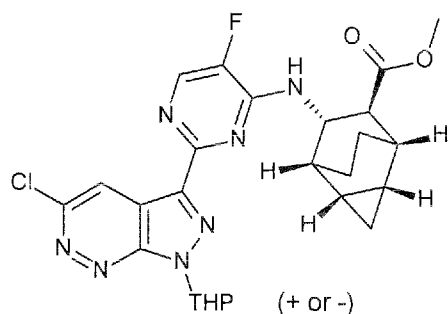


[A] 5-Chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-c]pyridazine



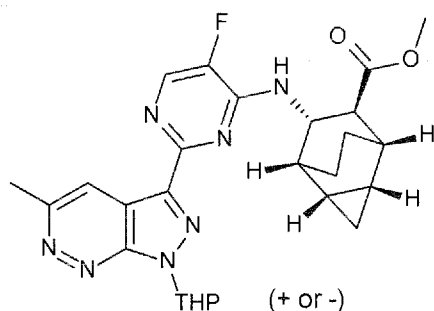
To a stirred mixture solution of 5-chloro-3-iodo-1 H-pyrazolo[3.4-c]pyridazine (Example 161/step D, 1.5 g, 5.35 mmol) and 3,4-dihydro-2H-pyran (2.25 g, 2.44 mL, 26.7 mmol) in toluene (5 mL) was added 2,2,2-trifluoroacetic acid (61 mg, 535 μmol) at room temperature and resulting reaction mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (1.2 g, 61.5% yield) as a white solid. MS: 365.1 (M+H)⁺.

[B] (+ or -H1 R.2S.4R.5S.6S.7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3.4-c]pyridazin-3-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (-)-(1 R.2S.4R.5S.6S.7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 767 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (88.7 mg, 76.7 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (534 mg, 483 μmol , 921 μmol) at room temperature and the resulting reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were added 5-chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3.4-c]pyridazine (420 mg, 1.15 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (88.7 mg, 76.7 μmol) and the reaction mixture solution was stirred at 145 °C for another 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (80 mg, 19.7% yield) as a yellow oil. MS: 528.1 (M+H)⁺.

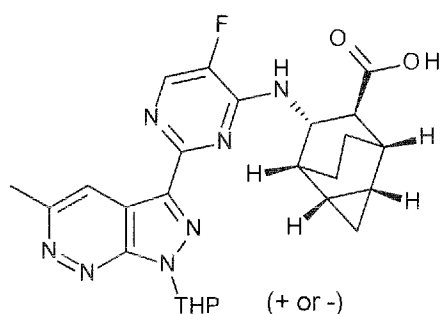
[C] (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



- 5 A stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (70 mg, 133 μ mol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (56.8 μ l, 199 μ mol), tetrakis(triphenylphosphine)palladium(0) (15.3 mg, 13.3 μ mol) and potassium carbonate (36.6 mg, 265 μ mol) in DMF (3 mL) was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product. MS: 508.1(M+H)⁺. This crude product was used directly in the next step without further purification.

15

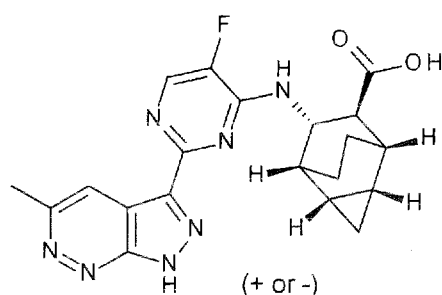
[D] (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



- 20 To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (40 mg, 78.8 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (18.9 mg, 788 μ mol) pre-dissolved in water (5

mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product. MS: 494.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

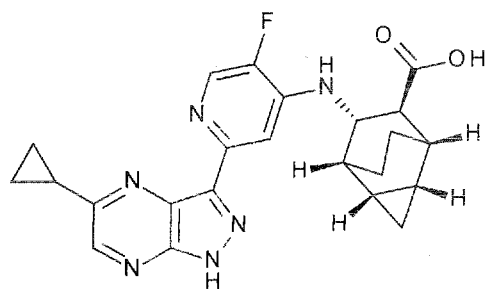
1E 1 (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1 H-Dvrazolo[3,4-clpvridazin-3-yl)pyrimidin-4-yl]amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



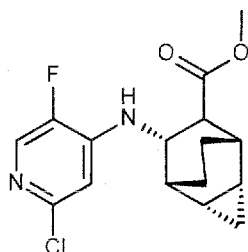
To a stirred mixture solution of (+ or -)-1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-c]pyridazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (70 mg, 142 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. After solvent was removed under reduced pressure, the crude product was purified by prep-HPLC to afford the title compound (1.6 mg, 2.8% yield) as a white foam. MS: 410.1(M+H)⁺.

Example 170

(rac)-1R,2S,4R,5S,6S,7S)-7-((2-(S-Cyclopropyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-S-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

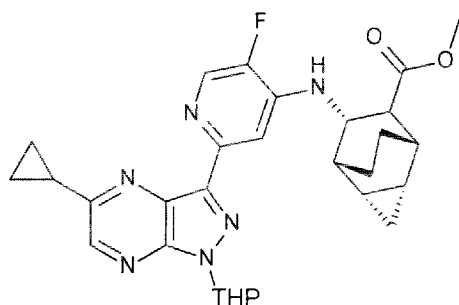


[A] rac-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a solution of rac-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (3.5 g, 17.9 mmol) and 2-chloro-5-fluoro-4-iodopyridine (5.95 g, 19.7 mmol) in dioxane (5 mL) were added Xantphos (1.04 g, 1.79 mmol), Pd₂(dba)₃ (1.64 g, 1.79 mmol) and Cs₂CO₃ (11.7 g, 35.8 mmol) at room temperature and the resulting reaction mixture was stirred at 100 °C for 30 min. After cooling to room temperature, the solvent was removed under reduced pressure, and the crude product was then purified by silica gel flash chromatography (EtOAc:petroleum ether = 0 to 30%) to afford the title compound (4.9 g, 74% yield) as a white solid. MS: 427.1 [M+H]⁺.

IB1 (rac)- (1R,2S,4R,5S,7S)-Methyl 7-((5-fluoro-2-(5-cyclopropyl-1-tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate

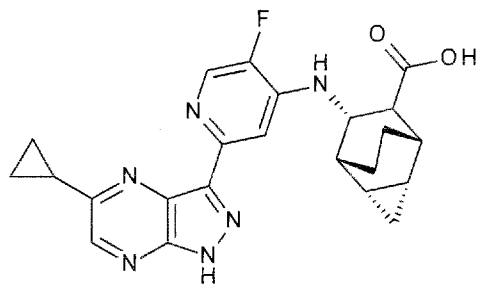


A stirred mixture solution of rac-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 770 μmol), 1,1,1,2,2,2-hexabutyldistannane (536 mg, 924 μmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (10 mL) was heated at 125 °C for 3 h. After cooling to room temperature, 3-iodo-5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (344 mg, 1 mmol) and Pd(PPh₃)₄ (100 mg, 86.5 μmol) in dioxane (5 mL) were added to the above mixture. The combined reaction mixture was re-heated at 145 °C for another 50 min. After cooling back to room temperature, the solvent was removed under reduced pressure. The crude product was then purified by silica gel flash chromatography (EtOAc:petroleum ether = 0 to 80%) to

afford the title compound (50 mg, 12.8% yield) as a yellow oil. MS: 507.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

TCI (rac-1R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid

5



A mixture solution of rac-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (180 mg, 338 μmol) and LiOH·H₂O (70.9 mg, 47 μmol, 1.69 mmol) in water (5 mL) and THF (5 mL) was stirred at room temperature for 16 h. After solvent was evaporated under reduced pressure, the residue was re-suspended in TFA (10 mL) and stirred at room temperature for another 24 h. Solvent was evaporated in vacuo to give a crude product which was then purified by prep-HPLC to afford the title compound (50 mg, 34.1% yield) as a white solid. MS: 434.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.51 (s, 1H), 8.12-8.37 (m, 2H), 4.41-4.48 (m, 1H), 2.40-2.48 (m, 2H), 2.32-2.38 (m, 1H), 2.25-2.32 (m, 1H), 1.55-1.71 (m, 3H), 1.41-1.49 (m, 1H), 1.13-1.22 (m, 3H), 0.96-1.04 (m, 3H), 0.77-0.84 (m, 2H).

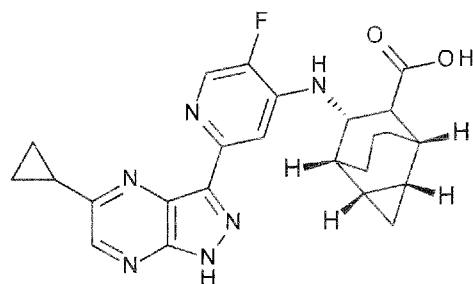
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Example 171

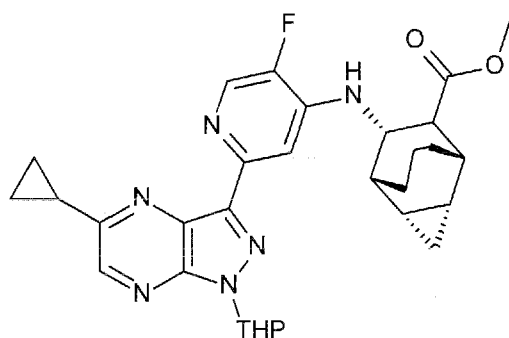
(rac)-(1S,2R,4S,5R,9S,10S)-10-((2-(5-cyclopropyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2]decane-9-carboxylic acid

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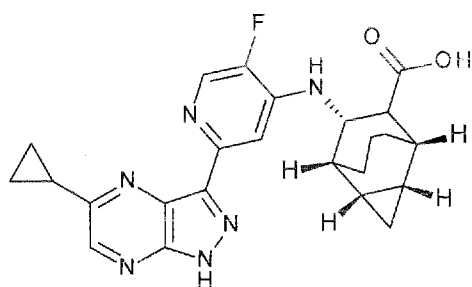
fA1 (rac)-(1S,2R,4S,5R,10S)-Methyl 10-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2]decane-9-

25 carboxylate



A stirred mixture solution of rac-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-chloro-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylate (250 mg, 738 μmol), 1,1,1,2,2,2-hexabutyldistannane (514 mg, 885 μmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in dioxane (10 mL) was heated at 125 °C for 3 h. After cooling back to room temperature, 5-cyclopropyl-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (355 mg, 959 μmol), $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) and dioxane (10 mL) were added to the above mixture. The resulting reaction mixture was then re-heated at 145 °C for another 50 min. After cooling to room temperature, the solvent was evaporated under reduced pressure to give a crude product, which was purified by silica gel flash chromatography (EtOAc:petroleum ether = 0 to 80%) to afford the title compound (50 mg, 12.4% yield) as a yellow oil. MS: 546.1 [M+H]⁺.

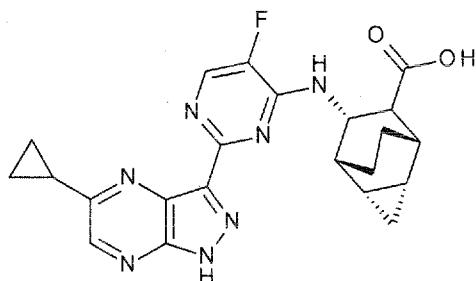
Example 17 (rac)-(1S,2R,4S,5R,9S,10S)-10-((2-(5-cyclopropyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylic acid



Similar to the synthesis of example 170/step C, rac-(1S,2R,4S,5R,9S,10S)-methyl 10-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyridin-4-yl)amino)tricyclo[3.3.2.0.2,4]decane-9-carboxylate (80 mg, 146 μmol) was used to afford the title compound (30 mg, 45% yield) after prep-HPLC purification. MS: 448.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.53 (s, 1H), 8.12-8.37 (m, 2H), 4.51 (br d, J=6.97 Hz, 1H), 2.94 (dd, J=4.40, 6.85 Hz, 1H), 2.83-2.89 (m, 2H), 2.44-2.60 (m, 4H), 1.85-2.02 (m, 4H), 1.78 (br s, 2H), 1.26 (tt, J=3.97, 8.31 Hz, 1H), 1.09-1.18 (m, 2H), 0.97-1.08 (m, 1H), 0.56-0.69 (m, 1H).

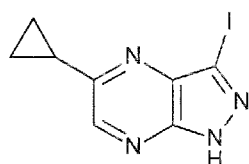
Example 172

(+ or -)-{1R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1 H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



5

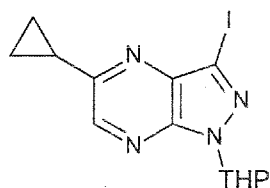
[A] 5-Cyclopropyl-3-iodo-1 H-pyrazolo[3,4-b]pyrazine



A stirred mixture solution of 5-cyclopropyl-1 H-pyrazolo[3,4-b]pyrazin-3-amine (8 g, 45.7 mmol), isoamyl nitrite (6.42 g, 54.8 mmol), diiodomethane (24.5 g, 91.3 mmol) in MeCN (40 mL) was heated at 100 °C for 4 h. After cooling to room temperature, the solvent was removed in vacuo to give a crude product (13 g, 99.5% yield). MS: 287.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

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[B] 5-Cyclopropyl-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyrazine



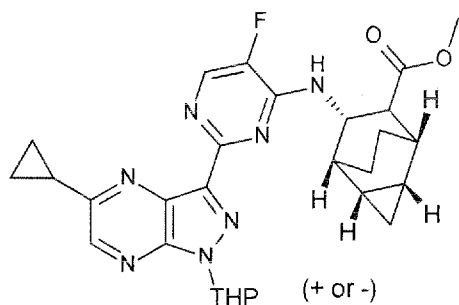
15

To a stirred mixture solution of 5-cyclopropyl-3-iodo-1 H-pyrazolo[3,4-b]pyrazine (13 g, 45.4 mmol) and 3,4-dihydro-2H-pyran (19.1 g, 20.7 mL, 227 mmol) in toluene (35 mL) was added 2,2,2-trifluoroacetic acid (51.8 mg, 4.54 mmol) at room temperature and the resulting reaction mixture was heated at 100 °C for 12 h before it was cooled back to room temperature. The reaction mixture was then extracted with EtOAc (100 mL) and washed with brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80%

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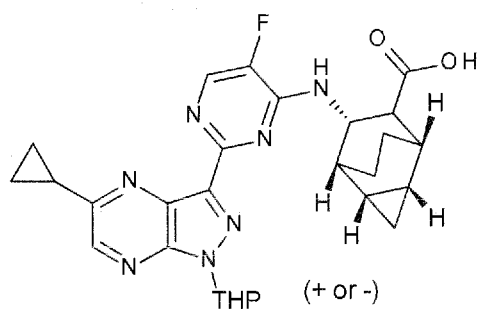
EtOAc-hexane gradient) to afford the title compound (5 g, 29.7% yield) as a white solid. MS: 371.1 (M+H)⁺.

TCI (+ or -)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



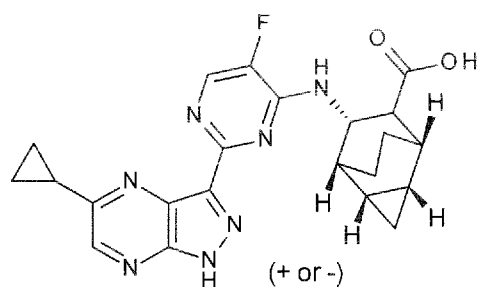
To a stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (250 mg, 767 μmol) and Pd(PPh₃)₄ (88.7 mg, 76.7 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (534 mg, 483 μL, 921 μmol) at room temperature. Then the reaction mixture solution was stirred at 125 °C for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) were then added 5-cyclopropyl-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (426 mg, 1.15 mmol) and Pd(PPh₃)₄ (88.7 mg, 76.7 μmol). The resulting reaction mixture solution was re-heated at 145 °C for an additional 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (50 mg, 12.2% yield) as a yellow oil. MS: 534.1(M+H)⁺.

D1 (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyrazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (50 mg, 93.7 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (22.4 mg, 937 μ mol) pre-dissolved in water (5 mL). The resulting mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). Combined organics were then dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product. MS: 520.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

[E] (+ or -)(1R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyrazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid

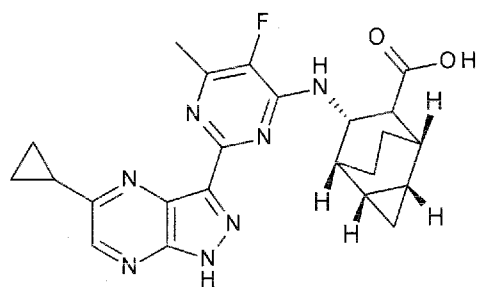


To a stirred mixture solution of (+ or -)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3.4-b]pyrazin-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (50 mg, 96.2 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. Solvent was removed under reduced pressure to give a crude product, which was purified by prep-HPLC to afford the title compound (2 mg, 4.8% yield) as a white foam. MS: 436.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.41 (s, 1H), 8.01-8.05 (m, 1H), 4.41-4.48 (m, 1H), 2.40-2.48 (m, 2H), 2.32-

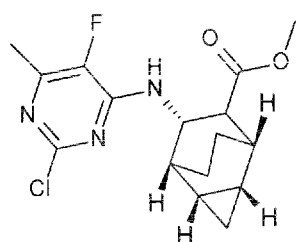
2.38 (m, 1H), 2.25-2.32 (m, 1H), 1.55-1.71 (m, 3H), 1.41-1.49 (m, 1H), 1.13-1.22 (m, 3H), 0.96-1.04 (m, 3H), 0.77-0.84 (m, 2H).

Example 173

- 5 **(rac-1R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid**



1A 1 (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



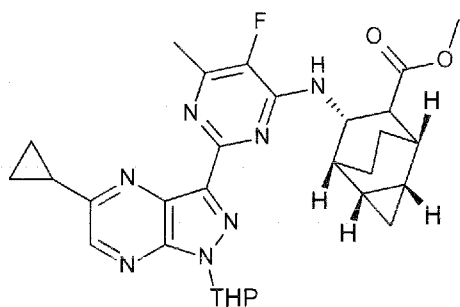
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To a stirred mixture solution of 2,4-dichloro-5-fluoro-6-methylpyrimidine (1.39 g, 7.68 mmol) and (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (1 g, 5.12 mmol) in THF (35 mL) was added N-ethyl-N-isopropylpropan-2-amine (662 mg, 5.12 mmol) at room temperature and the resulting reaction mixture solution was stirred at 70 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-40% EtOAc-hexane gradient) to afford the title compound (1.6 g, 91.9% yield) as white foam. MS: 340.1 (M+H)⁺

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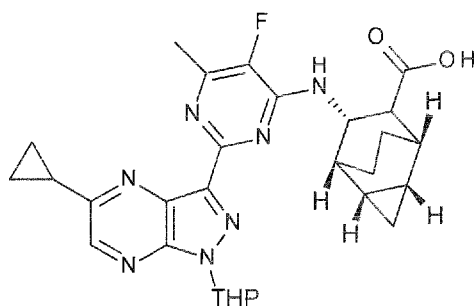
20

1B 1 (rac)-d R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (250 mg, 736 μ mol) and $\text{Pd}(\text{PPh}_3)_4$ (85 mg, 73.6 μ mol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (512 mg, 464 μ L, 883 μ mol) at room temperature and the resulting reaction mixture solution was stirred at 125 $^\circ\text{C}$ for 2 h before it was cooled back to room temperature. To the above stirred mixture solution in dioxane (16 mL) was added 5-cyclopropyl-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (Example 172/step B, 409 mg, 1.1 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (85 mg, 73.6 μ mol) and the reaction mixture solution was stirred at 145 $^\circ\text{C}$ for another 1 h under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (100 mg, 24.8% yield) as a yellow oil. MS: 548.1 (M+H) $^+$.

[C] (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid

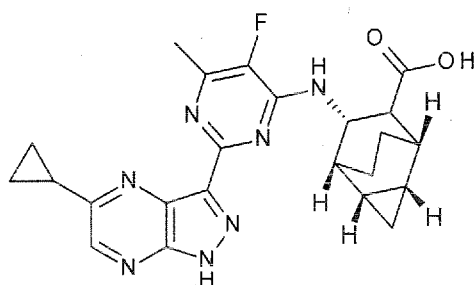


20

To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (100 mg, 183 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (43.7 mg, 1.83 mmol) pre-dissolved in water (5

ml). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). Combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product. MS: 534.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

(rac)-d R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1 H-pyrazolo[3.4-b]pyrazin-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3.4-b]pyrazin-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (100 mg, 187 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. Solvent was removed under reduced pressure and the crude product was purified by prep-HPLC to afford the title compound (4 mg, 4.7% yield) as a white foam. MS: 450.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.26-8.52 (m, 1H), 4.31-4.50 (m, 1H), 2.39-2.51 (m, 2H), 2.24-2.37 (m, 5H), 1.53-1.72 (m, 3H), 1.39-1.48 (m, 1H), 1.10-1.18 (m, 2H), 0.92-1.07 (m, 3H), 0.71-0.85 (m, 2H), 0.23-0.39 (m, 1H).

Example 174

(rac)-(1 R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

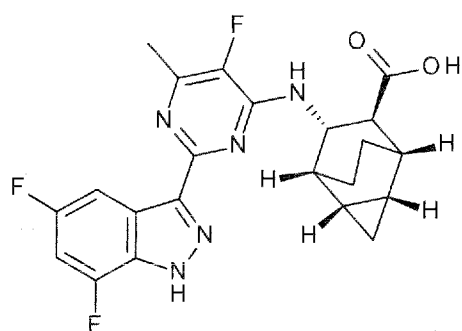
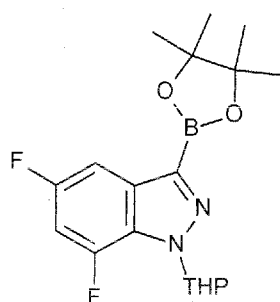


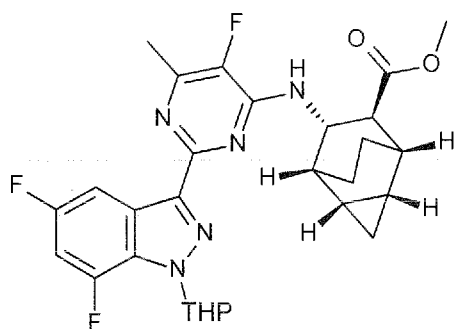
Table 1 5,7-Difluoro-1-(tetrahydro-2H-pyran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole



- 5 To a stirred mixture solution of 5,7-difluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (3 g, 8.24 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.18 g, 16.5 mmol) and potassium acetate (2.43 g, 24.7 mmol) in dioxane (75 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (603 mg, 824 μ mol) and the resulting reaction mixture solution was stirred at 110 °C for 16 h. After cooling to room temperature.
- 10 the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (2.5 g, 83.3% yield) as a yellow oil. MS: 365.1 ($\text{M}+\text{H}$)⁺.

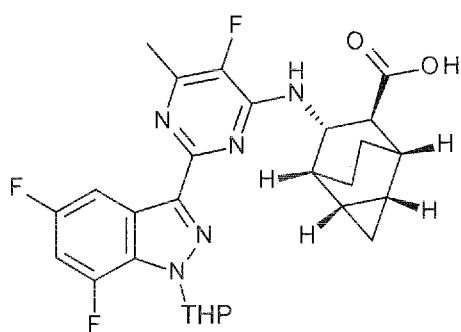
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FBI (racH 1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)-3,2,2,4,1-nonatriene-6-carboxylate



To a stirred mixture solution of 5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1 H-indazole (300 mg, 824 μmol), (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (Example 173/step A, 308 mg, 906 μmol) and 2 N Na_2CO_3 (824 μL , 1.65 mmol) in dioxane (15 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 68.3 μmol). The resulting reaction mixture solution was stirred at 110 °C for 20 min under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (150 mg, 33.6% yield) as a yellow solid. MS; 542.1 (M+H)⁺.

[C] (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid

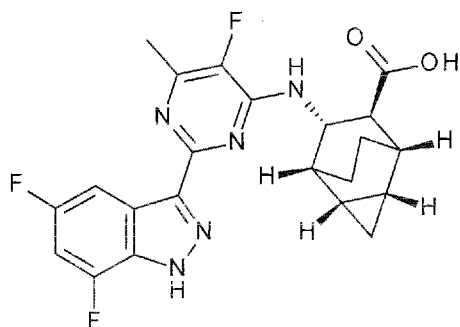


To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (150 mg, 277 μmol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (66.3 mg, 2.77 mmol, Eq. 10) pre-dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer

was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). Combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product. MS: 528.1 $(\text{M}+\text{H})^+$. This crude product was used directly in the next step without further purification.

5

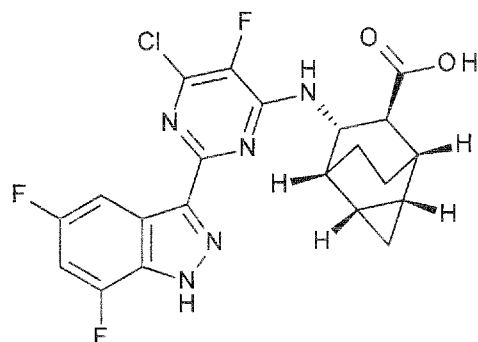
[D] (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

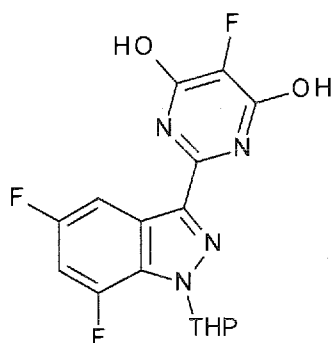


To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-difluoro-1-(tetrahydro-
 10 2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (150 mg, 284 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. After solvent was removed in vacuo, the crude product was purified by prep-HPLC to afford the title compound (20 mg,
 15 15.9% yield) as a white foam. MS: 444.1 $(\text{M}+\text{H})^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 7.96-8.02 (m, 1H), 7.22-7.30 (m, 1H), 4.80-4.84 (m, 1H), 2.90-2.95 (m, 1H), 2.71-2.76 (m, 1H), 2.59-2.64 (m, 1H), 2.58 (d, $J=2.93$ Hz, 3H), 1.79-1.99 (m, 2H), 1.65-1.74 (m, 2H), 1.14-1.23 (m, 1H), 0.89-1.01 (m, 2H), 0.43-0.53 (m, 1H).

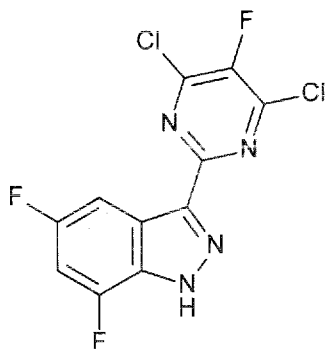
20 Example 175

(rac)-(1R,2S,4R,5S,6S,7S)-7-((6-Chloro-2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



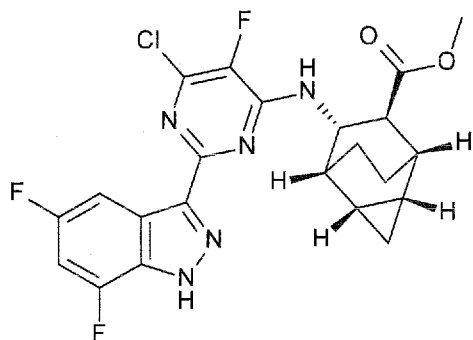
IA 1 2-(5,7-Difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoropyrimidine-4,6-diol

To a suspension of sodium methanoate (3.08 g, 57.1 mmol) in MeOH (100 mL) was added 5J-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazole-3-carboximidamide (4 g, 14.3 mmol) and dimethyl 2-fluoromalonate (4.28 g, 28.5 mmol). The resulting reaction mixture mixture was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was concentrated in vacuo to give the crude title compound (5 g, 95.6% yield). MS: 367.2 [M+H]⁺. This crude product was used directly in the next step without further purification.

[B] 3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)-5,7-difluoro-1 H-indazole

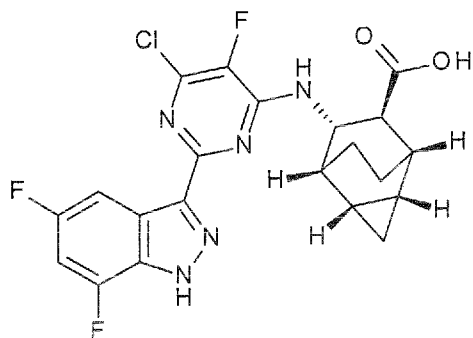
To a suspension of 2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoropyrimidine-4,6-diol (5 g, 13.7 mmol) in phosphorus oxychloride (83.7 g, 50 mL, 546 mmol) was slowly added *N,N*-dimethylaniline (1.65 g, 1.76 mL, 13.7 mmol). The mixture was heated to 80 °C and kept at that temperature under N₂ atmosphere for 12 h. The reaction mixture was concentrated and poured into ice-water (100 mL) and extracted with EtOAc (100 mL twice). The combined organic layers were washed with, brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (350 mg, 86.2% yield) as a light yellow solid. MS: 480.0 [M+H]⁺.

fCl (rac)-(6S,7S)-Methyl 7-((6-chloro-2-(5,7-difluoro-1 H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred solution of (rac)-(2S,4R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (294 mg, 1.5 mmol) in THF (150 mL) was added 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-5,7-difluoro-1 H-indazole (400 mg, 1.25 mmol) and N-ethyl-N-isopropylpropan-2-amine (243 mg, 328 μ L, 1.88 mmol) at room temperature and the resulting reaction mixture solution was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the product (560 mg, 93.5% yield) as a light yellow solid. MS: 478.1 [M+H]⁺.

[D] (rac)-(1R,2S,4R,5S,6S,7S)-7-((6-Chloro-2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

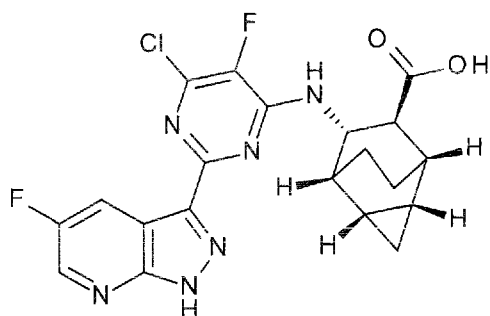


A mixture of (rac)-(6S,7S)-methyl 7-((6-chloro-2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (560 mg, 1.17 mmol) and lithium hydroxide hydrate (492 mg, 11.7 mmol) in THF/H₂O (20 mL, 1:1) was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (20 mL).

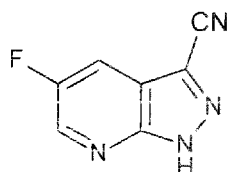
The separated aqueous layer was then acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to afford the title compound (500 mg, 95% yield) as a white solid. MS: 464.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 7.93 (d, $J=8.44$ Hz, 1H), 6.96-7.04 (m, 1H), 4.54 (d, $J=5.38$ Hz, 1H), 2.65 (d, $J=5.87$ Hz, 1H), 2.53 (s, 1H), 2.40-2.44 (m, 1H), 1.77-1.84 (m, 1H), 1.68 (s, 1H), 1.51-1.60 (m, 2H), 0.97-1.06 (m, 1H), 0.76-0.90 (m, 2H), 0.31-0.37 (m, 1H).

Example 176

- 10 (rac)-(1R,2S,4R,5S,6S,7S)-7-[(6-Chloro-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino]tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

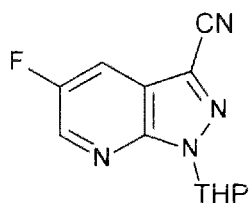


1A] 5-Fluoro-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile



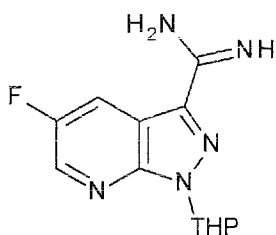
- 15 To a solution of 5-fluoro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-1a, 30 g, 86.4 mmol) in DMSO (300 mL) was added CuCN (15.5 g, 172.8 mmol) at room temperature and the resulting reaction mixture was stirred at 150 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (300 mL) and washed with water (300 mL) and brine (300 mL). The organic layer was then dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product (12.7 g) as a yellow oil. This crude product was used directly in the next step without further purification.
- 20

[BI 5-Fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile



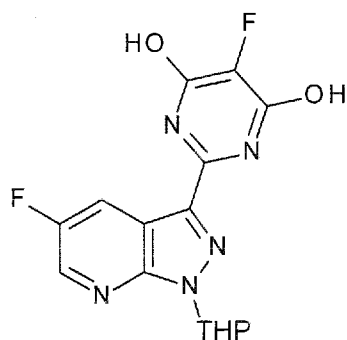
To a stirred solution of 5-fluoro-1 H-pyrazolo[3.4-b]pyridine-3-carbonitrile (12.6 g, 77.6 mmol) in DCM (200 mL) was added TsOH.H₂O (10.2 g, 54.4 mmol) and THP (9.12g, 108.6 mmol) and the resulting reaction mixture was stirred at room temperature for 1 h. After TLC (petroleum ether:EtOAc = 5:1) showed completion of the reaction, the mixture solution was neutralized with aqueous saturated NaHCO₃ solution (200 mL), extracted with EtOAc (200 mL three times), and washed with brine (200 mL). Combined organics were then dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product (22.1 g). This crude product was used directly in the next step without further purification.

fCl 5-Fluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyridine-3-carboximidamide



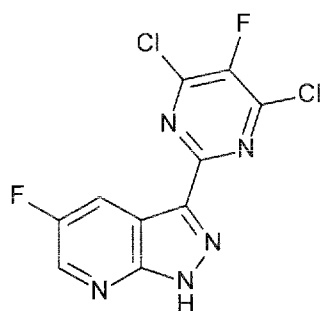
To a solution of 5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3.4-b]pyridine-3-carbonitrile (22 g, 89.3 mmol) in MeOH (200 mL) was added NaOMe (4.8 g, 89.3mmol) at 15 °C and the resulting reaction mixture was stirred at 15 °C for 12 h. AcOH (8 g, 133.9 mmol) and NH₄Cl (7.1 g, 133.9 mmol) were added to the above mixture, and the resulting mixture was stirred at 60 °C for another 12 h. After TLC (petroleum ether:EtOAc = 1:1) showed completion of the reaction, solvent was removed under reduced pressure to give a crude product, which was then purified by silica gel flash chromatography (DCM:MeOH = 20:1) to afford the title compound (8.2 g, 35% yield) as a yellow solid. MS: 264.1 (M+1)⁺.

[D] 5-Fluoro-2-(5-fluoro-1-(tetrahydro-2H-Pyran-2-yl)-1 H-pyrazolo[3.4-b]pyridine-3-yl)pyrimidine-4,6-dione



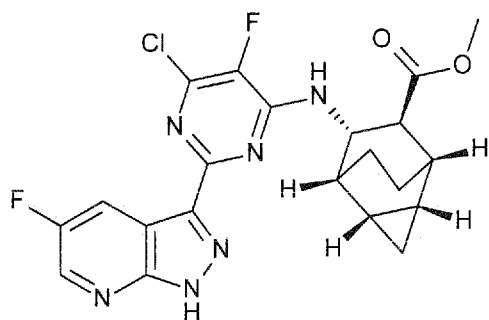
To a suspension of sodium methanolate (1.23 g, 22.8 mmol) in MeOH (25 mL) was added 5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide (2 g, 7.6 mmol) and dimethyl 2-fluoromalonate (2.28 g, 15.2 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was concentrated in vacuo to give a crude title compound (2.5 g, 94.2% yield). MS: 350.1 [M+H]⁺. This crude product was used directly in the next step without further purification.

10 fE1 (rac)-3-(4,6-Dichloro-5-fluoropyrimidin-2-yl)-5-fluoro-1H-pyrazolo[3,4-b]pyridine



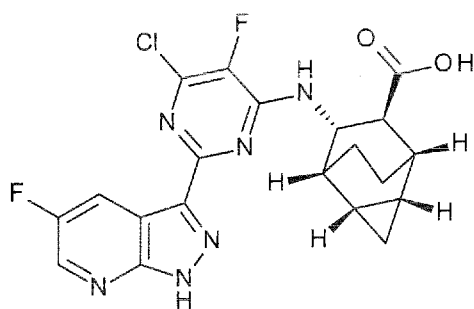
To a suspension of 5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidine-4,6-diol (2.5 g, 7.16 mmol) in phosphorus oxychloride (43.9 g, 26.2 mL, 286 mmol) was slowly added *N,N*-dimethylaniline (867 mg, 925 μ L, 7.16 mmol). The mixture was heated to 80 °C and kept at that temperature under N₂ atmosphere for 12 h. The reaction mixture was concentrated and poured into ice-water (50 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (1.5 g, 69.4% yield) as a light yellow solid. MS: 302.0 [M+H]⁺

fI1 (rac)- (6S,7S)-Methyl 7-(6-chloro-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]non-6-carboxylate



To a stirred solution of (rac)-3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-5-fluoro-1 H-pyrazolo[3,4-b]pyridine (1 g, 3.31 mmol) in THF (50 mL) was added 3-(4,6-dichloro-5-fluoropyrimidin-2-yl)-5,7-difluoro-1 H-indazole (646 mg, 3.31 mmol) and N-ethyl-N-isopropylpropan-2-amine (642 mg, 865 μ i, 4.97 mmol) at room temperature and the resulting reaction mixture solution was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (150 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (700 mg, 45.9% yield) as a light yellow solid. MS: 461.1 [M+H]⁺.

fGI (rac)-(1 R,2S,4R,5S,6S,7S)-7-((6-chloro-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid



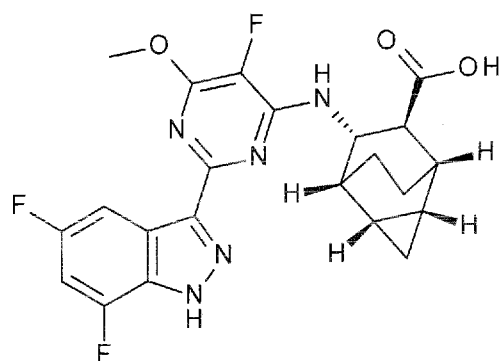
A mixture of (rac)- (6S,7S)-methyl 7-((6-chloro-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (880 mg, 1.91 mmol) and lithium hydroxide hydrate (801 mg, 19.1 mmol) in THF/H₂O (20 mL, 1:1) was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (20 mL). The separated aqueous layer was then acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford the title compound (760

mg, 89.1% yield) as a white solid. MS: 447.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH- d_4) δ 8.58-8.62 (m, 1H), 8.56 (d, $J=1.59$ Hz, 1H), 4.69 (d, $J=5.50$ Hz, 1H), 2.78 (d, $J=5.62$ Hz, 1H), 2.64 (s, 1H), 2.54 (d, $J=2.20$ Hz, 1H), 1.77-1.94 (m, 2H), 1.64-1.72 (m, 2H), 1.15 (td, $J=4.10, 8.44$ Hz, 1H), 0.97-1.02 (m, 1H), 0.93 (d, $J=4.52$ Hz, 1H), 0.44-0.50 (m, 1H).

5

Example 177

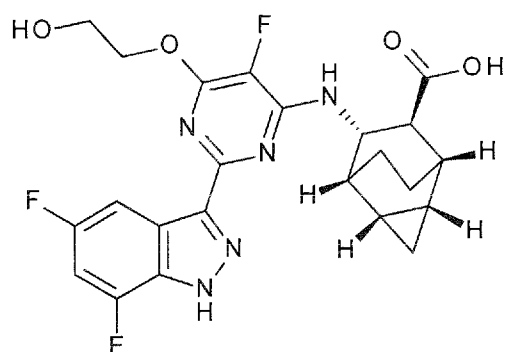
(rac)-(1R,2S,4R,5S,6S,7S)-7-((2-{5,7-Difluoro-1H-indazol-3-yl)-5-fluoro-6-methoxypyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



- 10 A mixture of (rac)-(6S,7S)-7-((6-chloro-2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (100 mg, 216 μ mol) and sodium methoxide (58.2 mg, 1.08 mmol) in MeOH (5 mL) was stirred at 95 $^{\circ}C$ for 16 h. The reaction mixture was concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (3 mg, 2.88% yield) as a white solid. MS: 460.2 $[M+H]^+$.
- 15 ^1H NMR (400 MHz, MeOH- d_4) δ 7.95 (d, $J=8.44$ Hz, 1H), 6.93-7.01 (m, 1H), 4.47 (d, $J=5.26$ Hz, 1H), 4.02 (s, 3H), 2.55 (d, $J=6.48$ Hz, 1H), 2.44 (s, 1H), 2.38 (s, 1H), 1.76 (d, $J=9.29$ Hz, 1H), 1.46-1.70 (m, 3H), 1.01 (dt, $J=4.52, 8.25$ Hz, 1H), 0.76-0.89 (m, 2H), 0.31-0.38 (m, 1H).

20 **Example 178**

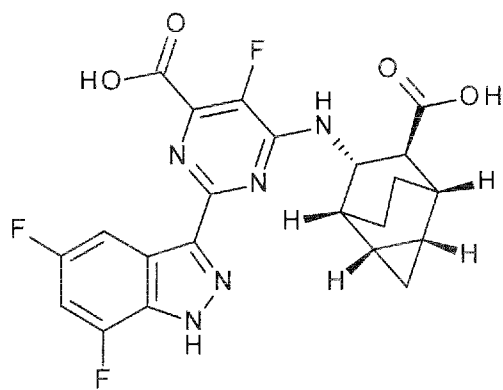
(rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoro-6-(2-hydroxyethoxy)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



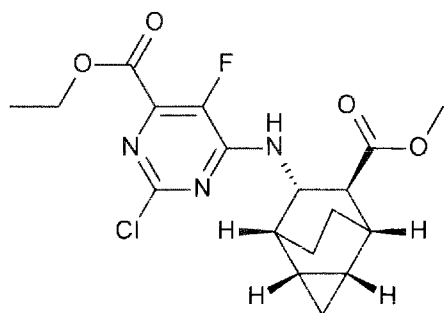
A mixture of (rac)-(6S,7S)-7-((6-chloro-2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0,2,4]nonane-6-carboxylic acid (100 mg, 216 μmol) and potassium tert-butoxide (72.6 mg, 647 μmol) in ethylene glycol (5 ml) was stirred at 95 °C for 4 h. The reaction mixture was concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (11 mg, 4.96% yield) as a white solid. MS: 506.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 7.95 (d, J=8.44 Hz, 1H), 6.94-7.02 (m, 1H), 4.46-4.56 (m, 3H), 3.80-3.86 (m, 2H), 2.57 (d, J=5.38 Hz, 1H), 2.46 (s, 1H), 2.39 (d, J=1.96 Hz, 1H), 1.77 (d, J=9.29 Hz, 1H), 1.62-1.71 (m, 1H), 1.48-1.60 (m, 2H), 1.01 (tt, J=4.17, 8.36 Hz, 1H), 0.76-0.89 (m, 2H), 0.34 (q, J=7.62 Hz, 1H).

Example 179

(rac)-6-(((1S,2R,4S,5R,6S,7S)-7-Carboxytricyclo[3.2.2.0,2,4]nonan-6-yl)amino)-2-(5,7-difluoro-1H-indazol-3-yl)-5-fluoropyrimidine-4-carboxylic acid

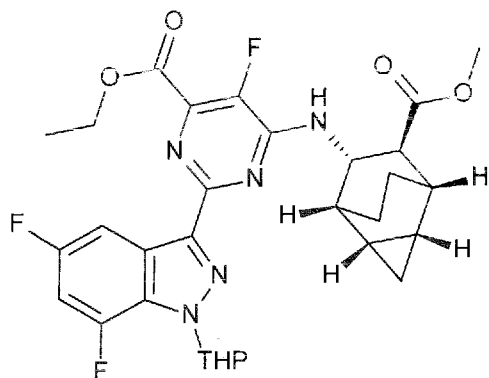


[A] (rac)-Ethyl 2-chloro-5-fluoro-6-(((6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0,2,4]nonan-6-yl)amino)pyrimidine-4-carboxylate



To a stirred solution of (rac)-(2S,4R,6S,7S)-methyl 7-aminotricyclo[3.2.2.0(2,4)]nonane-6-carboxylate (817 mg, 4.18 mmol) in THF (100 mL) was added ethyl 2,6-dichloro-5-fluoropyrimidine-4-carboxylate (1 g, 4.18 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (811 mg, 1.09 mL, 6.28 mmol) and the resulting reaction mixture solution was stirred at room temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (1.5 g, 90.1% yield) as a yellow solid. MS: 362.0 [M+H]⁺.

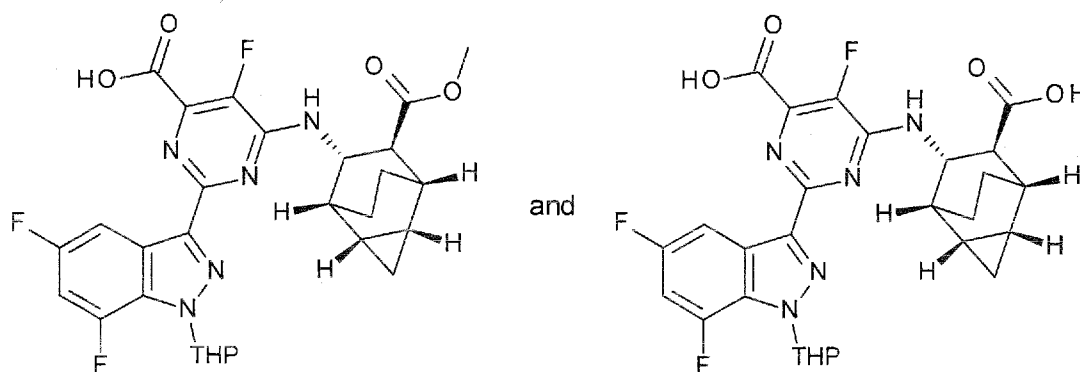
IB1 (rac)-Ethyl 2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoro-6-(((6S,7S)-7-methoxycarbonyl)tricyclo[3.2.2.0(2,4)]nonan-6-yl)amino)pyrimidine-4-carboxylate



To a stirred mixture solution of 5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (300 mg, 824 μmol), (rac)-ethyl 2-chloro-5-fluoro-6-(((6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0(2,4)]nonan-6-yl)amino)pyrimidine-4-carboxylate (360 mg, 906 μmol) and 2 M Na₂CO₃ (824 μL, 1.65 mmol) in dioxane (15 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 68.3 μmol). The reaction mixture was then stirred at 110 °C for 20 min under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine.

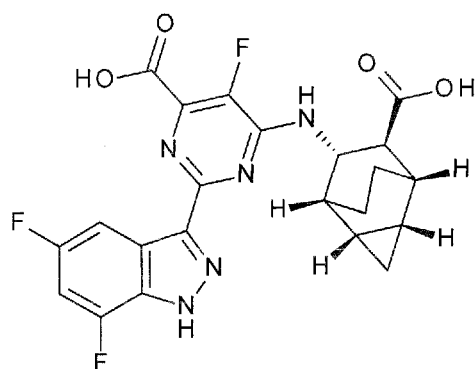
dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (260 mg, 52% yield) as a yellow solid. MS: 600.2 $[\text{M}+\text{H}]^+$.

- 5 [CI (rac)-6-(((6S,7S)-7-Carboxytricyclo[3.2.2.0^{2,4}]nonan-6-yl)amino)-2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoropyrimidine-4-carboxylic acid and (rac)-2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoro-6-(((6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0^{2,4}]nonan-6-yl)amino)pyrimidine-4-carboxylic acid



- 10 A mixture of (rac)-ethyl 2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoro-6-(((6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0^{2,4}]nonan-6-yl)amino)pyrimidine-4-carboxylate (260 mg, 434 μmol) and lithium hydroxide hydrate (182 mg, 4.34 mmol) in THF/ H_2O (10 mL, 1:1) was stirred at room temperature for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (20 mL). The separated aqueous
- 15 layer was then acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give (rac)-6-(((6S,7S)-7-carboxytricyclo[3.2.2.0^{2,4}]nonan-6-yl)amino)-2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidine-4-carboxylic acid (80 mg, 33.1% yield) as a yellow solid.
- 20 MS: 558.2 $[\text{M}+\text{H}]^+$; and (rac)-2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-5-fluoro-6-(((6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0^{2,4}]nonan-6-yl)amino)pyrimidine-4-carboxylic acid (120 mg, 48.4% yield) as another yellow solid. MS: 572.1 $[\text{M}+\text{H}]^+$.

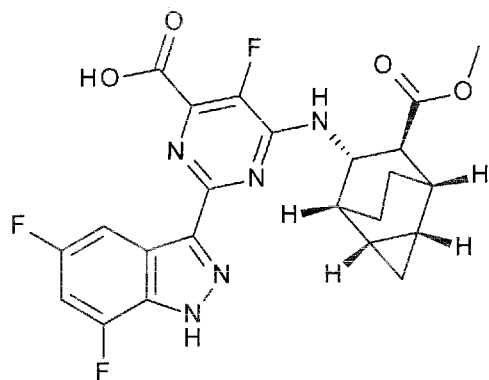
- 25 [D1 (rac)-6-(((1S,2R,4S,5R,6S,7S)-7-Carboxytricyclo[3.2.2.0^{2,4}]nonan-6-yl)amino)-2-(5,7-difluoro-1 H-indazol-3-yl)-5-fluoropyrimidine-4-carboxylic acid



A mixture of (rac)-6-(((6S,7S)-7-carboxytricyclo[3.2.2.0.2,4]nonan-6-yl)amino)-2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoropyrimidine-4-carboxylic acid (80 mg, 143 μmol) in TFA (10 mL) was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (15 mg, 21% yield) as a white solid. MS: 474.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.08 (dd, $j=1.77, 8.74$ Hz, 1H), 7.13-7.20 (m, 1H), 4.72 (d, $J=6.72$ Hz, 1H), 2.84-2.90 (m, 1H), 2.72 (s, 1H), 2.58 (s, 1H), 1.93-1.98 (m, 1H), 1.78-1.87 (m, 1H), 1.70 (d, $J=5.14$ Hz, 2H), 1.12-1.18 (m, 1H), 0.90-1.04 (m, 2H), 0.47 (q, $J=7.46$ Hz, 1H).

Example 180

(rac)-2-(5,7-Difluoro-1H-indazol-3-yl)-5-fluoro-6-(((1S,2R,4S,5R,6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0.2,4]nonan-6-yl)amino)pyrimidine-4-carboxylic acid



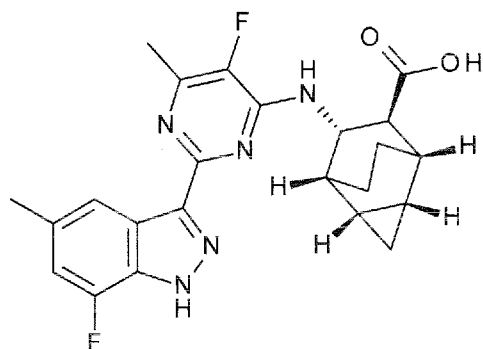
A mixture of (rac)-2-(5,7-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-5-fluoro-6-(((6S,7S)-7-(methoxycarbonyl)tricyclo[3.2.2.0.2,4]nonan-6-yl)amino)pyrimidine-4-carboxylic acid (120 mg, 210 μmol) in TFA (10 mL) was stirred at room temperature for 16 h. After LC-MS showed that the reaction was completed, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (20 mg, 27.2% yield) as a white solid. MS: 488.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz,

MeOH-d₄) δ 8.06 (d, J=8.44 Hz, 1H), 7.16 (t, J=9.54 Hz, 1H), 4.68 (d, J=5.62 Hz, 1H), 3.67 (s, 3H), 2.85 (d, J=4.89 Hz, 1H), 2.68 (d, J=5.38 Hz, 1H), 2.50 (s, 1H), 1.89-1.95 (m, 1H), 1.78-1.86 (m, 1H), 1.59-1.68 (m, 2H), 1.15 (d, J=4.52 Hz, 1H), 0.88-1.02 (m, 2H), 0.48 (d, J=7.34 Hz, 1H).

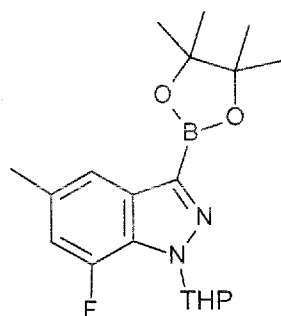
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Example 181

(rac)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-5-methyl-1H-indazol-3-yl)-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



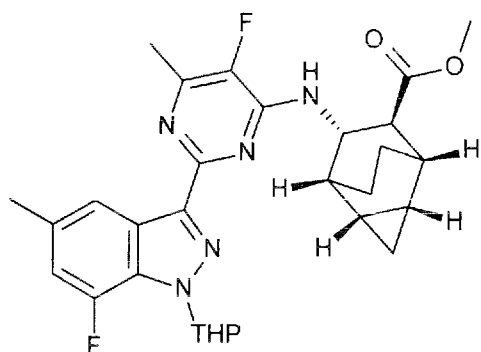
10 [A] 7-Fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole



To a stirred mixture solution of 7-fluoro-3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Intermediate G-7, 300 mg, 833 μ mol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (423 mg, 1.67 mmol) and potassium acetate (245 mg, 2.5 mmol) in dioxane (12 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (60.2 mg, 82.2 μ mol). The resulting reaction mixture solution was stirred at 110 °C for 26 h before it was cooled back to room temperature. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with
 15 brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product. MS: 361.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

20

1B 1 (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(7-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



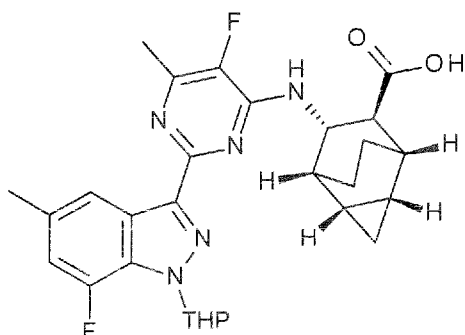
5

To a stirred mixture solution of 7-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (400 mg, 1.11 mmol), (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoro-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Example 173/step A, 377 mg, 1.11 mmol) and 2 M Na₂CO₃ (1.11 mL, 2.22 mmol) in dioxane (15 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 68.3 μmol). The resulting reaction mixture solution was then stirred at 110 °C for 60 min under microwave heating. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (180 mg, 30.2% yield) as yellow oil. MS: 538.1 (M+H)⁺.

15

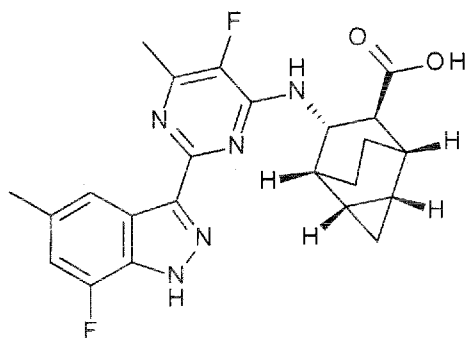
fCl (rac)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

20



To a stirred mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(7-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (180 mg, 335 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (80.2 mg, 3.35 mmol) pre-dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). Combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product. MS: 524.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

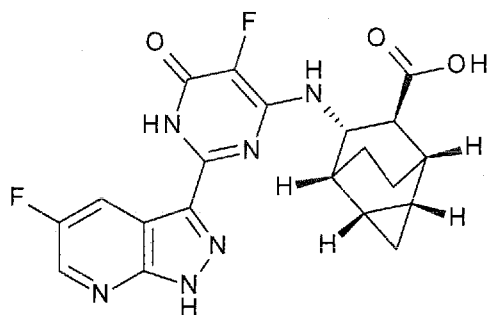
[D] (rac)-(1 R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(7-fluoro-5-methyl-1H-indazol-3-yl)-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(7-fluoro-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-indazol-3-yl)-6-methylpyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (180 mg, 344 μ mol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture solution was stirred at room temperature for 12 h. After solvent was removed under reduced pressure, the crude product was then purified by prep-HPLC to afford the title compound (30 mg, 19.9% yield) as a white foam. MS: 440.1 (M+H)⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.11-8.14 (m, 1H), 7.08-7.14 (m, 1H), 4.80-4.84 (m, 1H), 2.86-2.91 (m, 1H), 2.67-2.72 (m, 1H), 2.57-2.61 (m, 1H), 2.55 (s, 6H), 1.90-1.99 (m, 1H), 1.79-1.90 (m, 1H), 1.65-1.74 (m, 2H), 1.13-1.21 (m, 1H), 0.97-1.04 (m, 1H), 0.90-0.97 (m, 1H), 0.43-0.53 (m, 1H).

Example 182

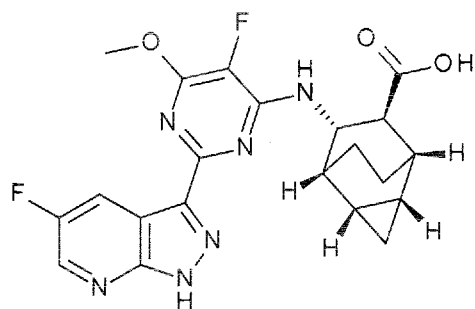
(rac)-(1 R,2S,4R,5S,6S,7S)-7-((S-Fluoro-2-(S-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)-e-oxo-1,6-dihydropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A mixture of (rac)-(6S,7S)-7-((6-chloro-5-fluoro-2-(5-fluoro-1 H-pyrazo[o[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (550 mg, 1.23 mmol) in 2 M sodium hydroxide (12.3 ml, 24.6 mmol) was stirred at 95 °C for 64 h. The reaction mixture was acidified with concentrated hydrochloric acid to pH 4 and concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (90 mg, 16.2% yield) as a white solid. MS: 429.3 [M+Hf. ¹H NMR (400 MHz, DMSO-d₆) δ 14.60 (s, 1H), 12.40 (s, 2H), 8.71 (d, J=1.10 Hz, 1H), 8.38 (d, J=7.95 Hz, 1H), 6.73 (d, J=5.01 Hz, 1H), 4.43 (s, 1H), 2.84 (d, J=6.11 Hz, 1H), 2.42 (s, 2H), 1.66 (s, 2H), 1.40-1.57 (m, 2H), 1.14 (d, J=3.06 Hz, 1H), 1.00 (d, J=3.67 Hz, 1H), 0.79 (s, 1H), 0.29 (q, J=7.34 Hz, 1H).

Example 183

(rac)-(1R,2S,4R,5S,6S,7S)-7-((S-fluoro-2-(S-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-e-methoxypyrimidin-4-yl)amino)tricyclo[3,2,2,0(2,4)]nonane-6-carboxylic acid

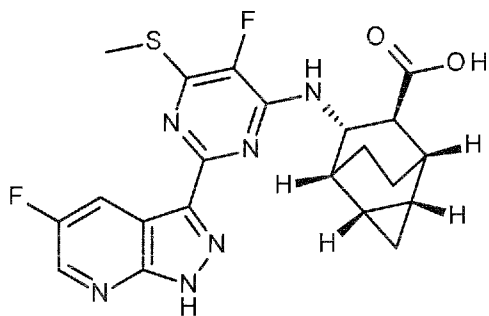


A mixture of (rac)-(6S,7S)-7-((6-chloro-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0(2,4)]nonane-6-carboxylic acid (100 mg, 0.22 mmol) and sodium methoxide (58.2 mg, 1.08 mmol) in MeOH (5 mL) was stirred at 70 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (15 mg, 15.4% yield) as a white solid. MS: 443.3 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.52 (dd, J=2.81, 8.44 Hz, 1H), 8.42-8.46 (m, 1H), 4.52 (d, J=6.36 Hz, 1H), 4.02 (s, 3H), 2.57 (d, J=6.48 Hz, 1H), 2.36-2.48 (m, 2H), 1.65-1.78

(m, 2H), 1.48-1.62 (m, 2H), 0.98-1.06 (m, 1H), 0.85-0.90 (m, 1H), 0.80 (td, J=3.96, 7.86 Hz, 1H), 0.34 (q, J=7.70 Hz, 1H).

Example 184

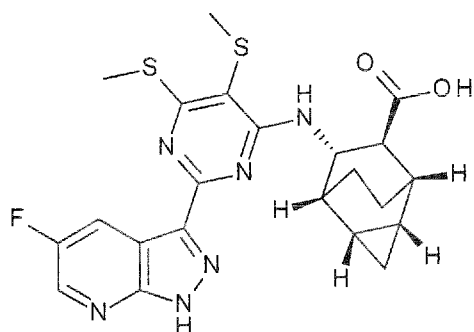
5 (rac)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-(methylthio)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



A mixture of (rac)-(6S,7S)-7-((6-chloro-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3.4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (170 mg, 380 μ mol) and
 10 sodium methanethiolate (133 mg, 1.9 mmol) in MeCN (5 mL) was stirred at 95 °C for 16 h. The reaction mixture was diluted with water (10 mL) and acidified with 2N HCl to pH 6 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (27 mg, 14.7% yield) as a white solid.
 15 MS: 459.3 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.49 (dd, J=2.81, 8.44 Hz, 1H), 8.44 (d, J=1.71 Hz, 1H), 4.51 (d, J=6.11 Hz, 1H), 2.60 (s, 4H), 2.46 (d, J=2.45 Hz, 1H), 2.39 (dd, J=2.38, 4.71 Hz, 1H), 1.63-1.80 (m, 2H), 1.48-1.62 (m, 2H), 1.02 (tt, J=4.20, 8.39 Hz, 1H), 0.83-0.88 (m, 1H), 0.76-0.83 (m, 1H), 0.30-0.38 (m, 1H).

20 Example 185

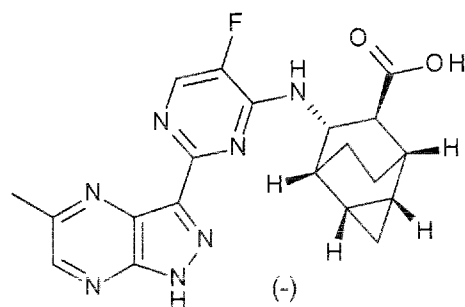
(rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)-5,6-bis(methylthio)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



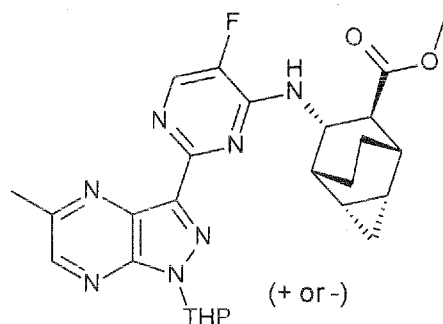
A mixture of (rac)-(6S,7S)-7-((6-chloro-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (170 mg, 380 μmol) and sodium methanethiolate (133 mg, 1.9 mmol) in MeCN (5 mL) was stirred at 95 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and acidified with 2N HCl to pH 6 and extracted with EtOAc (40 mL three times). The combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (4 mg, 2.05% yield) as a white solid. MS: 487.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 14.30 (s, 1H), 12.29 (s, 1H), 8.66 (s, 1H), 8.49-8.60 (m, 1H), 6.68 (d, $J=7.09$ Hz, 1H), 4.57 (s, 1H), 2.91 (d, $J=5.62$ Hz, 1H), 2.59 (s, 3H), 2.42-2.45 (m, 2H), 2.26 (s, 3H), 1.67 (s, 2H), 1.50 (br d, $J=8.80$ Hz, 2H), 0.93-1.12 (m, 2H), 0.80 (s, 1H), 0.32-0.41 (m, 1H).

Example 186

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



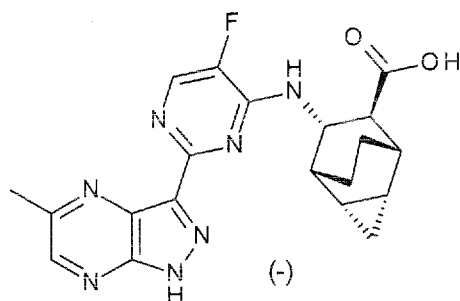
[AT (+ or -)-(1R,2S,4R,5S,7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



A stirred mixture solution of (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (300mg, 921 μmol), 1,1,1,2,2,2-hexabutyldistannane (631 mg, 550 μmol , 1.09 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μmol) in

dioxane (10 mL) was heated at 125 °C for 3 h before it was cooled back to room temperature. 3-Iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyrazine (400 mg, 1.16 mmol), Pd(PPh₃)₄ (100 mg, 86.5 μmol) and dioxane (10 mL) were added to the above mixture and the resulting mixture solution was re-heated at 145 °C for another 80 min. After solvent was removed in vacuo, the crude product was then purified by silica gel flash chromatography (EtOAc: petroleum ether = 0 to 80%) to afford the title compound (100 mg, 21.4 % yield) as a yellow oil. MS: 507.2 [M+H]⁺.

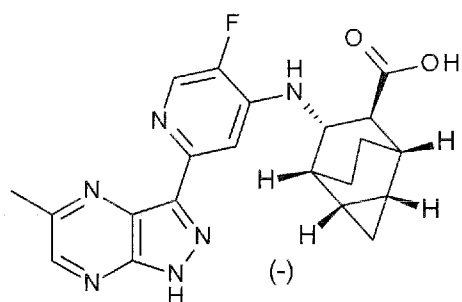
[B] (-)-(1 R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1 H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



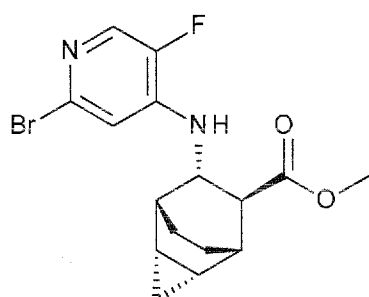
A mixture solution of (+ or -)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (100 mg, 118 μmol) and LiOH·H₂O (4.96 mg) in THF (10 mL) and water (10 mL) was stirred at room temperature for 16 h. After solvent was removed under reduced pressure, the residue was re-suspended in TFA (10 mL) and stirred at room temperature for another 16 h. Solvent was removed in vacuo, and the crude product was purified by prep-HPLC to afford the title compound (8 mg, 3.44 % yield) as a white solid. MS: 409.1 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.39-8.58 (m, 1H), 8.15 (br s, 1H), 4.55 (br s, 1H), 2.59-2.81 (m, 5H), 2.40 (br d, J=2.32 Hz, 1H), 1.84 (br s, 1H), 1.59-1.73 (m, 1H), 1.44-1.59 (m, 2H), 0.93-1.08 (m, 1H), 0.73-0.87 (m, 2H), 0.25-0.41 (m, 1H).

Example 187

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

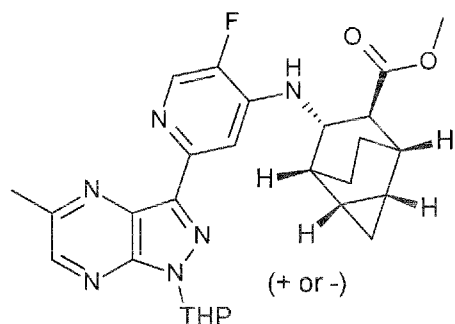


[A] (rac)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((2-bromo-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate



- 5 To a solution of (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0.2.4]nonane-6-carboxylate (3.5 g, 17.9 mmol) and 2-bromo-5-fluoro-4-iodopyridine (5.95 g, 19.7 mmol) in dioxane (5 ml) was added Xantphos (1.04 g, 1.79 mmol), Pd₂(dba)₃ (1.64 g, 1.79 mmol), and Cs₂CO₃ (11.7 g, 35.8 mmol) at room temperature and the resulting mixture solution was stirred at 100 °C for 30 min. After cooling to room temperature, the solvent was removed in vacuo to give a crude product, which was then purified by silica gel flash chromatography (EtOAc:petroleum ether = 0 to 30%) to afford the title compound (4.9 g, 74 % yield) as a white solid. MS: 369.1 [M+H]⁺.

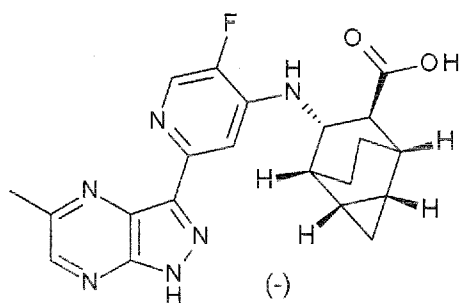
15 fBI (+ or -)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolof[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate



A stirred mixture solution of (-)-(1 R,2S,4R,5S,6S,7S)-methyl 7-((2-bromo-5-fluoropyridin-4-yl)amino)tricyclo[3.2.2.0.2.4]nonane-6-carboxylate (300 mg, 813 pmol), 1,1,1,2,2,2-

hexabutyldistannane (631 mg, 550 μ I, 1.09 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 μ mol) in dioxane (10 mL) was heated at 125 °C for 3 h before it was cooled back to room temperature. Then 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazine (400 mg, 1.16 mmol), $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 86.5 Mmol) and dioxane (10 mL) were added to the above mixture. The resulting mixture solution was then re-heated at 145 °C for another 80 min. After cooling to room temperature, the solvent was removed in vacuo, the crude product was purified by silica gel flash chromatography (EtOAc: petroleum ether = 0 to 80%) to give a racemic mixture of product (100 mg, 24.3 % yield). Subsequent chiral separation by SFC afforded the title compound as a yellow oil. MS: 506.2 [M+H]⁺

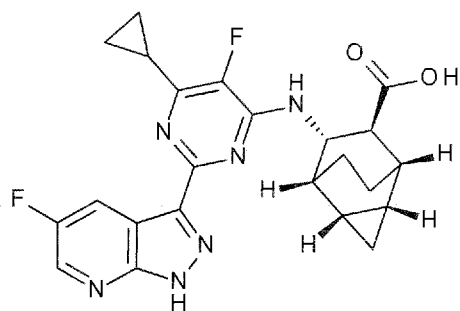
[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



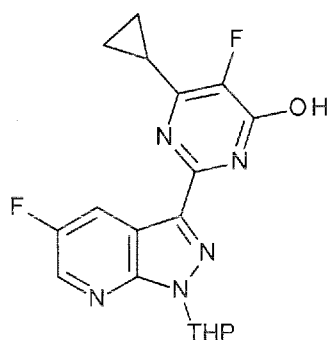
A mixture solution of (+ or -) (1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)pyridin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (280 mg, 332 μ mol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (13.9 mg, 9.22 μ I, 332 μ mol) in THF (10 mL) and water (10 mL) was stirred at room temperature for 16 h. After solvent was removed under reduced pressure, the residue was re-suspended in TFA (10 mL) and stirred at room temperature for 16 h. Solvent was evaporated in vacuo and the crude product was purified by prep-HPLC to afford the title compound (25 mg, 61.2% yield) as a white solid. MS: 408.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 14.28 (br s, 1H), 12.53 (br s, 1H), 8.60 (s, 1H), 8.30 (br d, J=3.30 Hz, 1H), 8.05 (br d, J=6.97 Hz, 1H), 6.83 (br s, 1H), 3.90 (br s, 1H), 2.90 (br d, J=6.24 Hz, 1H), 2.72 (s, 3H), 2.45 (br d, J=2.08 Hz, 1H), 1.73 (br s, 2H), 1.36-1.64 (m, 3H), 1.10 (br dd, J=3.48, 6.30 Hz, 1H), 0.99-1.07 (m, 1H), 0.82 (br dd, J=3.85, 7.89 Hz, 1H), 0.29 (q, J=7.30 Hz, 1H).

Example 188

(rac-1R,2S,4R,5S,6S,7S)-7-((6-Cyclopropyl-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

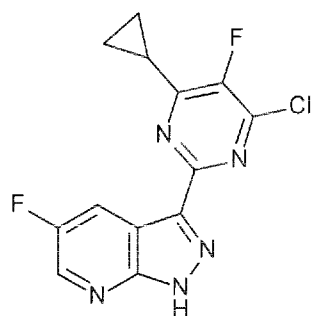


1A] 3-(4-Chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-5-fluoro-1H-pyrazolo[3,4-b]pyridine



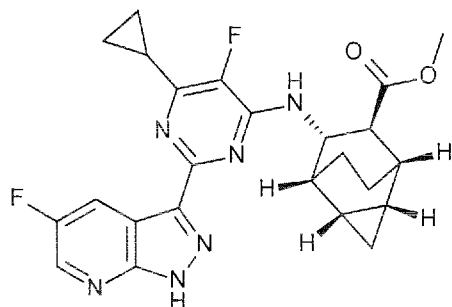
To a stirred mixture solution of 5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide hydrochloride (Example 176/step C, 749 mg, 2.5 mmol) and methyl 3-cyclopropyl-2-fluoro-3-oxopropanoate (400 mg, 2.5 mmol) in MeOH (30 mL) was added sodium methoxide (270 mg, 5 mmol) at room temperature. The resulting reaction mixture was heated to reflux temperature overnight while a white solid precipitated. After cooling to room temperature, most of MeOH was removed under reduced pressure. After adding water (10 mL), the combined remaining mixture was ultrasonated for 5 min before filtration. The collected filter cake was then dried under vacuum to give a crude product (530 mg, 56.8% yield) as a white solid. MS: 374.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

15 [E] 3-(4-Chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-5-fluoro-1H-pyrazolo[3,4-b]pyridine



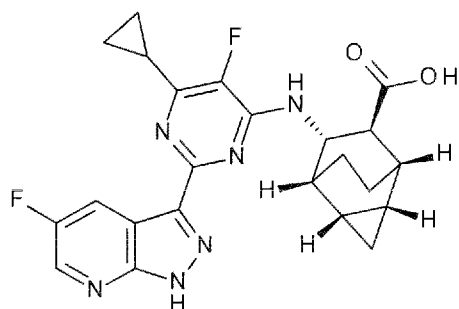
To a suspension of 6-cyclopropyl-5-fluoro-2-(5-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ol (500 mg, 1.34 mmol) in phosphorus oxychloride (8.21 g, 4.9 ml, 53.6 mmol) was slowly added *N,N*-dimethylaniline (162 mg, 1.34 mmol). After the addition, the mixture solution was heated to 80 °C for 12 h. After TLC (DCM:MeOH=20:1) showed completion of the reaction, the mixture solution was concentrated and poured into water (20 mL) and extracted with EtOAc (30 mL x2). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product (200 mg, 48.5% yield) as a yellow solid. MS: 308.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

[F] (rac)-(1 R,2S,4R,5S,6S,7S)-Methyl 7-((6-cyclopropyl-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (rac)-(1 R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (intermediate B-12, 127 mg, 650 μmol) and 3-(4-chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-5-fluoro-1 H-pyrazolo[3,4-b]pyridine (200 mg, 650 μmol) in THF (20 mL) was added *N,N*-diisopropylethylamine (126 mg, 975 μmol). The resulting reaction mixture solution was stirred at 70 °C for 10 h before it was cooled back to room temperature. The reaction mixture was then poured into water (20 mL) and extracted with EtOAc (50 mL twice). Combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane gradient) to afford the title compound (150 mg, 49.5% yield) as a white foam. MS: 467.1(M+H)⁺

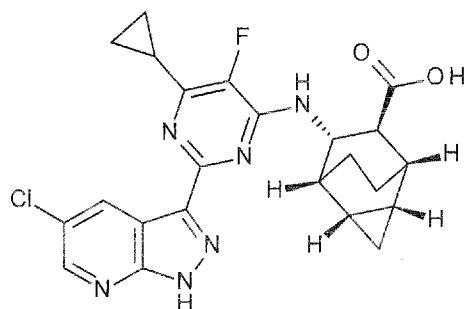
[G] (rac)-(1 R,2S,4R,5S,6S,7S)-7-((6-Cyclopropyl-5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



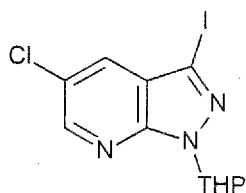
To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-cyclopropyl-5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylate (200 mg, 429 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (103 mg, 4.29 mmol) pre-dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). Combined organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated to give a crude product, which was then purified by prep-HPLC to afford the title compound (20 mg, 10.3% yield) as a white foam. MS: 453.1 ($\text{M}+\text{H}$)⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 8.54-8.61 (m, 1H), 8.44-8.51 (m, 1H), 4.49-4.57 (m, 1H), 2.76-2.82 (m, 1H), 2.60-2.64 (m, 1H), 2.44-2.51 (m, 1H), 2.25-2.33 (m, 1H), 1.67-1.81 (m, 2H), 1.53-1.62 (m, 2H), 1.19-1.25 (m, 2H), 1.03-1.12 (m, 4H), 0.78-0.88 (m, 1H), 0.29-0.41 (m, 1H).

Example 189

(rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-cyclopropyl-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2]nonane-6-carboxylic acid

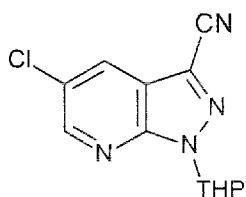


5-Chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine



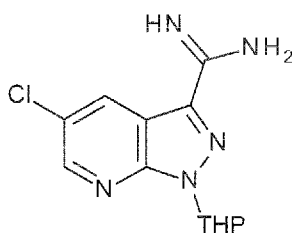
To a stirred mixture solution of 5-chloro-3-iodo-1H-pyrazolo[3,4-b]pyridine (Intermediate A-3/step E, 12.6 g, 45.4 mmol) and 3,4-dihydro-2H-pyran (19.1 g, 20.7 mL, 227 mmol) in toluene (35.0 mL) was added 2,2,2-trifluoroacetic acid (518 mg, 4.54 mmol) at room temperature and the resulting reaction mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc (100 mL), washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (8 g, 47.9% yield) as a white solid. MS: 363.1 (M+Hf.

[B] 5-Chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile



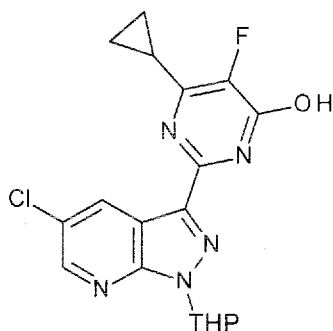
A mixture solution of 5-chloro-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (6 g, 16.5 mmol) and copper(I) cyanide (4.43 g, 49.5 mmol) in DMF (90 mL) was stirred at 100 °C for overnight. The solution was poured into ice water, and then the reaction mixture was extracted with ethyl acetate and washed with ammonium hydroxide solution and water. The organic layer was dried over sodium sulfate and concentrated in vacuo to afford the crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient, product peak at about 5-10%) to afford the title compound (1.6 g, 37%) as a yellow solid. MS: 263.1 (M+H)⁺.

[C] 5-Chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide



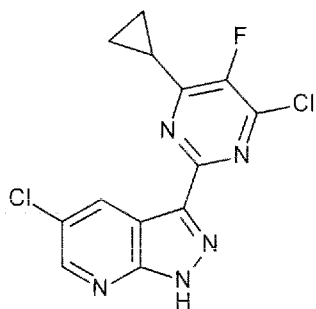
To a stirred solution of sodium methanolate (988 mg, 18.3 mmol) in MeOH (100 mL) was added 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile (1200 mg, 4.57 mmol) and the resulting mixture solution was stirred at 40 °C for 3 h. After cooling to room temperature, acetic acid (1.37 g, 1.31 mL, 22.8 mmol) and ammonium chloride (733 mg, 13.7 mmol) were added to the above solution and the resulting reaction mixture was stirred at 70 °C overnight. After cooling to room temperature, the mixture solution was filtered and the filtrate was concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-20% Methanol-DCM gradient) to afford the title compound (1.2 g, 93.9% yield) as a yellow foam. MS: 280.1 (M+H)⁺.

12-(5-Chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-cyclopropyl-5-fluoropyrimidin-4-ol



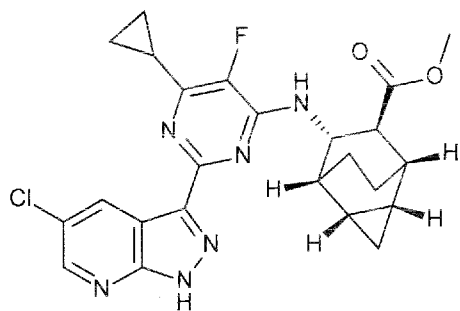
To a stirred mixture solution of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide (699 mg, 2.5 mmol) and methyl 3-cyclopropyl-2-fluoro-3-oxopropanoate (400 mg, 2.5 mmol) in MeOH (30 mL) was added sodium methoxide (270 mg, 5 mmol). After the addition, the resulting mixture solution was heated to reflux overnight while a white solid precipitated. After cooling to room temperature, most of MeOH was evaporated off under vacuum. Water (10 mL) was added and the combined remaining mixture was ultrasonated for 5 min before filtration. The filter cake was collected and dried under vacuum to give a crude product (974 mg, 100% yield) as a white solid. MS: 390.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

[E] 5-Chloro-3-(4-chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-1H-pyrazolo[3,4-b]pyridine



To a suspension of 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-cyclopropyl-5-fluoropyrimidin-4-ylamine (900 mg, 2.31 mmol) in phosphorus oxychloride (14.2 g, 8.45 mL, 92.4 mmol) was slowly added *N,N*-dimethylaniline (280 mg, 2.31 mmol). After the addition, the resulting reaction mixture was heated at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated and poured into water (20 mL) and extracted with EtOAc (30 mL twice). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (500 mg, 66.8% yield) as a yellow oil. MS: 324.1 (M+H)⁺.

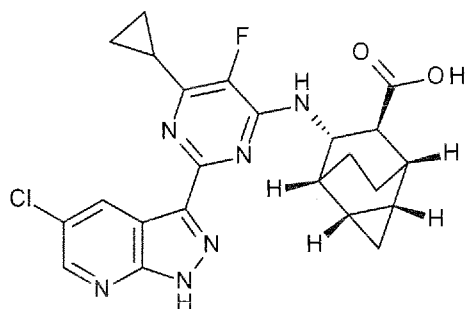
[F] (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-cyclopropyl-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (Intermediate B-12, 422 mg, 2.16 mmol) and 5-chloro-3-(4-chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-1H-pyrazolo[3,4-b]pyridine (700 mg, 2.16 mmol) in THF (20 mL) was added *N,N*-diisopropylethylamine (419 mg, 3.24 mmol). The resulting reaction mixture solution was then stirred at 70 °C for 10 h before it was cooled back to room temperature. The mixture solution was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-100% EtOAc-hexane

gradient) to afford the title compound (200 mg, 19.2% yield) as a yellow oil. MS : 483.1 (M+H)⁺.

[G] (rac)-(1R,2S,4R,5S,6S,7S)-7-((2-(5-Chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-cyclopropyl-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (rac)-1R,2S,4R,5S,6S,7S)-methyl 7-((2-(5-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-cyclopropyl-5-fluoropyrimidin-4-

yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (200 mg, 414 μmol) in THF (5 mL) and

MeOH (5 mL) was added lithium hydroxide (99.2 mg, 4.14 mmol) pre-dissolved in water (5 mL). The resulting reaction mixture solution was stirred at room temperature for 12 h before

being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to

pH 4 and extracted with EtOAc (40 mL three times). Combined organics were then dried

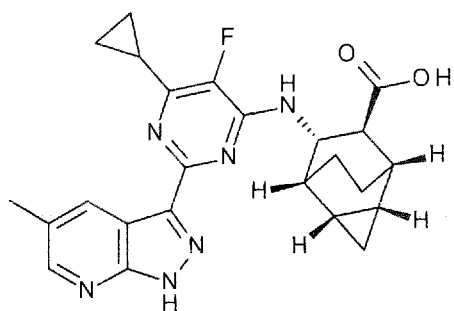
over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford the title compound (7 mg, 3.6% yield) as a white foam.

MS: 469.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.72 (d, J=2.32 Hz, 1H), 8.60 (d, J=2.32 Hz, 1H), 7.20-7.27 (m, 1H), 4.40-4.48 (m, 1H), 3.14-3.20 (m, 1H), 2.85-2.92 (m, 1H), 2.57-2.62 (m, 1H), 2.40-2.46 (m, 1H), 2.21-2.30 (m, 1H), 1.40-1.79 (m, 4H), 1.21-1.27 (m, 2H),

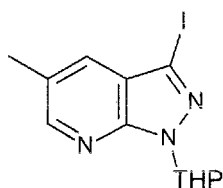
0.96-1.17 (m, 4H), 0.71-0.83 (m, 1H), 0.22-0.34 (m, 1H).

Example 190

(rac)-(1R,2S,4R,5S,6S,7S)-7-((6-Cyclopropyl-5-fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

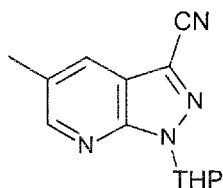


[A] 3-Iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile



To a stirred mixture solution of 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (Intermediate A-7, 5 g, 19.3 mmol) and 3,4-dihydro-2H-pyran (13 g, 14.1 mL, 154 mmol) in toluene (100 mL) was added 2,2,2-trifluoroacetic acid (440 mg, 3.86 mmol) and the resulting reaction mixture solution was stirred at 100 °C for 12 h before it was cooled back to room temperature. The reaction mixture was then poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (5.4g, 81.5% yield) as a white solid. MS: 344.1 (M+1)⁺.

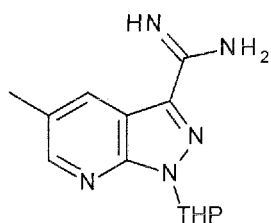
[B] 5-Methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile



A mixture solution of 3-iodo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine (3 g, 8.74 mmol) and copper(I) cyanide (2.35 g, 26.2 mmol) in DMF (30 mL) was stirred at 100 °C overnight. After cooling to room temperature, the reaction mixture was poured into ice water, and then the reaction mixture was extracted with EtOAc and washed with ammonium hydroxide solution and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified

by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (1.5 g, 70% yield) as a yellow solid. MS: 243.1 (M+H)⁺.

[C] 5-Methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyridine-3-carboximidamide

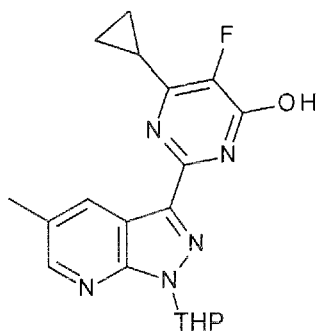


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To a solution of sodium methanolate (988 mg, 18.3 mmol) in MeOH (100 mL) was added 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile (1.3 g, 5.37 mmol) and the resulting reaction mixture was stirred at 40 °C for 3 h before it was cooled back to room temperature. AcOH (1.61 g, 1.53 mL, 26.8 mmol) and ammonium chloride (861 mg, 16.1 mmol) were added to the above mixture and the resulting solution was stirred at 70 °C overnight. After cooling to room temperature, the mixture was filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (7-20% Methanol-DCM gradient) to afford the title compound (600 mg, 43.1 % yield) as a yellow foam. MS: 260.1 (M+H)⁺.

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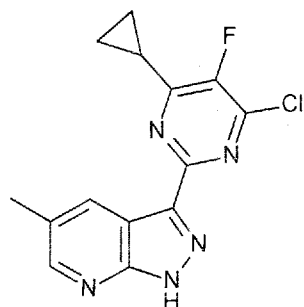
[D] 6-Cyclopropyl-5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ol



To a stirred mixture solution of 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1 H-pyrazolo[3,4-b]pyridine-3-carboximidamide (648 mg, 2.5 mmol) and methyl 3-cyclopropyl-2-fluoro-3-oxopropanoate (400 mg, 2.5 mmol) in MeOH (30 mL) was added sodium methoxide (270 mg, 5 mmol) and the resulting mixture solution was heated to reflux overnight while a white solid precipitated. After cooling to room temperature, most of MeOH was evaporated off under vacuum. Water (10 mL) was added and the remaining mixture solution was

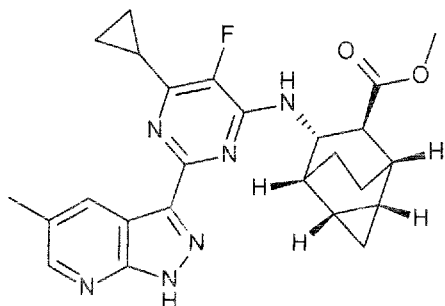
ultrasonated for 5 min before filtration. The filter cake was collected and then dried under vacuum to give a crude product (800 mg, 86.7% yield) as a white solid. MS: 370.1 (M+H)⁺. This crude product was used directly in the next step without further purification.

5 [E] 3-(4-Chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-5-methyl-1H-pyrazolo[3,4-b]pyridine



To a suspension of 6-cyclopropyl-5-fluoro-2-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-ol (800 mg, 2.17 mmol) in phosphorus oxychloride (13.3 g, 7.93 ml, 86.6 mmol) was slowly added *N,N*-dimethylaniline (262 mg, 280 μ l, 2.17 mmol). After the addition, the mixture solution was heated to 80 °C for 12 h before it was cooled back to room temperature. After TLC (DCM:MeOH = 20:1) showed completion of the reaction, the reaction mixture was concentrated and poured into water (20 mL) and extracted with EtOAc (30 mL twice). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-30% EtOAc-hexane gradient) to afford the title compound (658 mg, 100% yield) as a yellow oil. MS: 304.1 (M+H)⁺.

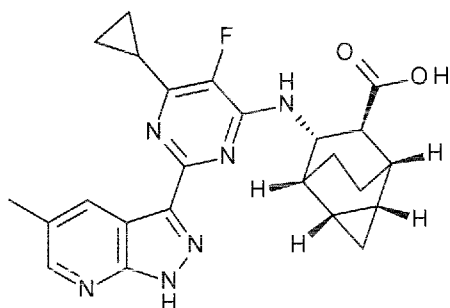
[F] (rac)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((6-cyclopropyl-5-fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate



To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (450 mg, 2.3 mmol) and 3-(4-chloro-6-cyclopropyl-5-fluoropyrimidin-2-yl)-5-methyl-1H-pyrazolo[3,4-b]pyridine (700 mg, 2.3 mmol)

in THF (20 mL) was added *N,N*-diisopropylethylamine (447 mg, 602 μ l, 3.46 mmol) and the resulting reaction mixture solution was stirred at 70 °C for 10 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL twice). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (20-60% EtOAc-hexane gradient) to afford the title compound (200 mg, 18.8% yield) as a yellow oil. MS: 463.1 (M+H)⁺.

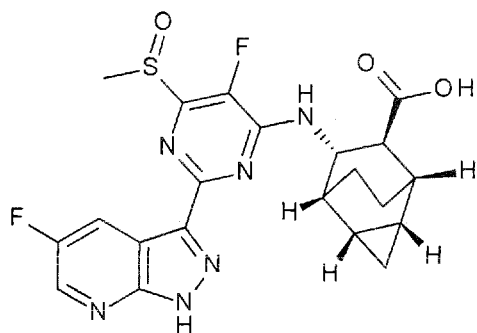
(rac)-(1R,2S,4R,5S,6S,7S)-7-((6-cyclopropyl-5-fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid



To a stirred mixture solution of (rac)-(1R,2S,4R,5S,6S,7S)-methyl 7-((6-cyclopropyl-5-fluoro-2-(5-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylate (200 mg, 432 μ mol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide (104 mg, 4.32 mmol) pre-dissolved in water (5 mL). The reaction mixture solution was stirred at room temperature for 12 h before being diluted with water (10 mL) and extracted with diethyl ether (20 mL). The organic layer was discarded and the aqueous layer was acidified with concentrated hydrochloric acid to pH 4 and extracted with EtOAc (40 mL three times). Combined organics were then dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude product, which was then purified by prep-HPLC to afford the title compound (5 mg, 2.6% yield) as a white foam. MS: 449.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.40-8.54 (m, 2H), 7.15-7.24 (m, 1H), 4.42-4.52 (m, 1H), 2.83-2.93 (m, 1H), 2.57-2.64 (m, 1H), 2.48 (s, 3H), 2.41-2.45 (m, 1H), 2.20-2.31 (m, 1H), 1.41-1.75 (m, 5H), 0.95-1.18 (m, 6H), 0.71-0.82 (m, 1H), 0.23-0.33 (m, 1H).

Example 191

(rac)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(5-fluoro-1H-pyrazolo[3,4-b]pyridin-3-yl)-6-(methylsulfinyl)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid

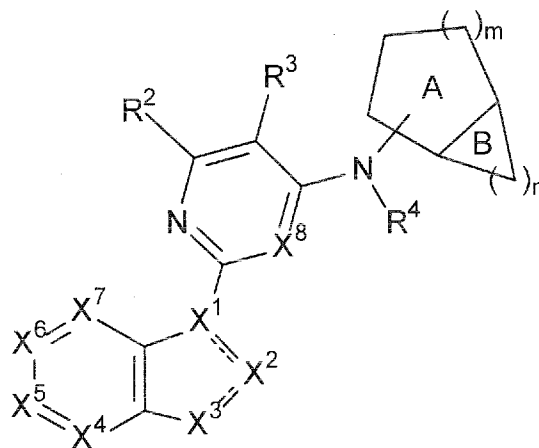


To a stirred solution of (rac)-(6S,7S)-7-((5-fluoro-2-(5-fluoro-1 H-pyrazolo[3,4-b]pyridin-3-yl)-6-(methylthio)pyrimidin-4-yl)amino)tricyclo[3.2.2.0^{2,4}]nonane-6-carboxylic acid (150 mg, 327 μ mol) in DCM (20 mL) was added 3-chlorobenzoperoxoic acid (67.7 mg, 393 μ mol) in an ice-bath. The reaction mixture was stirred at 0 °C for 3 h before being poured into aqueous saturated NaHCO₃ solution (20 mL) and extracted with DCM (20 mL three times). The combined organics were then washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to give a crude title compound, which was purified by prep-HPLC to afford the title compound (8 mg, 4.9% yield) as a white solid. MS: 475.3 [M+H]⁺. ¹H NMR (400 MHz, MeOH-d₄) δ 8.43-8.59 (m, 2H), 4.58 (d, J=6.48 Hz, 1H), 2.96-3.04 (m, 3H), 2.67 (d, J=4.16 Hz, 1H), 2.55 (s, 1H), 2.43 (d, J=2.32 Hz, 1H), 1.67-1.81 (m, 2H), 1.56 (t, J=10.15 Hz, 2H), 1.03 (tt, J=4.08, 8.45 Hz, 1H), 0.76-0.90 (m, 2H), 0.30-0.39 (m, 1H).

5

CLAIMS

- 10 1. A compound having the formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



(I)

15

wherein

==== is a single or double bond;

20

R¹ is selected from the group consisting of -H, -halogen, -CN, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(O)R^{**}, -N(R^{**})-C(O)-OR^{**}, -N(R^{**})-C(O)-NR^{**}R^{**}, -N(R^{**})-S(O)₂R^{**}, -(optionally substituted C₁₋₆ alkyl), -OR^{**}, -(optionally substituted heterocyclyl), -(optionally substituted C₁₋₄ alkyne)-(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl), and -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl), and

25

wherein the -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -G(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{*}, -NR^{***}R^{***}, -NR^{***}-C(O)R^{***}, -N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, -N(R^{***})-S(O)₂R^{***}, -OR^{***}, -O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***}, -S(O)₂-NR^{***}R^{***}, -N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂; wherein R^{***} is H, C₁₋₆ alkyl, heterocyclyl or carbocyclyl; and wherein -(optionally substituted) can also be C₁₋₆ alkyl in the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl);

R² is selected from the group consisting of -H, -halogen, -CN, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{**}, -NR^{**}R^{*}, -NR^{*}-C(O)R^{**}, -N(R^{**})-C(O)-OR^{**}, -N(R^{**})-C(O)-NR^{**}R^{**}, -N(R^{**})-S(O)₂R^{**}, -(optionally substituted C₁₋₆ alkyl), -OR^{**}, -SR^{**}, -S(O)R^{*}, -S(O)₂R^{**}, -(optionally substituted heterocyclyl), -(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl), and -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{*} is H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl), and

wherein the -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{***}, -NR^{***}R^{***}, -NR^{***}-C(O)R^{***}, -N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, -N(R^{***})-S(O)₂R^{***}, -OR^{***}, -O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***}, -S(O)₂-NR^{***}R^{***}, -N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂; wherein R^{***} is H, C₁₋₃ alkyl, benzyl, heterocyclyl or carbocyclyl; and wherein -(optionally substituted) can also be C₁₋₆ alkyl in the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl);

R³ is selected from the group consisting of -H, -halogen, -CN, -NO₂, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{**}, -OR^{**}, -SR^{**}, -S(O)R^{**}, -S(O)₂R^{**}, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted C₃₋₆ cycloalkyl), -(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl), and -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl), wherein R^{**} is H,

-(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl), and

wherein the -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(O)R^{***}, -COOR^{***}, -C(O)NR^{***}R^{***}, -NR^{***}R^{***}, -NR^{***}-C(O)R^{***}, -N(R^{***})-C(O)-OR^{***}, -N(R^{***})-C(O)-NR^{***}R^{***}, -N(R^{***})-S(O)₂R^{***}, -OR^{***}, -O-C(O)R^{***}, -O-C(O)-NR^{***}R^{***}, -SR^{***}, -S(O)R^{***}, -S(O)₂R^{***}, -S(O)₂-NR^{***}R^{***}, -N(R^{***})-S(O)₂-NR^{***}R^{***}, -P(O)(OR^{***})₂, or -O-P(O)(OR^{***})₂; wherein R^{***} is H, C₁₋₆ alkyl, benzyl, heterocyclyl or carbocyclyl; and wherein -(optionally substituted) can also be C₁₋₆ alkyl in the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl); or

alternatively, R² and R³ are linked together to form, with the carbon atoms to which they are attached, a carbocyclic or heterocyclic 5 to 7-membered ring which optionally comprises 0 to 3 heteroatoms in the ring and which may be substituted with one or more substituents Independently selected from R⁶.

R⁴ is selected from the group consisting of -H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted carbocyclyl), and -(optionally substituted heterocyclyl), wherein the -(optionally substituted) can be independently -halogen, -CN, -NO₂, oxo, -C(O)R^{**}, -COOR^{**}, -C(O)NR^{**}R^{**}, -NR^{**}R^{**}, -NR^{**}-C(O)R^{**}, -N(R^{**})-C(O)-OR^{**}, -N(R^{**})-C(O)-NR^{**}R^{**}, -N(R^{**})-S(O)₂R^{**}, -OR^{**}, -O-C(O)R^{**}, -O-C(O)-NR^{**}R^{**}, -SR^{**}, -S(O)R^{**}, -S(O)₂R^{**}, -S(O)₂-NR^{**}R^{**}, -N(R^{**})-S(O)₂-NR^{**}R^{**}, -P(O)(OR^{**})₂, or -O-P(O)(OR^{**})₂; wherein R^{**} is C₁₋₆ alkyl or C₃₋₆ cycloalkyl which can optionally be substituted with halogen; and wherein -(optionally substituted) can also be C₁₋₆ alkyl in the case of -(optionally substituted heterocyclyl) or -(optionally substituted carbocyclyl);

R^{5a} is selected from the group consisting of -halogen, -OR^{*}, and -CN, wherein R^{*} is -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally substituted carbocyclyl);

R^{5b} is selected from the group consisting of -H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted heterocyclyl), -(optionally substituted carbocyclyl),

-(optionally substituted C₁₋₄ alkylene)-(optionally substituted heterocyclyl) and
 -(optionally substituted C₁₋₄ alkylene)-(optionally substituted carbocyclyl),
 wherein R* is -(optionally substituted d_e alkyl), -(optionally substituted
 heterocyclyl), or -(optionally substituted carbocyclyl);

wherein the -(optionally substituted heterocyclyl) and -(optionally substituted
 carbocyclyl) in R^{5a} and R^{5b} may furthermore be bridged and the bridge may
 contain 0 to 2 carbonatoms and 0 to 2 heieroatoms, and wherein the
 -(optionally substituted) in R^{5a} and R^{5b} can be independently -halogen, -CN,
 -CF₃, -CHF₂, -CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -NR*R*, -NR*COR*,
 -NR*C(0)NR*R*, -NR*S(0₂)NR*R*, -C(0)OR*, -C(0)NR*R*, -OH, or -O-d_e
 alkyl, wherein each R* is H, d₆ alkyl or C₃₋₆ cycloalkyl; and wherein -(optionally
 substituted) can also be d₆ alkyl in the case of -(optionally substituted
 heterocyclyl) or -(optionally substituted carbocyclyl);

R⁶ is independently selected from the group consisting of -H, -Hal, -OR**, oxo,
 -CN, -NO₂, -C(0)R**, -COOR**, -C(0)NR**R**, -NR**R*, -NR**C(0)R**,
 -NR**C(0)NR**R*, -NR**S(0₂)NR**R*, -(CH₂)_pSR**, -(CH₂)_pS(0)R**,
 -(CH₂)_pS(0₂)R**, -(CH₂)_pS(0₂)NR**, -(optionally substituted d-e alkyl),
 -O-(optionally substituted d₆ alkyl), -(optionally substituted carbocyclyl) and
 -(optionally substituted heterocyclyl), wherein R** is H, -(optionally substituted
 d₆ alkyl), -(optionally substituted C₁₋₄ alkylene)-O-(optionally substituted C₁₋₆
 alkyl), and wherein the (optionally substituted) can be independently -H,
 -halogen, -OH, or -CN;

R⁷ is selected from the group consisting of -H and -d₆ alkyl;

R⁸ is independently selected from the group consisting of -H, -Hal, -CN,
 -NR**R*, -(optionally substituted C₁₋₆ alkyl), -OR**, -(optionally substituted
 heterocyclyl), -(optionally substituted carbocyclyl), wherein R** is H, -(optionally
 substituted d₆ alkyl), -(optionally substituted heterocyclyl), or -(optionally
 substituted carbocyclyl), and wherein the -(optionally substituted) may be
 halogen;

R^9 is independently selected from the group consisting of -H, -C₁₋₆ alkyl, -Hal, -OR*, -NR*R*, -CN, and CF₃, wherein R* is -H or -C₁₋₆ alkyl;

R^{10} is independently selected from the group consisting of -H, -Hal, -CN, -NO₂,
 5 -(optionally substituted C₁₋₆ alkyl), -NR*R*, and -OR*, wherein R* is -H, or
 -(optionally substituted C₁₋₆ alkyl), and wherein the -(optionally substituted)
 may be halogen;

X^1 is selected from the group consisting of N and C;

X^2 is selected from the group consisting of N and CR⁹;

X^3 is selected from the group consisting of N, NR⁹, CR⁹ and CR⁹₂, as valency
 15 permits;

X^4 is selected from the group consisting of N and CR⁹;

X^5 is selected from the group consisting of N and CR⁸;

X^6 is selected from the group consisting of N and CR¹;

X^7 is selected from the group consisting of N and CR⁸;

with the proviso that $X^1 \text{-----} X^2 \text{-----} X^3$ is $X^1 \text{--} X^2 \text{=} X^3$ if X^1 is N and $X^1 \text{-----} X^2$
 25 $\text{-----} X^3$ is $X^1 \text{=} X^2 \text{--} X^3$ if X^1 is C; and with the further proviso that at least one of
 X^1 , X^2 , and X^3 is N or NR⁹;

X^8 is selected from the group consisting of N and CR¹⁰;

30 the ring **A** is a saturated monocyclic carbocyclic ring having 5 to 8 ring carbon
 atoms or a saturated bridged carbocyclic ring having 5 to 8 ring carbon atoms
 and 1 to 3 carbon atoms in the bridge or a saturated bridged heterocyclic ring
 having 5 to 8 ring carbon atoms and 0 to 2 heteroatoms in the ring, and 0 to 2
 carbon atoms and 0 to 2 heteroatoms in the bridge, wherein the ring A can be

optionally substituted in any available position by one or more substituents which are selected from the group consisting of -L-R⁵;

the ring B, which is fused to the ring A, is a saturated monocyclic carbocyclic ring having 3 to 6 ring carbon atoms, wherein the ring B can be optionally substituted in any available position by one or more substituents which are selected from the group consisting of -L-R⁵;

-L-R⁵ is selected from -L^a-R^{5a} and -L^b-R^{5b};

L^a is selected from the group consisting of -(CH₂)_p-C(O)-, -(CH₂)_p-CR⁷(OR⁷)-, -(CH₂)_p-C(O)-N(R⁷)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-C(O)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-S(O)₂-, -(CR⁷R⁷)_p-S(O)₂-, -(CR⁷R⁷)_p-S(O)-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(O)₂-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-(optionally substituted heterocyclylene)- and a bond; the optional substituent of the heterocyclylene is independently selected from one or more groups selected from -Hal, -CN, -NO₂, -OH and -NH₂;

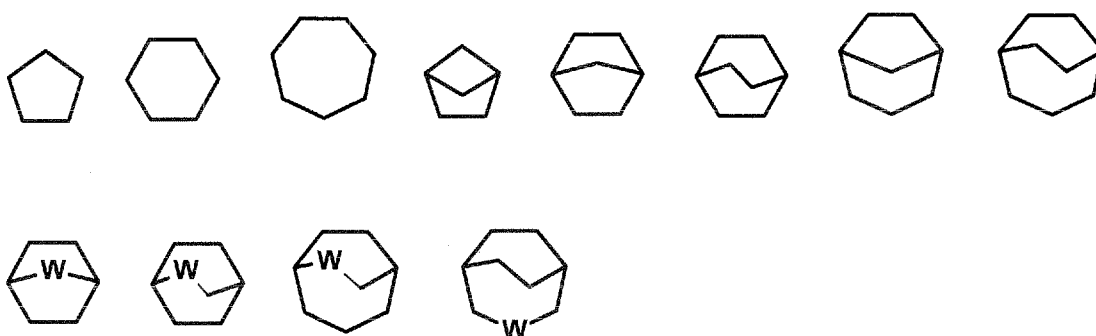
L^b is selected from the group consisting of -(CH₂)_p-C(O)-O-, -(CH₂)_p-C(O)-, -(CH₂)_p-CR⁷(OR⁷)-, -(CH₂)_p-C(O)-N(R⁷)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-, -(CH₂)_p-N(R⁷)-C(O)-(CH₂)_p-, -(CH₂)_p-N(R⁷)-C(O)-O-, -(CH₂)_p-N(R⁷)-C(O)-N(R⁷)-, -(CH₂)_p-N(R⁷)-S(O)₂-, -N(R⁷)-S(O)₂-N(R⁷)-, -(CH₂)_p-O-C(O)-, -(CH₂)_p-O-C(O)-N(R⁷)-, -(CR⁷R⁷)_p-O-, -(CR⁷R⁷)_p-S(O)-, -(CR⁷R⁷)_p-S(O)₂-, -(CR⁷R⁷)_p-S-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(O)-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(O)₂-(CR⁷R⁷)_p-, -(CR⁷R⁷)_p-S(O)₂-N(R⁷)-, -(CR⁷R⁷)_p-S(O)₂-N(R⁷)-C(O)-, -(CR⁷R⁷)_p-P(O)(OR⁷)O-, -Q-P(O)(OR⁷)Q-, -P(O)₂O-, -(CR⁷R⁷)_p-(optionally substituted heterocyclylene)- and a bond; the optional substituent of the heterocyclylene is independently selected from one or more groups selected from -Hal, -CN, -NO₂, -OH and -NH₂;

m is 1 to 3;

n is 1 to 4;

p is 0 to 6.

2. The compound according to claim 1, wherein the ring A is selected from the group consisting of



wherein each W is independently selected from C, N, O and S, wherein ring A can be substituted in any available position by one or two substituents which are selected from the group consisting of $-L-R^5$.

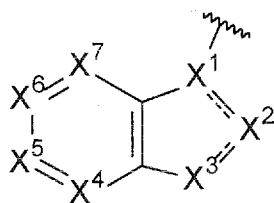
3. The compound according to claim 1 or 2, wherein the ring B is



4. The compound according to any of the preceding claims, wherein R^3 is -halogen.
5. The compound according to any of the preceding claims, wherein R^1 is selected from the group consisting of -H, -halogen, -CN, and $-C_{1-5}$ alkyl, which is optionally substituted by one or more selected from -halogen, -heterocyclyl and -carbocyclyl.
6. The compound according to any of the preceding claims, wherein R^2 is -H and/or R^4 is -H and/or R^6 is -H and/or R^7 is -H.
7. The compound according to any of the preceding claims, wherein L^b is selected from the group consisting of $-C(O)-O-$, $-O-C(O)-$, $-C(O)-N(R^7)-$, $-N(R^7)-C(O)-$, and $-(CR^7R^7)_p-O-$.

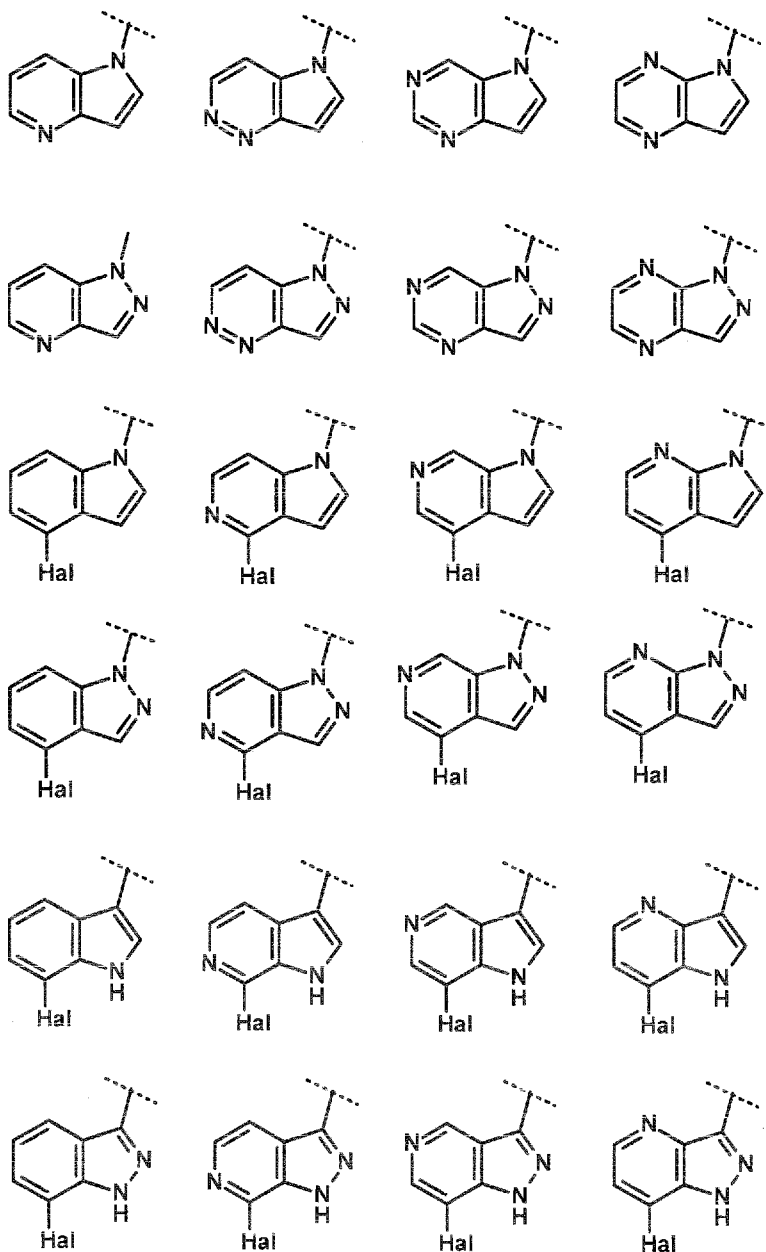
8. The compound according to any of the preceding claims, wherein R^{5b} is selected from the group consisting of -H, C_{1-6} alkyl, -heterocyclyl, and -carbocyclyl.

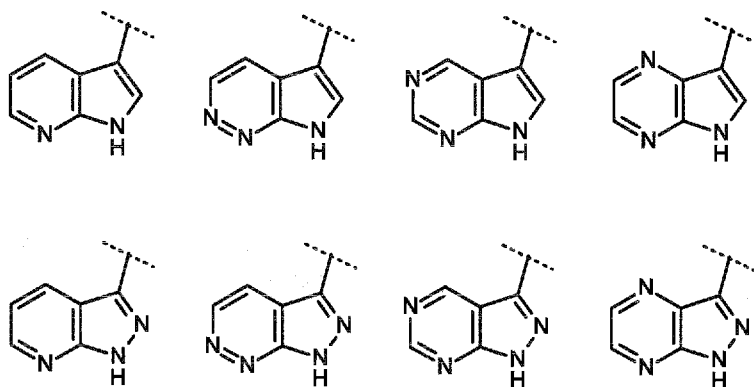
9. The compound according to any of the preceding claims, wherein



5

is selected from the group consisting of





wherein Hal is selected from F, Cl, Br and I, and wherein X^6 is CR^1 .

10. The compound according to any of the preceding claims, wherein R^2 is selected from the group consisting of -H, -CN, -OH, -C(=O)R^{**}, -COOR^{**}, -C(=O)NR^{**}R^{**}, -NR^{**}R^{**}, -O-(optionally substituted C₁₋₆ alkyl) and -(optionally substituted C₁₋₆ alkyl), wherein R^{**} is H or -(optionally substituted C₁₋₆ alkyl), and wherein the optional substituent is halogen; and wherein R³ is selected from the group consisting of -H, -halogen, -CN, -NO₂, -OH, -O-(optionally substituted C₁₋₆ alkyl) and -(optionally substituted C₁₋₆ alkyl), wherein the optional substituent is halogen.
11. A pharmaceutical composition comprising:
a compound having the formula (I) as defined in any of claims 1 to 10, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).
12. A compound having the formula (I) as defined in any of claims 1 to 10, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, wherein the compound is for use in the treatment, amelioration or prevention of influenza.
13. A method of treating, ameliorating or preventing influenza, the method comprising administering to a patient in need thereof an effective amount of a compound having the formula (I) as defined in any of claims 1 to 10, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2017/072837

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/04(2006.01)i; C07D 471/04(2006.01)i; C07D 487/04(2006.01)i; A61K 31/16(2006.01)i; A61P 31/16(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D401/-; C07D471/-; C07D487/-; A61K31/-; A61P31/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS; CNKI; WPI; EPODOC; REGISTRY(STN); CAPLUS(STN); MARPAT(STN); SAVIRA; pyrimidine; pyridine; influenza; influ+; Structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 103562205 A (VERTEX PHARM. INC.) 05 February 2014 (2014-02-05) description, paragraphs[0017]-[0055], [0076]-[0078], [0349]-[0358]	1-13
X	CN 103492381 A (VERTEX PHARM. INC.) 01 January 2014 (2014-01-01) description, paragraphs[0017]-[0054], [0071], [0570]-[0581]	1-13
X	CN 103492382 A (VERTEX PHARM. INC.) 01 January 2014 (2014-01-01) description, paragraphs[0017]-[0054], [0258], [0730]-[0738]	1-13
X	CN 102458408 A (VERTEX PHARM. INC.) 16 May 2012 (2012-05-16) description, paragraphs[0018]-[0067], [0103]-[0105], [0137], Figures.1-8	1-13
X	WO 2013184985 A1 (VERTEX PHARM. INC.) 12 December 2013 (2013-12-12) description, paragraphs[001 15]-[00125], [00267]	1-13
A	WO 2015103453 A1 (SQUIBB BRISTOL MYERS CO.) 09 July 2015 (2015-07-09) pages 5-21, page 55 line 26, Tables4-19	1-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 April 2017

Date of mailing of the international search report

03 May 2017

Name and mailing address of the ISA/CN

STATE INTELLECTUAL PROPERTY OFFICE OF THE
P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088
China

Facsimile No. (86-10)62019451

Authorized officer

CHEN, Wenrui

Telephone No. (86-10)010-82246747

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2017/072837

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 13 is directed to a method for treatment of the human body by therapy. This search report has been established on the basis of the use of the said compounds for manufacture of medicaments thereof.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2017/072837

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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				JP	2013545818	A	26 December 2013
				WO	2012083122	A1	21 June 2012
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				US	2013345218	A1	26 December 2013
				MX	2013006840	A	31 January 2014
				WO	2012083122	A8	05 December 2013
				EP	2651938	A1	23 October 2013
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				RU	2013132681	A	27 January 2015
				MX	2013006836	A	26 September 2013
				US	8871774	B2	28 October 2014
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				SI	2442809	T1	31 January 2017
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				EP	2442809	B1	31 August 2016

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2017/072837

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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				US	2014142119	A1	22 May 2014
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				TW	1483941	B	11 May 2015
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WO	2013184985	A1	12 December 2013	EP	2858984	A1	15 April 2015
WO	2015103453	A1	09 July 2015	TW	201609693	A	16 March 2016
				MX	2016008723	A	07 September 2016
				JP	2017501202	A	12 January 2017
				CA	2935329	A1	09 July 2015
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