(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 August 2017 (10.08.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/133669 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 31/16* (2006.01)
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/CN2017/072839

(22) International Filing Date:
3 February 2017 (03.02.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2016/073636
5 February 2016 (05.02.2016) CN

(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: **LIU, Yongfu**; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN). **WU, Jun**; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN). **WANG, Lisha**; Klingnaustrasse 19, 4058 Basel (CH). **SHEN, Hong**; Building No. 5, Lane 720 Cailun Road, Shanghai 201203 (CN). **SHI, Tianlai**; Riehenstrasse 43, 4058 Basel (CH).

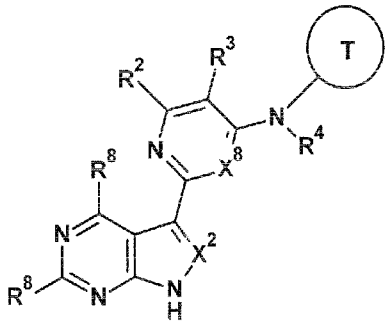
(74) Agent: **ZHONGZI LAW OFFICE**; 7F, New Era Building, 26 Pinganli Xidajie, Xicheng District, Beijing 100034 (CN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: 5, 7-DIAZAINDOLE AND 5, 7-DIAZAINDAZOLE DERIVATIVES AND THEIR USE IN THE TREATMENT, AMELIORATION OR PREVENTION OF INFLUENZA



(I)

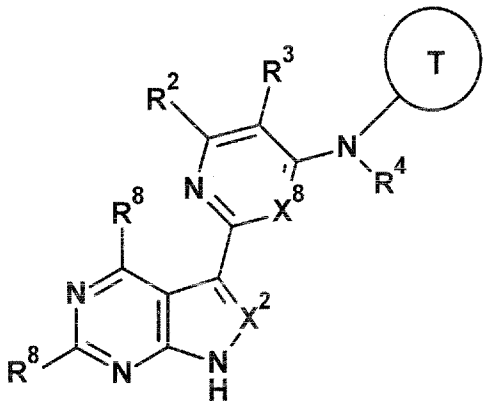
(57) Abstract: The present invention relates to a specific compound having the formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, which is useful in treating, ameloriating or preventing influenza.

WO 2017/133669 A1

5,7-Diazaindole and 5,7-diazaindazole derivatives and their use in the treatment, amelioration or prevention of influenza

Field of the invention

The present invention relates to a specific 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, ameloriating 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 (Tamilflu) 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 happenend 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, Bornaviridae, 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 (Tomassini 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.

WO 2007/041130 relates to certain deazapurine compounds which are stated to be useful as inhibitors of Janus kinases (JAK).

WO 2011/094290 discloses certain pyrazolopyrimidines which are described as being PKC theta inhibitors.

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.

Summary of the invention

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

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.

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).

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

Detailed description of the invention

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 Kölbl, 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.

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.

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. 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.

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 C_{3-6} cycloalkyl ring.

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

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., $-(CH_2)_q-$ with q = 1 to 3).

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.

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.

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, glucoheptonate, 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, 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 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-propanolates.

The term "codrug" refers to two or more therapeutic compounds bonded via a covalent 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 stoichiometric or non-stoichometric 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.

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.

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. Futhermore, 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 C_{1-4}-alkyleneglycol linkers, e.g. resulting in phosphonooxyalkyl amides. The amides include amides formed by reaction with one or more amino acids.

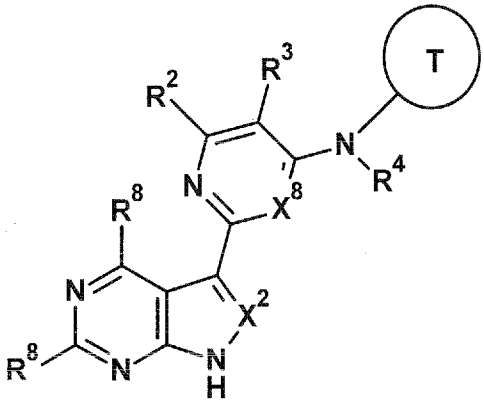
Substitued thiol functionalities can be converted into sulfoxides or sulfones.

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)

Throughout the present invention the following definitions apply.

R^2 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**)–$S(O)_2$R**, –(optionally substituted C_{1-6} alkyl), –OR**, –SR**, –S(O)R**, –$S(O)_2$R**, –(optionally substituted heterocyclyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), and –(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, –NO_2, 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***)–$S(O)_2$R***, –OR***, –O–C(O)R***, –O–C(O)–NR***R***, –SR***, –S(O)R***, –$S(O)_2$R***, –$S(O)_2$–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 C_{1-6} alkyl. R*** is H, benzyl, C_{1-6} alkyl, heterocyclyl or carbocyclyl. Preferably **R^2** 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**)–$S(O)_2$R**, –(optionally substituted C_{1-6} alkyl), –OR**, –(optionally substituted heterocyclyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), and –(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, –NO_2, 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)$_2$R***, –OR***, –O–C(O)R***, –O–C(O)–NR***R***, –SR***, –S(O)R***, –S(O)$_2$R***, –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 C_{1-6} alkyl. R*** is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. More preferably, **R^2** is selected from the group consisting of –H, –halogen, –CN, –NR**R**, –NR**–C(O)R**, –N(R**)–C(O)–OR**, –N(R**)–C(O)–NR**R**, –N(R**)–S(O)$_2$R**, –OR**, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-6} cycloalkyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl), and –(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, –NO$_2$, 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)$_2$R***, –OR***, –O–C(O)R***, –O–C(O)–NR***R***, –SR***, –S(O)R***, –S(O)$_2$R***, –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 C_{1-6} alkyl. R*** is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. Even more preferably **R^2** is –H.

R^3 is selected from the group consisting of –H, –halogen, –CN, –NO$_2$, –C(O)R**, –COOR**, –C(O)NR**R**, –OR**, –SR**, –S(O)R**, –S(O)$_2$R**, –(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, –NO$_2$, 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)$_2$R***, –OR***, –O–C(O)R***, –O–C(O)–NR***R***, –SR***, –S(O)R***, –S(O)$_2$R***, –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 C_{1-6} alkyl. R*** is H, C_{1-6} alkyl, benzyl, heterocyclyl or carbocyclyl. Preferably, **R^3** is selected from the group consisting of –H, –halogen, –CN, –NO$_2$, –C(O)R**, –COOR**, –C(O)NR**R**, –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, $–NO_2$, 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 C_{1-6} alkyl. R*** is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. More preferably, **R^3** is selected from the group consisting of –H, –halogen, –CN, –OR**, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl), and –(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, 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 C_{1-6} alkyl. R*** is H, C_{1-6} alkyl, heterocyclyl or carbocyclyl. Even more preferably **R^3** is –halogen.

R^4 is selected from the group consisting of –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted carbocyclyl), and –(optionally substituted heterocyclyl), wherein the –(optionally substituted) can be independently –halogen, –CN, $–NO_2$, 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 C_{1-6} alkyl. R** is C_{1-6} alkyl or C_{3-6} cycloalkyl which can optionally be substituted with halogen. Preferably **R^4** is $–C_{1-6}$ alkyl or –H, more preferably –H.

R^{5a} is selected from the group consisting of –halogen, –OR*, and –CN, wherein R* is –(optionally substituted C_{1-6} alkyl), –(optionally substituted heterocyclyl), or –(optionally substituted carbocyclyl). Preferably R^{5a} is selected from the group consisting of –halogen, –CN, and –O–(optionally substituted C_{1-6} alkyl).

R^{5b} is selected from the group consisting of –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl) and –(optionally substituted C_{1-4} alkylene)–(optionally substituted carbocyclyl), wherein R* is –(optionally substituted C_{1-6} alkyl), –(optionally substituted heterocyclyl), or –(optionally substituted carbocyclyl). Preferably R^5 is selected from the group consisting of –H, –(optionally substituted C_{1-6} alkyl), –(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*, –OH, or –O–C_{1-6} alkyl, wherein each R* is H or 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 C_{1-6} alkyl.

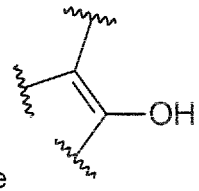
R^7 is selected from the group consisting of of –H and –C_{1-6} alkyl. Preferably R^7 is –H or $–CH_3$, more preferably R^7 is –H.

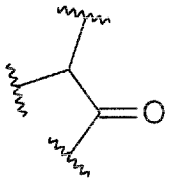
R^8 is independently selected from the group consisting of –H, –Hal, –CN, –NR**R**, –(optionally substituted C_{1-6} alkyl), –OR**, –(optionally substituted heterocyclyl), and –(optionally substituted carbocyclyl), wherein R** is H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted heterocyclyl), or –(optionally substituted carbocyclyl). The –(optionally substituted) is preferably halogen. Preferably R^8 is –H.

R^{9} is independently selected from the group consisting of –H, –C_{1-6} alkyl, –Hal, –OR*, –NR*R*, –CN, and CF_3, wherein R* is –H or –C_{1-6} alkyl. –Preferably **R**^{9} is –H or –Hal.

R^{10} is independently selected from the group consisting of –H, –Hal, –CN, –NO_2, –(optionally substituted C_{1-6} alkyl), –NR*R*, and –OR*, wherein R* is –H, or –(optionally substituted C_{1-6} alkyl). The –(optionally substituted) is preferably halogen. Preferably **R**^{10} is –H.

X^{2} is selected from the group consisting of N and CR^9. In one embodiment, **X**^{2} is N. In another embodiment, **X**^{2} is CR^9.

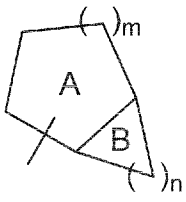
When X^2 is C-R^9 and R^9 is –OH, e.g., resulting in the partial structure 

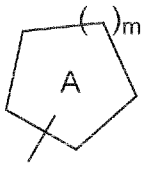
, any compound containing the tautomer thereof having the following partial structure 

is also comprised.

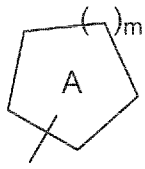
X^{8} is selected from the group consisting of N and CR^{10}. In one embodiment, **X**^{8} is N. In another embodiment, **X**^{8} is CR^{10}.

T is selected from the group consisting of



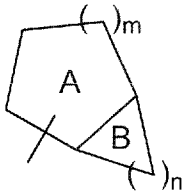
and 

.

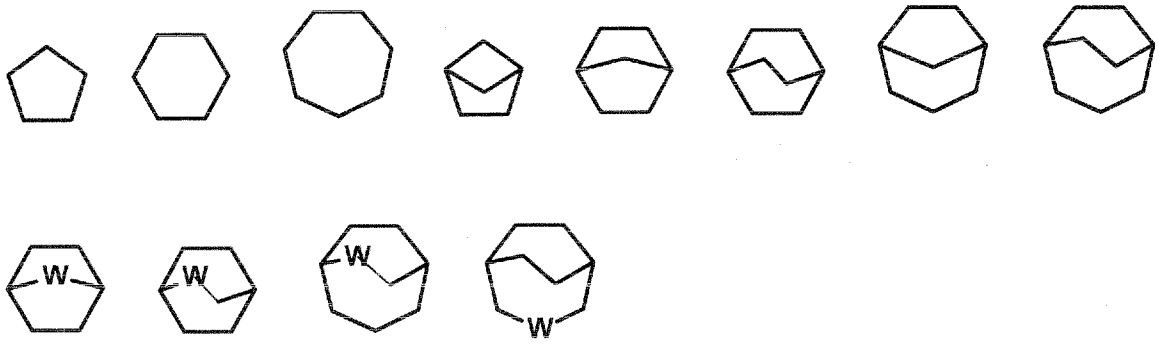
In a preferred embodiment, the ring **T** is 

.

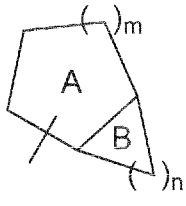
When $\mathbf{X}^2$ is CR^9, the ring **T** is preferably selected from the group consisting of

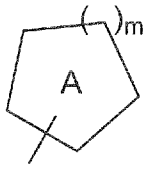


The ring **A** is a saturated monocyclic carbocyclic ring having 5 to 8 ring carbon atoms or a saturated bridged carbocyclic ring having 5 to 8 ring carbon atoms and 1 to 3 carbon atoms in the bridge or a saturated bridged heterocyclic ring having 5 to 8 ring carbon atoms and 0 to 2 heteroatoms (e.g., 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 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 hetero atoms 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 $-L-R^5$.

It is to be understood that the corners of the ring A in 

and 

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).

The ring **A** can be optionally substituted in any available position by one or more substituents which are selected from the group consisting of $-L-R^5$. In a preferred embodiment the ring **A** is substituted, for example by one or two substituents.

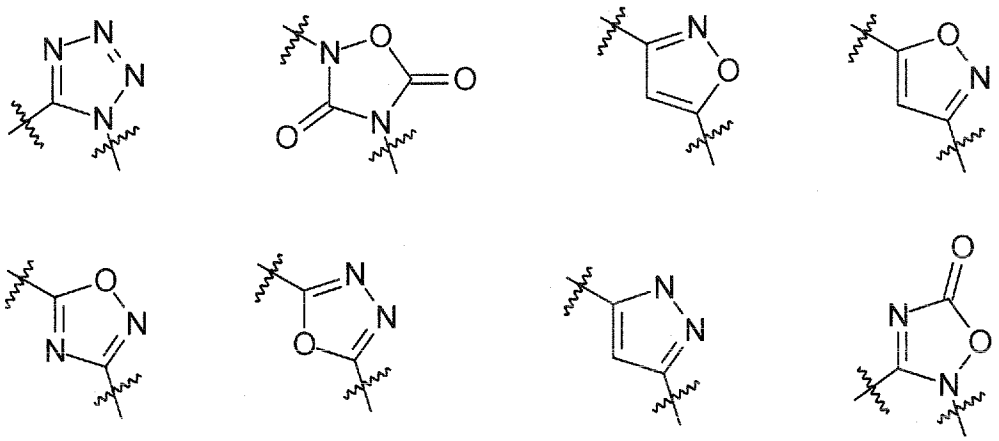
The ring **A** can be attached to the $-N(R^4)-$ moiety at any available position.

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

The ring **B** can be optionally substituted in any available position by one or more substituents which are selected from the group consisting of $-L-R^5$. Preferably the ring is unsubstituted.

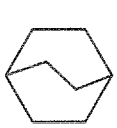
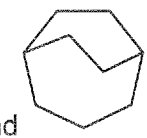
$-L-R^5$ is selected from $-L^a-R^{5a}$ and $-L^b-R^{5b}$, preferably $-L-R^5$ is $-L^b-R^{5b}$.

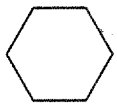
L^a is selected from the group consisting of $-(CH_2)_p-C(O)-$, $-(CH_2)_p-CR^7(OR^7)-$, $-(CH_2)_p-C(O)-N(R^7)-(CH_2)_p-$, $-(CH_2)_p-N(R^7)-C(O)-(CH_2)_p-$, $-(CH_2)_p-N(R^7)-S(O)_2-$, $-(CR^7R^7)_p-S(O)-$, $-(CR^7R^7)_p-S(O)_2-$, $-(CR^7R^7)_p-S(O)-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)_2-(CR^7R^7)_p-$, $-(CR^7R^7)_p-$(optionally substituted heterocyclylene)– and a bond. The optionally substituent of the heterocyclyene is independently selected from one or more groups selected from –Hal, –CN, $-NO_2$, –OH and $-NH_2$. 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 $-(CH_2)_p-C(O)-O-$, $-(CH_2)_p-C(O)-$, $-(CH_2)_p-CR^7(OR^7)-$, $-(CH_2)_p-C(O)-N(R^7)-(CH_2)_p-$, $-(CH_2)_p-N(R^7)-$, $-(CH_2)_p-N(R^7)-C(O)-(CH_2)_p-$, $-(CH_2)_p-N(R^7)-C(O)-C(O)-$, $-(CH_2)_p-N(R^7)-C(O)-O-$, $-(CH_2)_p-N(R^7)-C(O)-N(R^7)-$, $-(CH_2)_p-N(R^7)-S(O)_2-$, $-N(R^7)-S(O)_2-N(R^7)-$, $-(CH_2)_p-O-C(O)-$, $-(CH_2)_p-O-C(O)-N(R^7)-$, $-(CR^7R^7)_p-O-$, $-(CR^7R^7)_p-S(O)-$, $-(CR^7R^7)_p-S(O)_2-$, $-(CR^7R^7)_p-S-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)_2-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)_2-N(R^7)-$, $-(CR^7R^7)_p-S(O)_2-N(R^7)-C(O)-$, $-(CR^7R^7)_p-P(O)(OR^7)O-$, $-O-P(O)(OR^7)O-$, $-P(O)_2O-$, $-(CR^7R^7)_p-$(optionally substituted heterocyclylene)– and a bond. The optionally substituent of the heterocyclyene is independently selected from one or more groups selected from –Hal, –CN, $-NO_2$, –OH and $-NH_2$. 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 $-N(R^7)-C(O)-N(R^7)-$.

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

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

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

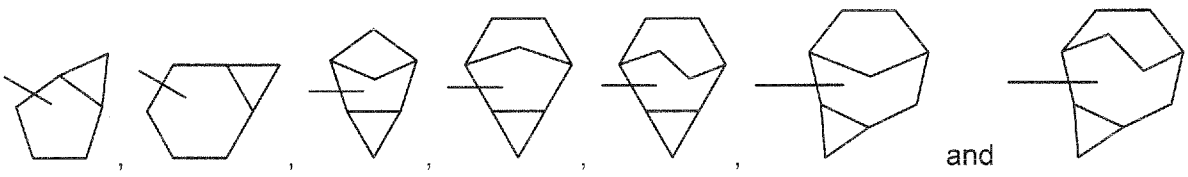
In another embodiment, L^b is selected from the group consisting of $-C(O)-O-$, $-O-C(O)-$, $-C(O)-N(R^7)-$, $-N(R^7)-C(O)-$, $-N(R^7)-C(O)-N(R^7)-$ and R^{5b} is selected from the group consisting of –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted heterocyclyl), and –(optionally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

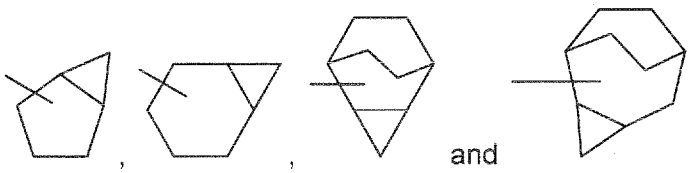
m is 1 to 3. Preferably **m** is 2 or 3.

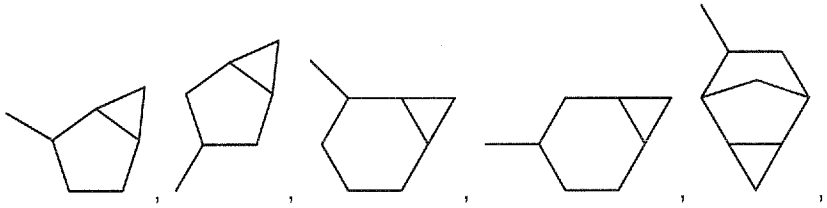
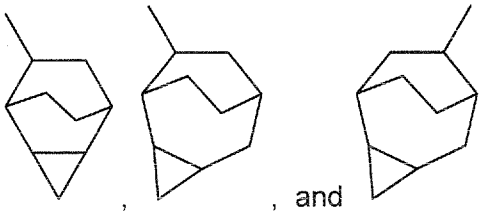
n is 1 to 4. Preferably **n** is 1.

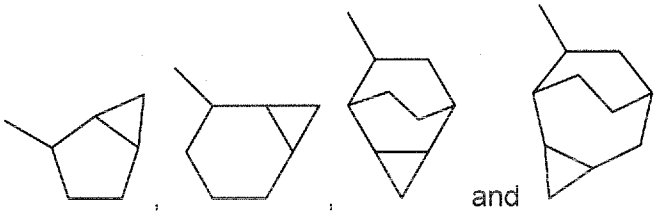
p is 0 to 6. Preferably **p** is 0 to 4, more preferably **p** is 0 or 1.

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


and

. Preferred examples include 
and .

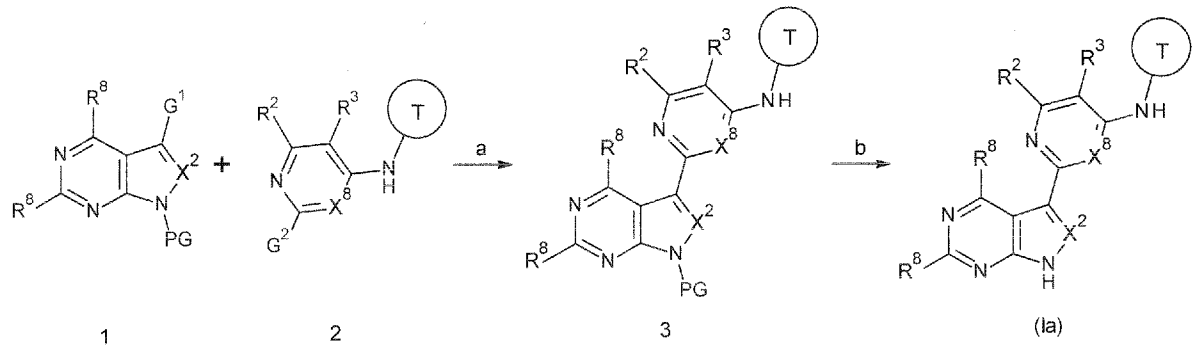
Preferred examples include  ,  , and .

Even more preferred are  , and .

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 (I), as shown in Scheme A below.

Generic Synthesis / Assay Description

Scheme A



1 2 3 (Ia)

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

Azaindole or azaindazole compounds **1** with G^1 = halogen (preferably iodine) are known. They can be prepared by methods described in the exemplary synthesis or by methods

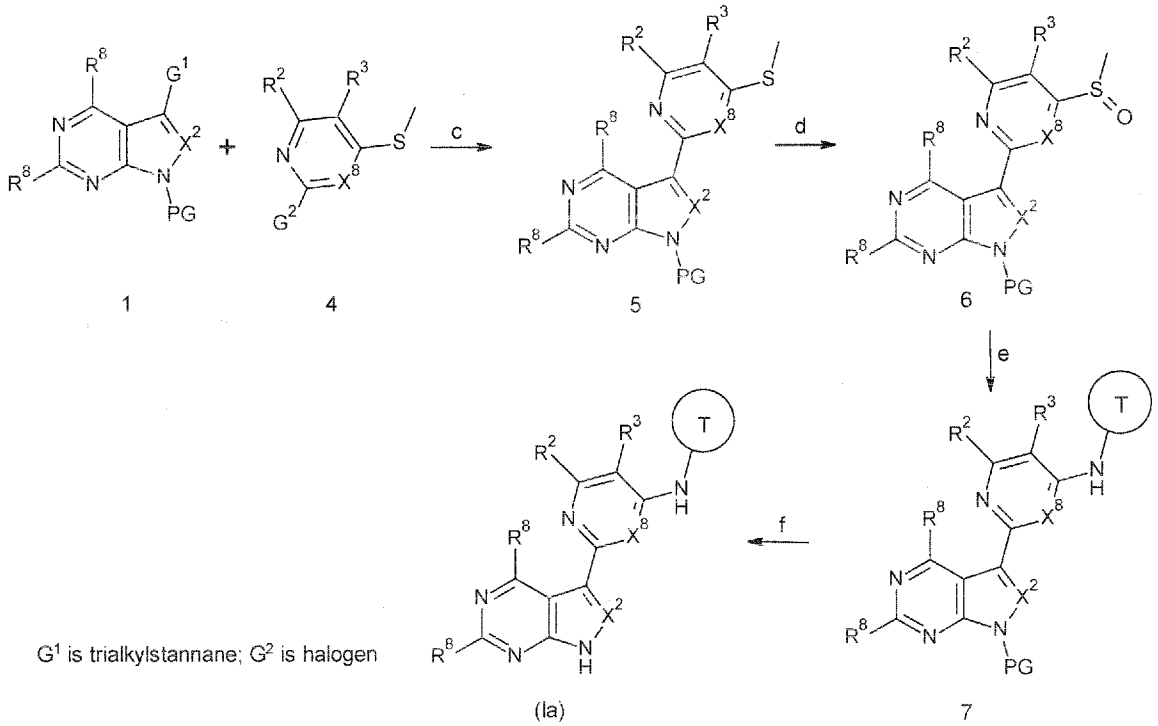
known to a person skilled in the art. If desired, the amine group of the compounds **1** can be protected by an amine protecting group, PG. Any known amine protecting group such as THP, SEM, Ts, or Boc can be employed.

Azaindole or azaindazole compounds **1** with G^1 = 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-dioxaborolane in a solvent like DMSO or dioxane in the presence of a base like potassium acetate and a catalyst like $PdCl_2(dppf)$ at an elevated temperature about 70 °C can be used. If desired, the azaindole or 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 azaindole or azaindazole 3-boronated intermediate (G^1 = boronic acid/ester) can then be reacted with a suitable heteroaryl halide, compound **2** (G^2 = halogen, bromine and chlorine preferred) in the presence of a catalyst like $Pd_2(dba)_3$, 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 product, 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** (G^2 = halogen, chlorine preferred) with a trialkyl tin reagent such as hexa-n-butylditin in a solvent like dioxane, in the presence of a catalyst like $Pd(PPh_3)_4$ 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 azaindole or azaindazole halide, compound **1** (G^1 = halogen, iodine preferred) in a solvent like dioxane, and in the presence of a catalyst like $Pd(PPh_3)_4$, 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** (G1 = halogen, iodine preferred) with a trialkyl tin reagent like Bu_6Sn_2 in solvent like dioxane, and in the presence of a catalyst like $Pd(PPh_3)_4$ 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 DIPEA, in a solvent like i-PrOH at an elevated temperature then affords compound **7** (step e). The definitions of structural formula (I), compounds **1**, **2**, **3**, **4**, **5, 6,** and **7** are independently as defined in any of the embodiments described above. PG 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 (I), where azaindole or azaindazole N1 substitution is H (step f). Specific conditions are described in the Examples Section below.

Scheme B

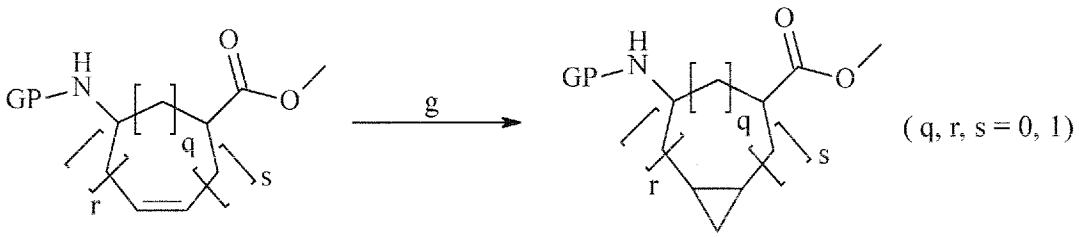


In another embodiment, cyclopropanation methodology that is known in the art is used to synthesize compounds **9**. Specific exemplary conditions are described in the exemplary synthesis or known to a person skilled in the art. Using a Simmons Smith reaction as an example (Scheme C), a cyclic alkene compound **8** 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 **8** and **9** are independently as defined in any of the embodiments described above. PG can be Boc or CBz.

Scheme C



8 9

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 injectionable 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.

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.

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-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:

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 acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,

c) disintegrants such as starches, croscaramellose, sodium methyl cellulose, agar, bentonite, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

In one embodiment the formulation is for oral administration and the formulation comprises one or more or all 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-alkane such as 1,1,1,2-tetrafluoroethane (HFA 134A^{TM}) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA^{TM}), 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.

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

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 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 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 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 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.

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.

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).

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.

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.

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, ameloriating or preventing a viral disease, more preferably a further medicament which is useful in treating, ameloriating 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), lipoxygenase 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]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
Boc:	*t*-butoxycarbonyl
mCPBA:	*m*-chloroperoxybenzoic acid
TIPSCl:	chloro(triisopropyl)silane
$CDCl_3$:	deuterated chloroform
DCM:	dichloromethane
DCE:	dichloroethane
DIEPA:	diisopropylethylamine
DMF:	dimethyl formamide
DCC:	dicyclohexylcarbodiimide
Xphos:	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
DHP:	3,4-dihydro-2*H*-pyran
DIEPA:	diisopropylethylamine
DMAP:	4-dimethylaminopyridine
DMSO:	dimethylsulfoxide
DPPA:	diphenylphosphoryl azide
EtOAc:	ethyl acetate
Hz:	hertz
NIS:	*N*-iodosuccinimide
LDA:	lithium diisopropylamide
MS (ESI):	mass spectroscopy (electron spray ionization)
MHz:	megahertz
TsOH:	4-methylbenzenesulfonic acid

μg:	microgram
μL:	microliter
μM:	micromoles per liter
mg:	milligram
mL:	milliliter
mmol:	millimole
EC_{50}:	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
PG:	protective group
PTS:	puridinium p-toluenesulfonate
THF:	tetrahydrofuran
THP:	tetrahydropyran-2-yl
$Pd(PPh_3)_4$:	tetrakis(triphenylphosphine)palladium
TLC:	thin layer chromatography
Ts:	*p*-totuenesulfonyl
TEA:	triethylamine
TFA:	2,2,2-trifluoroacetic acid
TFAA:	trifluoroacetic anhydride
Tf_2O:	trifluoromethanesulfonic anhydride
SEM:	2-(trimethylsilyl)ethoxymethyl
SEMCl:	2-(trimethylsilyl)ethoxymethyl chloride
$Pd_2(dba)_3$:	tris(dibenzylideneacetone)dipalladium

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) ISCO combi-flash chromatography instrument. Silica gel Brand and pore size: i) KP-SIL 60 Å, 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.

Intermediates and final compounds were purified by preparative HPLC on a reversed phase column using X Bridge™ Perp C_{18} (5 μm, OBD™ 30 × 100 mm) column or SunFire™ Perp C_{18} (5 μm, OBD™ 30 × 100 mm) column.

LC/MS spectra were obtained using a Waters UPLC-SQD Mass. Standard LC/MS conditions were as follows (running time 3 minutes):
Acidic condition: A: 0.1% formic acid and 1% acetonitrile in H_2O; B: 0.1% formic acid in acetonitrile;
Basic condition: A: 0.05% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile.

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

Biological Assays and Data

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, Balish 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.

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.

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% CO_2 overnight. The following day, cells were washed once with 1X PBS and then infected with virus, MOI 0.1 in 10µl of infection media for 60 min. 15µl 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% CO_2. 15µl 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). EC_{50} and CC_{50} 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: 10.1002/0471729256.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. Virons were disrupted by incubation with an equal volume of 2% Trition X-100 for 30 minutes at room temperature in a buffer containing 40 mM Tris-HCl, pH 8, 5 mM $MgCl_2$, 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 Lysolechithin. 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 ^{33}P-GTP. Then capped RNA substrate was added to the reaction at 0.07 uM (5'm^7G-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.

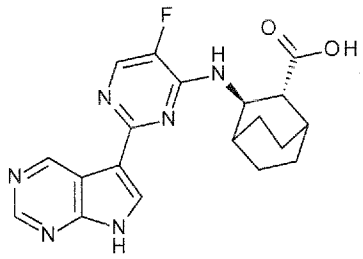
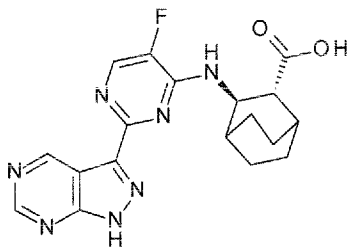
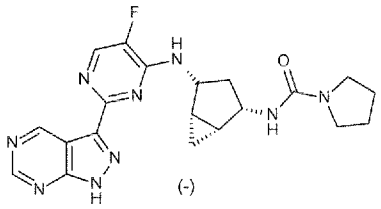
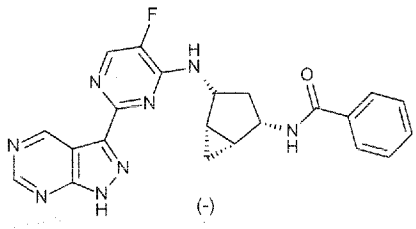
Material and methods for replication assay:

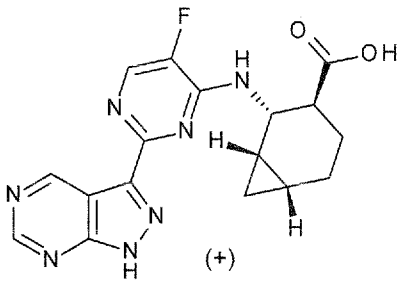
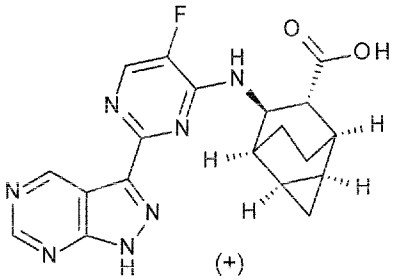
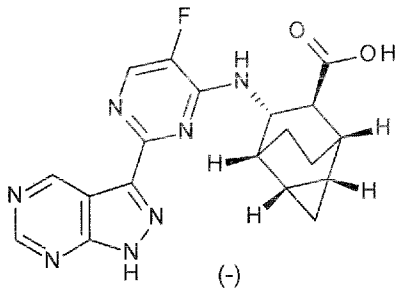
The concentrations refer to final concentrations unless mentioned otherwise. Cap-binding inhibitors were serially diluted 4 fold in 40% DMSO and 2ul of diluted compound was added to 17 ul reaction mix containing 0.35 nM vRNP enzyme, 20 mM HEPES (pH 7.5), 100 mM NaOAC, 1 mM $Mg(OAC)_2$, 0.1 mM $Mn(OAC)_2$, 0.1 mM EDTA, 2 mM DTT, 0.25 U RNase inhibitor (Epicentre), 70 uM ATP/CTP/UTP, 1.4 uM GTP and 0.175 μCi ^{33}P-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

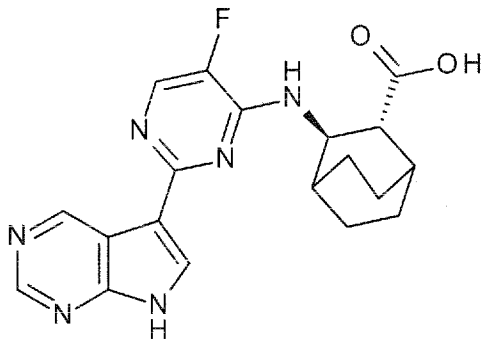
Table 1.

Compound	RNP IC_{50} (μM)	Replication IC_{50} (μM)	LRA IC_{50} (μM)
Example 1 	0.263	0.0116	1.314
Example 2 	0.069	na	0.068
Example 3 	5.487	0.1579	1.755
Example 4 	0.655	0.0886	0.043

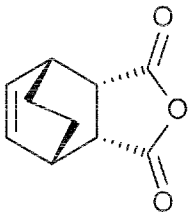
Example 5  (+)	3.770	na	1.941
Example 6  (+)	2.20	na	5.40
Example 7  (-)	0.060	0.0011	0.066

Example 1

(rac)-(2R,3R)-3-[[5-Fluoro-2-(7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)pyrimidin-4-yl]amino]bicyclo[2.2.2]- octane-2-carboxylic acid

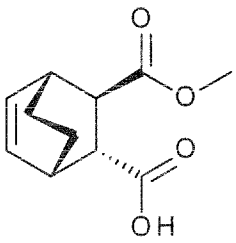


[A] *meso-endo*-Tetrahydro-4,7-ethanoisobenzofuran-1,3-dione



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) drop wise 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. It was used directly in the next step without further purification.

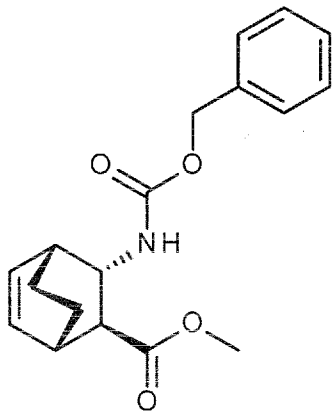
[B] (rac)-*trans*-3-(Methoxycabonyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid



To a stirred solution of sodium methoxide (40 g, 0.74 mol) in MeOH (250mL) 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

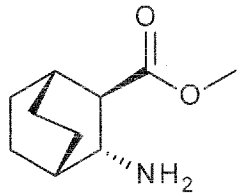
dried over anhy. Na_2SO_4, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (petroleum ether: EtOAc, 0~100% gradient) to afford a racemic mixture of title compounds (10 g, 67% yield) as a white solid. MS: 209.1 $[M-H]^+$.

[C] (rac)-(1S,2S,3S,4R)-Methyl 3-(((benzyloxy)carbonyl)amino)bicyclo[2.2.2]oct-5-ene-2-carboxylate



A mixture solution of (rac)-trans-3-(methoxycabonyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid (89 g, 423 mmol), diphenylphosphoryl azide (151 g, 119 ml, 550 mmol) and Et_3N (60 g, 593 mmol) in toluene (700 mL) was stirred at room temperature for 30 min and then at 90 °C for additional 2 hr. Benzyl alcohol (54.9 g, 508 mmol) was added and the resulting reaction mixture was stirred at 90 °C for 16 hr. After cooling to room temperature, the volatile was removed under reduced pressure and the residue was re-dissolved in DCM (300 mL) and washed with 1 N aq. NaOH solution (300 mL x 3). The organic layer was dried over anhy. Na_2SO_4, filtered, and then concentrated in vacuo to give a crude product, which was then purified by slilical gel column chromatography (EtOAc:peterolium ether= 0 to 20%) to afford the title compound (58 g, 43.4% yield) as yellow oil. MS: 316.1 $(M+1)^+$.

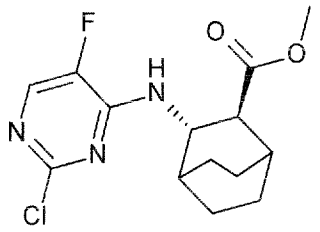
[D] (rac)-(1S,2S,3S,4R)-Methyl 3-aminobicyclo[2.2.2]oct-5-ene-2-carboxylate



A mixture solution of (rac)-(1S,2S,3S,4R)-methyl 3-(((benzyloxy)carbonyl)amino)bicyclo-[2.2.2]oct-5-ene-2-carboxylate (17 g, 53.9 mmol) and palladium on carbon (1 g, 53.9 mmol)

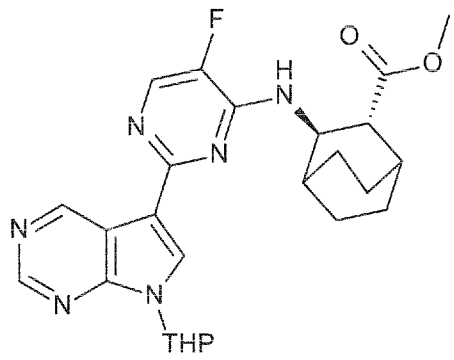
in MeOH (100 mL) was stirred at room temperature under H_2 atmosphere (1 atm) for 15 h. Afterwards, the reaction mixture was filtered and the filtration was concentrated in vacuo to give a crude title compound (10 g, 100% yield) as light yellow oil. MS: 184.1 $[M+H]^+$. It was used directly in the next step without further purification.

[E] (rac)-Methyl (2S,3S)-3-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[2.2.2]octane-2-carboxylate



A mixture solution of 2,4-dichloro-5-fluoropyrimidine (870 mg, 5.25 mmol), (2S,3S)-methyl 3-aminobicyclo[2.2.2]octane-2-carboxylate (800 mg, 4.37 mmol) and DIPEA (2 g, 15.75 mmol) in THF (20 mL) was stirred at 80 °C for 10 h before the solvent was removed under reduced pressure to give a crude product, which was purified by silica gel flash chromotography (petroleum ether:EtOAc = 3:1) to give a racemic mixture of title compound (600 mg, 44 % yield) as a yellow solid. MS: 314.2 ($M+H^+$). Under SFC chiral separation condition (AS-H, 250×20mmL.D, 20% Ethanol in CO_2), both enantiomers can be obtained as (+)-(1S,2R,3R,4S)-methyl 3-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate and (-)-(1R,2S,3S,4R)-methyl 3-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate as white solids.

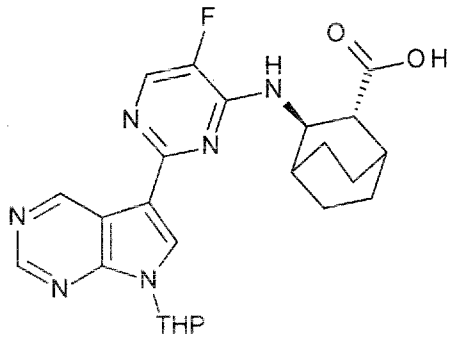
[F] (rac)-(2R,3R)-Methyl 3-((5-fluoro-2-(7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate



To a stirred mixture solution of (2R,3R)-methyl 3-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate (660 mg, 2.03 mmol) and $Pd(PPh_3)_4$ (234 mg,

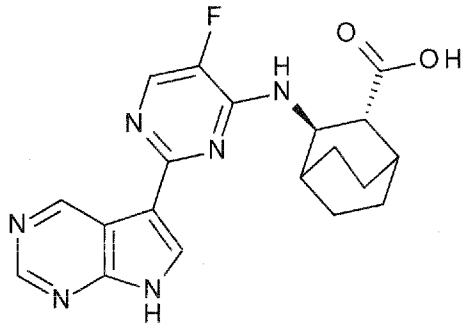
203 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (1.76 g, 1.6 mL, 3.04 mmol) and the reaction mixture was stirred at 125 °C for 2 h before it was cooled back to room temperature and re-dissolved in dioxane (16 mL). To the above mixture solution, it was then added 5-bromo-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-pyrrolo[2,3-d]pyrimidine (1.03 g, 3.65 mmol) and $Pd(PPh_3)_4$ (234 mg, 203 μmol). The resulting reaction mixture was then stirred at 145 °C for 1.5 h under microwave conditions. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organics were washed with brine, dried over anhy. 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 (120 mg, 12.3% yield) as a yellow solid. MS: 481.2 $[M+H]^+$.

[G] (rac)-(2R,3R)-3-((5-Fluoro-2-(7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylic acid



To a stirred mixture solution of (2R,3R)-methyl 3-((5-fluoro-2-(7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate (120 mg, 250 μmol) in THF (6 mL) and MeOH (6 mL) was added LiOH (48.5 mg, 2.03 mmol) in water (2 mL). The 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. The aqueous layer was acidified with concentrated aq. HCl solution to pH = 4 and extracted with EtOAc (40 mL x 3). The combined organics were dried over anhy. Na_2SO_4, filtered, and concentrated in vacuo to give a crude title compound (120 mg, 100% yield) as yellow oil. MS: 467.2 $[M+H]^+$. It was used directly in the next step without further purification.

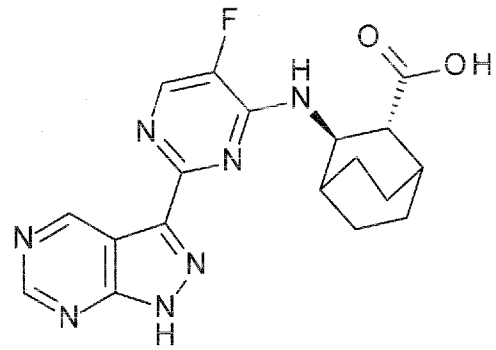
[H] (rac)-(2R,3R)-3-((5-Fluoro-2-(7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylic acid



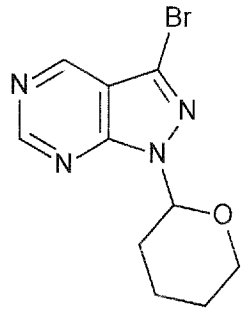
To a stirred mixture solution of (2R,3R)-3-((5-fluoro-2-(7-(tetrahydro-2H-pyran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylic acid (120 mg, 250 μmol) in DCM (3 mL) was added TFA (4.44 g, 3 mL, 38.9 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h. Afterwards, the reaction mixture was concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title product (10 mg, 10.4% yield) as white foam. MS: 383.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-*d*4) δ 9.73-9.93 (m, 1H), 8.73-8.95 (m, 1H), 8.17-8.26 (m, 1H), 7.99-8.12 (m, 1H), 4.94-4.96 (m, 1H), 2.69-2.89 (m, 1H), 2.10-2.15 (m, 1H), 1.82-2.05 (m, 4H), 1.62-1.79 (m,3), 1.50-1.62 (m, 2H).

Example 2

(rac)-(2R,3R)-3-[[5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl]amino]bicyclo[2.2.2]- octane-2-carboxylic acid

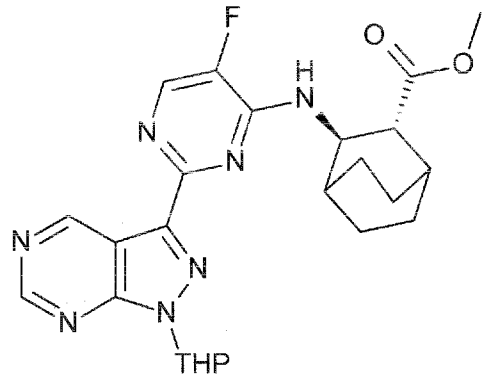


[A] 3-Bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine



To a stirred mixture solution of 3-bromo-1*H*-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 x 2). The combined organic layers were washed with brine, dried over anhy. 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 $[M+H]^+$

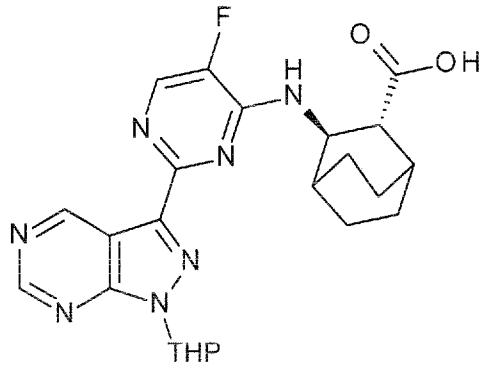
[B] (rac)-(2R,3R)-Methyl 3-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate



To a stirred mixture solution of (rac)-(2R,3R)-methyl 3-((2-chloro-5-fluoropyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate (Example 1/ Step E, 660 mg, 2.03 mmol) and $Pd(PPh_3)_4$ (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) and the resulting 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 stirred mixture solution, it was then added 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (1.03 g, 3.65 mmol) and $Pd(PPh_3)_4$ (234 mg, 203 µmol). The reaction mixture was stirred at 145 °C for 1.5 h under microwave conditions. After cooling to room temperature, the reaction mixture was poured into water

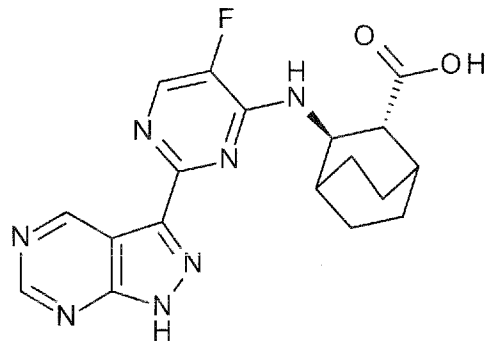
(20 mL) and extracted with EtOAc (50 mL x 2). The combined organics were washed with brine, dried over anhy. Na_2SO_4, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel flash chromatography (0-80% EtOAc-hexane gradient) to afford the title compound (200 mg, 20% yield) as a yellow solid. MS: 482.2 $[M+H]^+$.

[C] (rac)-(2R,3R)-3-((5-Fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylic acid



To a stirred mixture solution of (rac)-(2R,3R)-methyl 3-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylate (200 mg, 405 μmol) in THF (6 mL) and MeOH (6 mL) was added LiOH (48.5 mg, 2.03 mmol) in water (2 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. The aqueous layer was acidified with concentrated aq. HCl solution to pH = 4 and extracted with ETOAc (40 mL x 3). The combined organics were dried over anhy.s Na_2SO_4, filtered, and concentrated in vacuo to give a crude title compound (190 mg, 100% yield) as yellow oil. MS: 468.2 $[M+H]^+$. It was used directly in the next step without further purification.

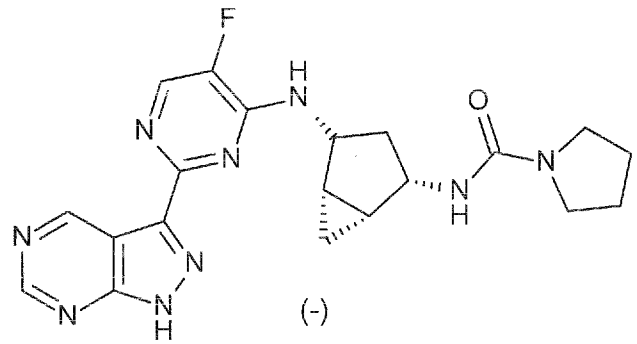
[D] (rac)-(2R,3R)-3-((5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylic acid



To a stirred mixture solution of (rac)-(2R,3R)-3-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[2.2.2]octane-2-carboxylic acid (190 mg, 396 μmol) in DCM (3 mL) was added TFA (4.44 g, 38.9 mmol) and the resulting reaction mixture 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 (7 mg, 4.5% yield) as white foam. MS: 384.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-*d*4) δ 9.95-10.00 (m, 1H), 9.01-9.05 (m, 1H), 8.14-8.21 (m, 1H), 4.60-4.64 (m, 1H), 2.81-2.85 (m, 1H), 2.14-2.18 (m, 1H), 2.00-2.04 (m, 1H), 1.83-1.93 (m, 3H), 1.73-1.79 (m, 3H), 1.47-1.61 (m, 4H).

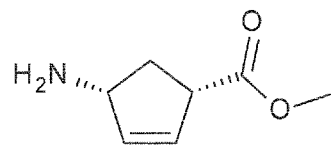
Example 3

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



(-)

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

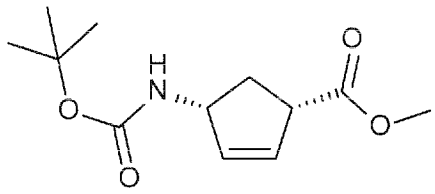


(-)

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) drop wise at 0 °C. After the

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 [M+H$^+$]. It was used directly in the next step without further purification.

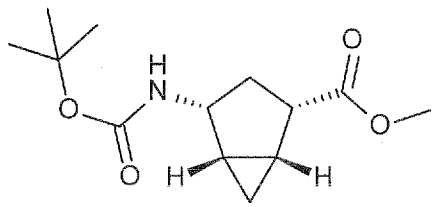
[B] (-)-Methyl (1S,4R)-4-(*tert*-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate



(-)

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. $NaHCO_3$ solution, and the separated organic layer was dried over anhy. 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 (10 g, 67% yield) as a white solid. MS: 242.1 [M+H]$^+$.

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

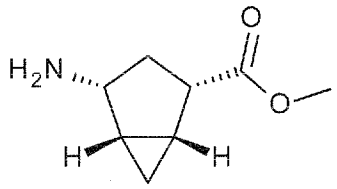


(-)

To a stirred solution of (-)-methyl (1S,4R)-4-(*tert*-butoxycarbonylamino)cyclopent-2-ene-1-carboxylate (2 g, 8.2 mmol) in DCM (50 mL) was added $ZnEt_2$ (1 M in hexane, 16.3 mL) drop wise 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 drop wise 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 warmed 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 anhy. 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 (900 mg, 44% yield) as a white solid. MS: 256.1 $[M+H]^+$.

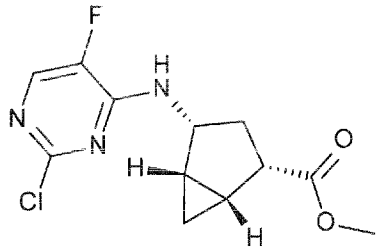
[D] (-)-Methyl (1S,2R,4S,5R)-2-aminobicyclo[3.1.0]hexane-4-carboxylate



(-)

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 $[M+H]^+$. It was used directly in the next step without further purification.

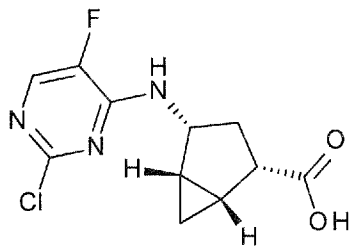
[E] (-)-Methyl (1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]-hexane-4-carboxylate



(-)

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 (10.0g, 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 $[M+H]^+$.

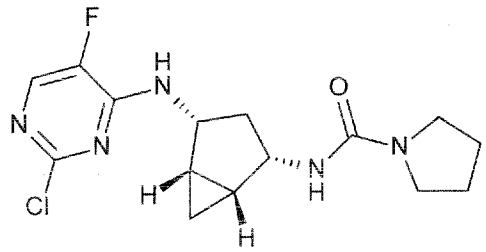
[F] (-)-(1S,2R,4S,5R)-2-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]bicyclo[3.1.0]hexane-4-carboxylic acid



(-)

A mixture solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-l)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 anhy. Na_2SO_4, 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.

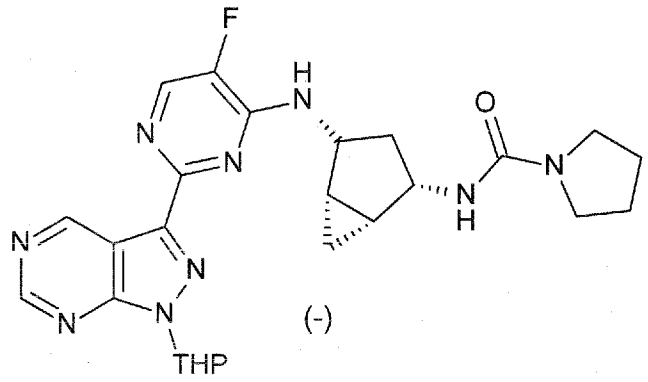
[G] (-)-*N*-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]-hexanyl]pyrrolidine-1-carboxamide



(-)

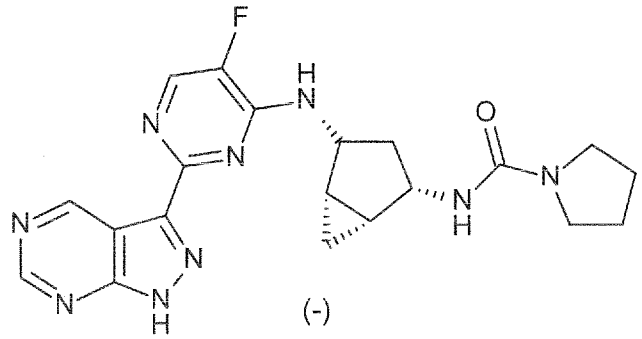
A stirred mixture solution of (-)-(1S,2R,4S,5R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino] bicyclo[3.1.0]hexane-4-carboxylic acid (500 mg, 1.84 mmol), DPPA (800 mg, 2.9 mmol) and TEA (808 mg, 8 mmol) in toluene (10 mL) was heated at 100 °C for 1 h. After cooling to room temperature, pyrrolidine (500 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 $[M+H]^+$.

[H] (-)-*N*-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydropyran-2-ylpyrazolo[3,4-d]pyrimidin-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 (220 mg, 647 μmol) and $Pd(PPh_3)_4$ (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 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, it was then added 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (367 mg, 1.29 mmol) and $Pd(PPh_3)_4$ (112 mg, 97.1 μmol). The reaction mixture solution was then stirred at 145 °C for 1 h under microwave conditions. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organics were washed with brine, dried over anhy. 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 (100 mg, 31% yield) as a yellow oil. MS: 508.2 $[M+H]^+$.

[l] (-)-*N*-[(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

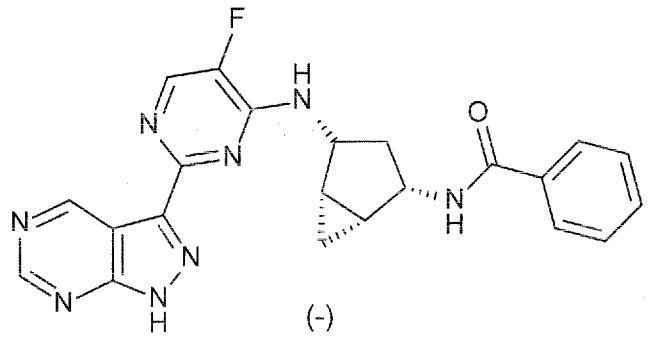


A solution of (-)-*N*-((1R,2S,4R,5S)-4-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)pyrrolidine-1-carboxamide (100mg, 197 μmol) in TFA (5 mL) and DCM (5 mL) was stirred at room

temperature for 16 h. Afterwards, the solvent was evaporated and the residue was purified by Prep-HPLC to afford the title compound (5 mg, 6% yield) as white foam. MS: 424.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ ppm 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).

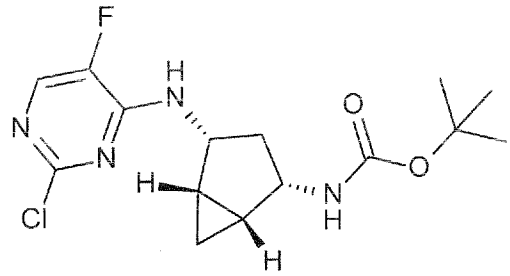
Example 4

(-)-*N*-[(1R,2S,4R,5S)-4-[[5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]benzamide



(-)

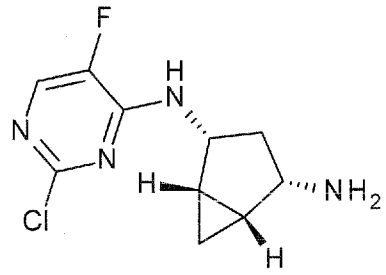
[A] (-)-*tert*-butyl *N*-[(1R,2S,4R,5S)-4-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]carbamate



(-)

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 (Example 3/Step F, 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 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 $[M+H]^+$.

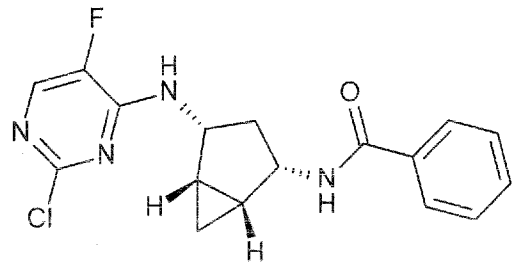
[B] (-)-(1S,2R,4S,5R)-*N*2-(2-Chloro-5-fluoro-pyrimidin-4-yl)bicyclo[3.1.0]hexane-2,4-diamine



(-)

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 $[M+H]^+$. It was used directly in the next step without further purification.

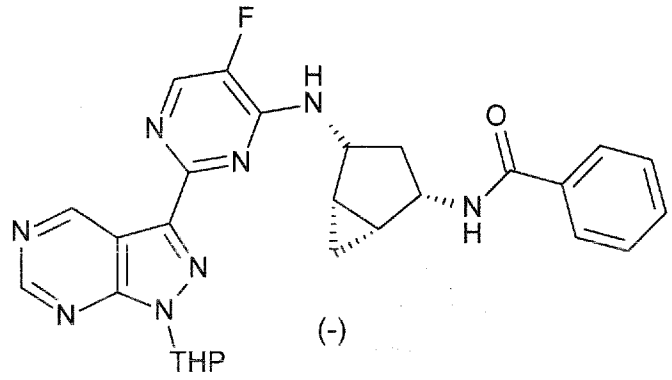
[C] (-)-*N*-[(1R,2S,4R,5S)-4-[(2-Chloro-5-fluoro-pyrimidin-4-yl)amino]-2-bicyclo[3.1.0]hexanyl]benzamide



(-)

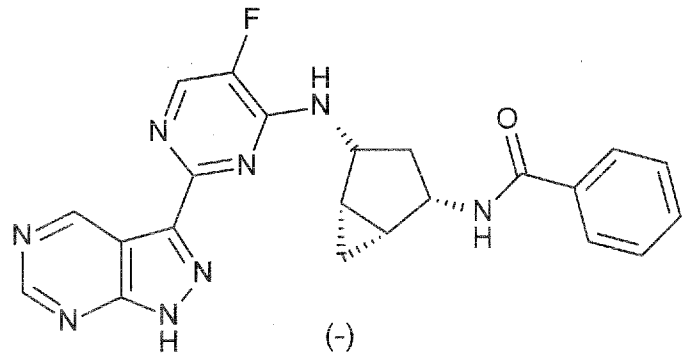
To a stirred solution of (-)-(1S,2R,4S,5R)-*N*2-(2-chloro-5-fluoro-pyrimidin-4-yl)bicyclo[3.1.0] -hexane-2,4-diamine (300 mg, 0.76 mmol) and TEA (500 mg, 5 mmol) in DCM (10 mL) was added benzoyl chloride (214 mg, 1.52 mmol) drop wise at 0 °C. After the addition, the resulting mixture was allowed to warm 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 $[M+H]^+$.

[D] (-)-*N*-[(1R,2S,4R,5S)-4-[[5-fluoro-2-(1-tetrahydropyran-2-ylpyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl]amino]-2-bicyclo[3.1.0]hexanyl]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)benzamide (220 mg, 634 μmol) and $Pd(PPh_3)_4$ (110 mg, 95.2 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (552 mg, 500 μL, 952 μmol) and the resulting 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 stirred mixture solution, it was then added 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (359 mg, 1.27 mmol) and $Pd(PPh_3)_4$ (110 mg, 95.2 μmol). The reaction mixture was stirred at 145 °C for 1 h under microwave conditions. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organics were washed with brine, dried over anhy. 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 (100 mg, 31% yield) as yellow oil. MS: 515.2 $[M+H]^+$.

[E] (-)-*N*-[(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]benzamide

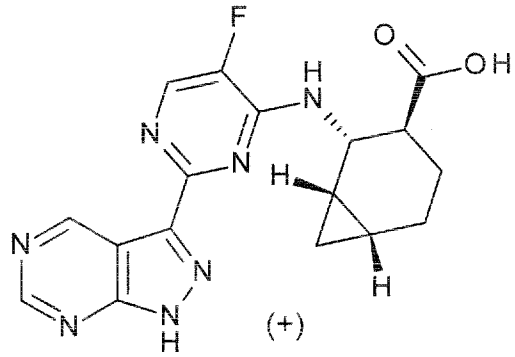


A solution of (-)-*N*-((1R,2S,4R,5S)-4-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-b]pyrazin-3-yl)pyrimidin-4-yl)amino)bicyclo[3.1.0]hexan-2-yl)benzamide (100mg, 194 μmol) in TFA (5 mL) and DCM (5 mL) was stirred at room temperature for 16

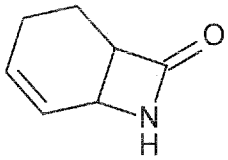
h. Afterwards, the solvent was evaporated to dryness and the residue was purified by Prep-HPLC to afford the title compound as a white solid (30 mg, 36% yield). MS: 431.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 0.35 - 0.45 (m, 1 H) 1.03 - 1.11 (m, 1 H) 1.41 - 1.51 (m, 1 H) 1.64 - 1.73 (m, 1 H) 1.77 - 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 5

(+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid

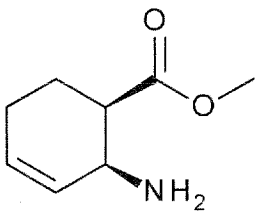


[A] 7-Azabicyclo[4.2.0]oct-4-en-8-one



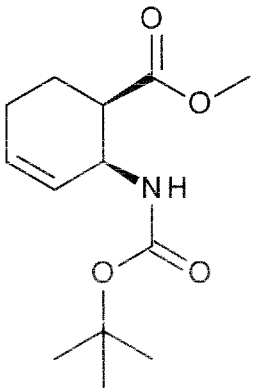
To a stirred solution of chlorosulfonyl isocyanate (7.7 mL, 89 mmol) in dry Et_2O (100 mL) was added cyclohexa-1,3-diene (8 g, 99 mmol) in dry Et_2O (100 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 30 min before it was poured into aqueous solution of K_2CO_3/Na_2SO_3 (36 g/1.1 g in 300 mL of water) and extracted with Et_2O (300 mL x 2) and EtOAc (100 mL x 2). The combined organic layers were dried over anhy. Na_2SO_4, filtered, and concentrated in vacuo to give a crude title compound (8 g, 65% yield) as yellow gum. MS: 124.1 $[M+H]^+$. It was used directly in the next step without further purification.

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



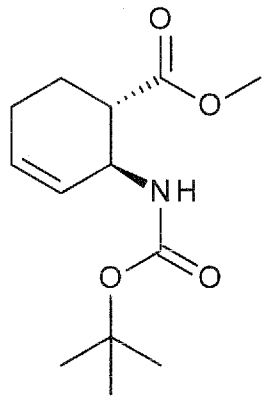
To a stirred solution of 7-azabicyclo[4.2.0]oct-4-en-8-one (8 g, 64 mmol) in MeOH (150 mL) was added AcCl (20 mL) drop wise at 0 °C. After the addition, the resulting reaction mixture was heated at 75 °C for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to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

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



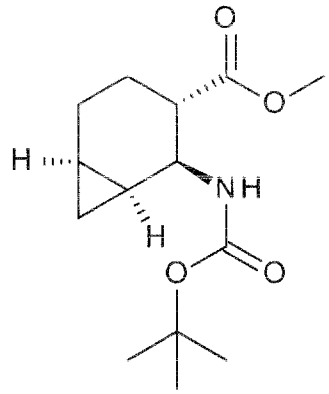
To a stirred solution of (rac)-methyl (1R,2S)-2-aminocyclohex-3-ene-1-carboxylate (12 g, 64 mmol) and TEA (30 g, 0.29 mol) in DCM (200 mL) was added Boc anhydride (20 g, 92.6 mmol) drop wise at 0 °C. After the addition, the resulting reaction mixture was slowly warmed up to room temperature and stirred for 2 h before it was quenched with satd. aq. $NaHCO_3$ solution and extracted with DCM. The organic layer was dried over anhy. 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 $[M+H]^+$.

[D] (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 (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 anhy. 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 racemic mixture of the title compound (5 g, 83% yield) as a white solid. MS: 256.1 $[M+H]^+$.

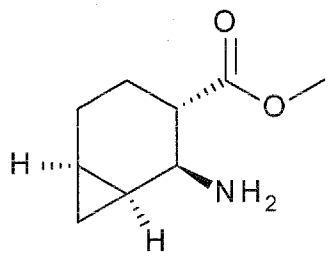
[E] (rac)-Methyl (1S,2S,3S,6R)-2-(*tert*-butoxycarbonylamino)norcarane-3-carboxylate



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 $ZnEt_2$ (1 M in hexane, 16.3 mL) drop wise 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 drop wise 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 anhy.

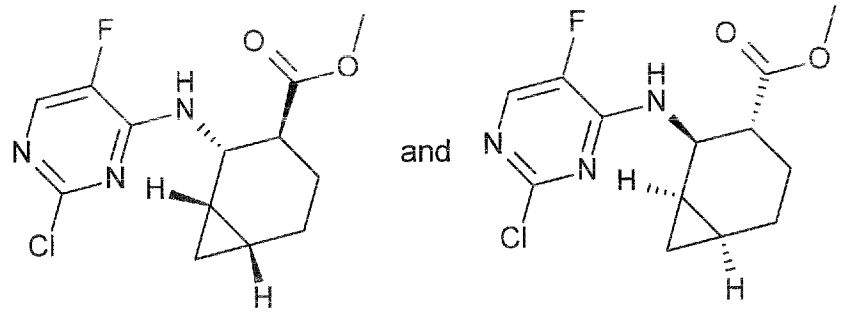
Na_2SO_4, filtered, and concentrated in vacuo to give a crude racemic mixture of the title compound (3 g) as a white solid. MS: 270.2 $[M+H]^+$. It was used directly in the next step without further purification.

[F] (rac)-Methyl (1S,2S,3S,6R)-2-aminonorcarane-3-carboxylate



A solution of (rac)-methyl (1S,2S,3S,6R)-2-(*tert*-butoxycarbonylamino)norcarane-3-carboxylate (3 g, 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 title compound (3 g) as yellow gum. MS: 170.2 $[M+H]^+$. It was used directly in the next step without further purification.

[G] (+)-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

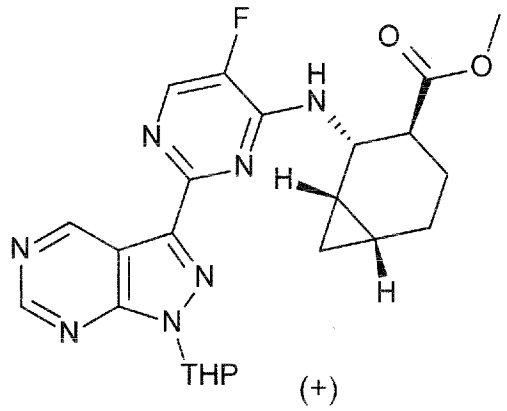


(+) (-)

A stirred solution of (rac)-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 reduced 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 CO_2) to afford the title compound (+)-(1S,2S,3S,6R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (620 mg, 21% yield), MS: 300.2 $[M+H^+]$ and (-)-(1R,2R,3R,6S)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (650 mg, 26% yield), MS: 300.2 $[M+H]^+$

as yellow solids.

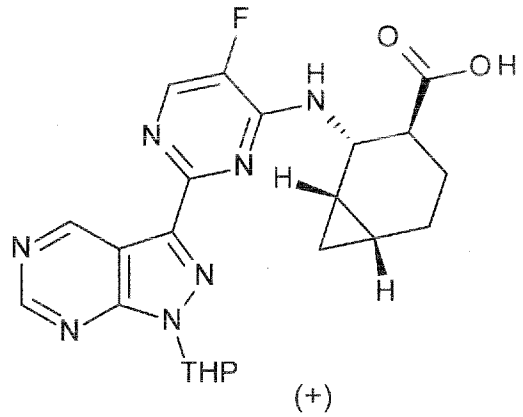
[H] (+)-(1S,2S,3S,6R)-methyl 2-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate



(+)

In analogy to the synthesis of Example 2/Step B, (+)-methyl (1S,2S,3S,6R)-2-[(2-chloro-5-fluoro-pyrimidin-4-yl)amino]norcarane-3-carboxylate (Example 1/Step E, 480 mg, 1.6 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 $[M+H]^+$.

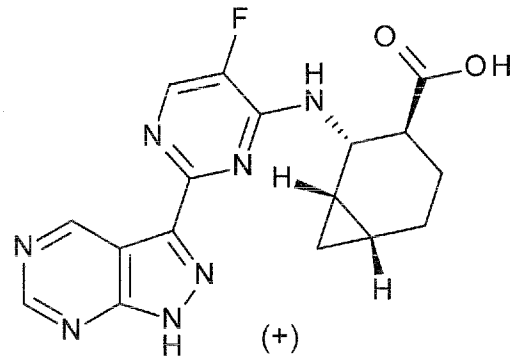
[I] (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid



(+)

In analogy to the synthesis Example 2/Step C, (+)-(1S,2S,3S,6R)-methyl 2-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylate (300 mg, 225 μmol) was used to give a crude title compound (300 mg, 100% yield) as yellow oil. MS: 454.2 $[M+H]^+$. It was used directly in the next step without further purification.

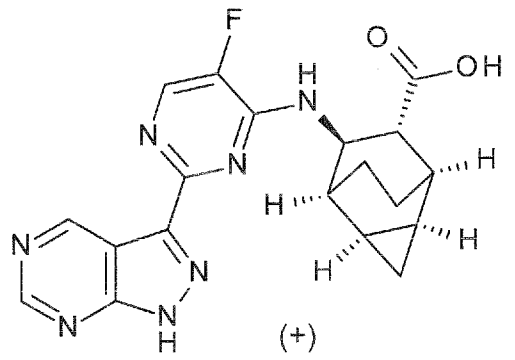
[J] (+)-(1S,2S,3S,6R)-2-[[5-Fluoro-2-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl]amino]norcarane-3-carboxylic acid



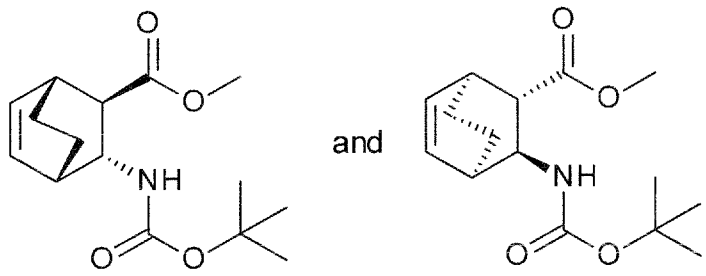
In analogy to the synthesis of Example 2/Step D, (+)-(1S,2S,3S,6R)-2-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)bicyclo[4.1.0]heptane-3-carboxylic acid (300 mg, 232 μmol) was used to afford the title compound (23 mg, 27% yield) yield as white 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 (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 6

(+)-(1S,2R,4S,5R,6R,7R)-7-((5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid

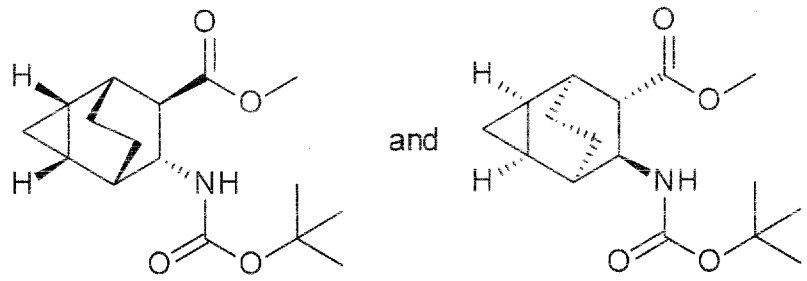


[A] (1R,2R,3R,4S)-Methyl 3-((*tert*-butoxycarbonyl)amino)bicyclo[2.2.2]oct-5-ene-2-carboxylate and (1S,2S,3S,4R)-methyl 3-((*tert*-butoxycarbonyl)amino)bicyclo[2.2.2]oct-5-ene-2-carboxylate



To a stirred solution of (rac)-*trans*-3-(methoxycabonyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid (Example 1/Step B, 10 g, 47.6 mmol), TEA (9.8 g, 97 mmol) in toluene (120 mL) was added DPPA (20 g, 77.8 mmol) drop wise 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 the title compound as a white solid (2 g, 15% yield). MS: 282.2 $[M+H]^+$.

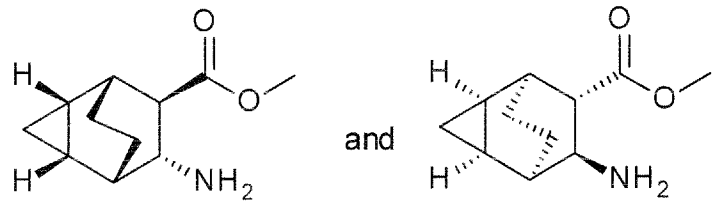
[B] (1S,2R,4S,5R,6R,7R)-Methyl 7-((*tert*-butoxycarbonyl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-((*tert*-butoxycarbonyl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate



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 $ZnEt_2$ (1 M in hexane, 8.0 mL) drop wise at 0 °C. After the mixture was stirred at 0°C for 15 min, CH_2I_2 (1.5 mL, 18.5 mmol) and additional $ZnEt_2$ (1 M in hexane, 8.0 mL) were added drop wise to the above mixture and 5 min later, one additional portion of CH_2I_2 (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. NH_4Cl solution and then extracted with DCM. The organic layer was washed with brine, dried over anhy. Na_2SO_4, filtered, and concentrated in vacuo to give

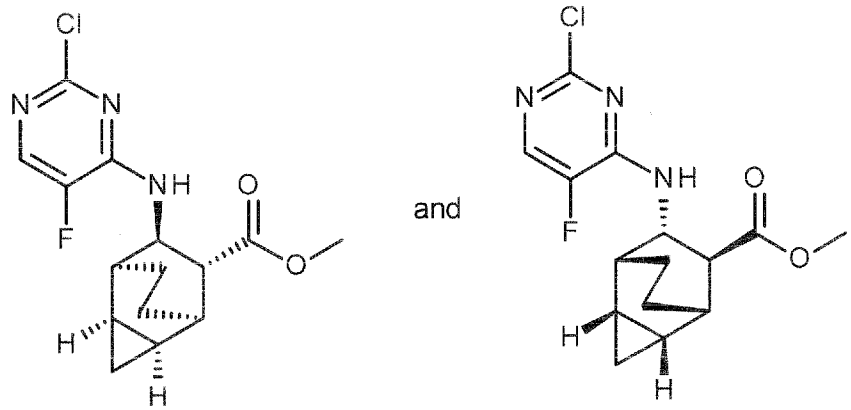
a crude racemic mixture of title compound (2 g) as a white solid. MS: 296.2 $[M+H]^+$. It was used directly in the next step without further purification.

[C] (1S,2R,4S,5R,6R,7R)-Methyl 7-aminotricyclo[3.2.2.02,4]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-aminotricyclo[3.2.2.02,4]nonane-6-carboxylate



To a stirred solution of racemic mixture of (1S,2R,4S,5R,6R,7R)-methyl 7-((*tert*-butoxycarbonyl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate and (1R,2S,4R,5S,6S,7S)-methyl 7-((*tert*-butoxycarbonyl)amino)tricyclo[3.2.2.02,4]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 $[M+H]^+$. It was used directly in the next step without further purification.

[D] (+)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate and (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate

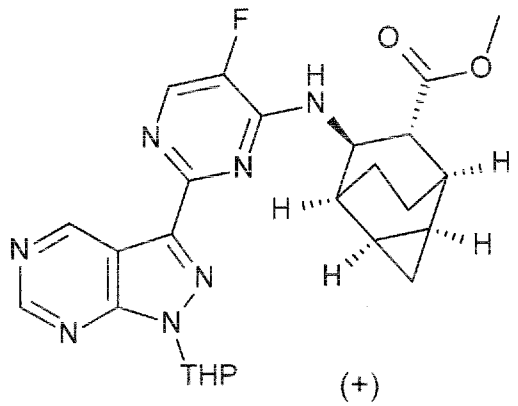


(+) (-)

To a stirred solution of racemic mixture of (1S,2R,4S,5R,6R,7R)-methyl 7-aminotricyclo[3.2.2.02,4]nonane-6-carboxylate (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, 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 x 2). The combined organic layers were washed with brine, dried over anhy. Na_2SO_4, 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 CO_2) to afford the title compound (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]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[3.2.2.02,4]nonane-6-carboxylate (8 g, 94% yield) as a light yellow solid. MS: 326.1 $[M+H]^+$.

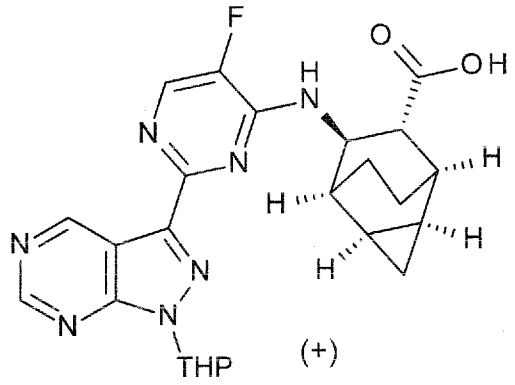
[E] (+)-(1S,2R,4S,5R,6R,7R)-Methyl 7-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate



(+)

To a stirred mixture solution of (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate (660 mg, 2.03 mmol) and $Pd(PPh_3)_4$ (234 mg, 203 μmol) in dioxane (4 mL) was added 1,1,1,2,2,2-hexabutyldistannane (1.76 g, 3.04 mmol) and the resulting 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 stirred mixture solution, it was then added 3-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (1.03 g, 3.65 mmol) and $Pd(PPh_3)_4$ (234 mg, 203 μmol). The reaction mixture solution was then stirred at 145 °C for 1.5 hr under microwave conditions. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organics were washed with brine, dried over anhy. 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, 20% yield) as a white solid. MS: 494.2 $[M+H]^+$.

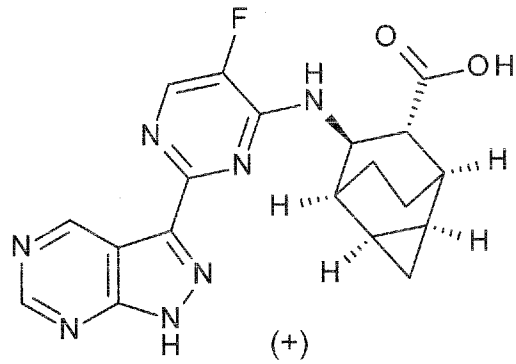
[F] (+)-(1S,2R,4S,5R,6R,7R)-7-((5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid



(+)

To a stirred mixture solution of (+)-(1S,2R,4S,5R,6R,7R)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate (190 mg, 192 μmo) in THF (6 mL) and MeOH (2 mL) was added LiOH (23 mg, 962 μmol) in water (2 mL). The reaction mixture solution was stirred at room temperature for 6 h and then diluted with water (10 mL), extracted with diethyl ether (20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated aq. HCl solution to pH = 4 and extracted with EtOAc (40 mL x 3). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a crude title compound (185 mg, 100% yield) as yellow oil. MS: 480.2 $[M+H]^+$. It was used directly in the next step without further purification.

[G] (+)-(1S,2R,4S,5R,6R,7R)-7-((5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid



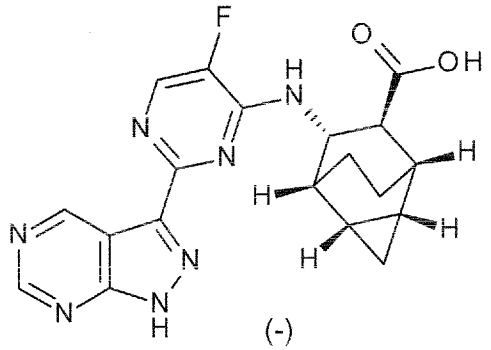
(+)

To a stirred mixture solution of (+)-(1S,2R,4S,5R,6R,7R)-7-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid (185 mg, 193 μmol) in DCM (3 mL) was added 2,2,2-trifluoroacetic acid (4.44 g, 38.9 mmol) and the resulting reaction mixture

was stirred at room temperature for 4 h before concentrated in vacuo to give a crude product, which was purified by Prep-HPLC to afford the title product (1.5 m, 1.97% yield) as white foam. MS: 396.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOH-*d*4) 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).

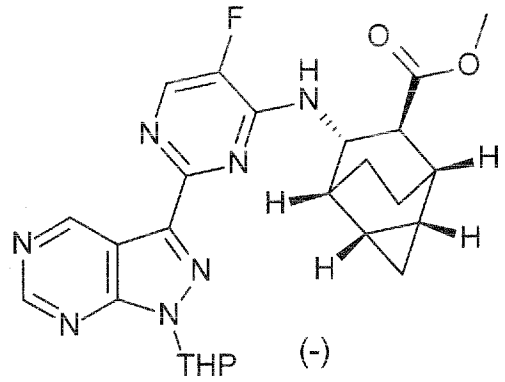
Example 7

(-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid



(-)

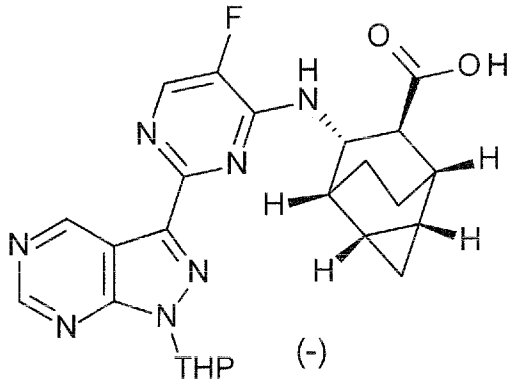
[A] (-)-(1R,2S,4R,5S,6S,7S)-Methyl 7-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate



(-)

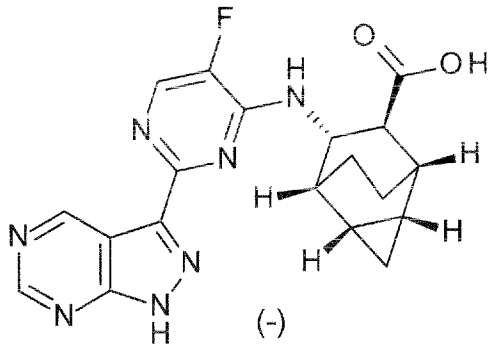
In analogy to the synthesis of Example 6/Step E, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((2-chloro-5-fluoropyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate (660 mg, 2.03 mmol) was used to afford the title compound (200 mg, 20% yield) as a yellow solid after silica gel flash chromatography (0-80% EtOAc-hexane gradient) purification. MS: 494.2 $[M+H]^+$.

[B] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid



In analogy to the synthesis of Example 6/Step F, (-)-(1R,2S,4R,5S,6S,7S)-methyl 7-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylate (160 mg, 113 μmol) was used to give a crude title compound (131 mg, 100% yield) as yellow oil. MS: 480.2 $[M+H]^+$. It was used directly in the next step without futher purification.

[C] (-)-(1R,2S,4R,5S,6S,7S)-7-((5-Fluoro-2-(1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid

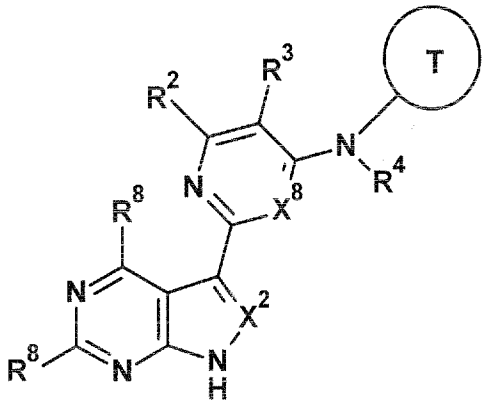


In analogy to the synthesis of Example 6/Step G, (-)-(1R,2S,4R,5S,6S,7S)-7-((5-fluoro-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)pyrimidin-4-yl)amino)tricyclo[3.2.2.02,4]nonane-6-carboxylic acid (131 mg, 95.6 μmol) was used to afford the title compound (3 mg, 7.94% yield) as 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) 0.88 - 0.96 (m, 1 H) 0.43 - 0.50 (m, 1 H).

New PCT-Patent Application
Savira pharmaceuticals GmbH et al.
Our Ref.: X3624 PCT

CLAIMS

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)

wherein

R^2 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**)–$S(O)_2$R**, –(optionally substituted C_{1-6} alkyl), –OR**, –SR**, –S(O)R**, –$S(O)_2$R**, –(optionally substituted heterocyclyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), and –(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), and

wherein the –(optionally substituted) can be independently –halogen, –CN, –NO_2, 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***)–$S(O)_2$R***, –OR***, –O–C(O)R***, –O–C(O)–NR***R***, –SR***,

–S(O)R***, –S(O)$_2$R***, –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, C_{1-6} alkyl, benzyl, heterocyclyl or carbocyclyl; and wherein –(optionally substituted) can also be C_{1-6} alkyl in the case of –(optionally substituted heterocyclyl) or –(optionally substituted carbocyclyl);

R^3 is selected from the group consisting of –H, –halogen, –CN, –NO$_2$, –C(O)R**, –COOR**, –C(O)NR**R**, –OR**, –SR**, –S(O)R**, –S(O)$_2$R**, –(optionally substituted C_{1-6} alkyl), –(optionally substituted C_{3-6} cycloalkyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl), and –(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) and
wherein the –(optionally substituted) can be independently –halogen, –CN, –NO$_2$, 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)$_2$R***, –OR***, –O–C(O)R***, –O–C(O)–NR***R***, –SR***, –S(O)R***, –S(O)$_2$R***, –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, C_{1-6} alkyl, benzyl, heterocyclyl or carbocyclyl; and wherein –(optionally substituted) can also be C_{1-6} alkyl in the case of –(optionally substituted heterocyclyl) or –(optionally substituted carbocyclyl);

R^4 is selected from the group consisting of –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted carbocyclyl), and –(optionally substituted heterocyclyl), wherein the –(optionally substituted) can be independently –halogen, –CN, –NO$_2$, 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)$_2$R**, –OR**, –O–C(O)R**, –O–C(O)–NR**R**, –SR**, –S(O)R**, –S(O)$_2$R**, –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 C_{1-6} alkyl or C_{3-6} cycloalkyl which can optionally be substituted with halogen; and wherein –(optionally substituted) can also be C_{1-6} 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 C_{1-6} alkyl), –(optionally substituted heterocyclyl), or –(optionally substituted carbocyclyl);

R^{5b} is selected from the group consisting of –H, –(optionally substituted C_{1-6} alkyl), –(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), –(optionally substituted C_{1-4} alkylene)–(optionally substituted heterocyclyl) and –(optionally substituted C_{1-4} alkylene)–(optionally substituted carbocyclyl), wherein R* is –(optionally substituted C_{1-6} 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 heteroatoms, and wherein the –(optionally substituted) in R^{5a} and R^{5b} 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*, –OH, or $–O–C_{1-6}$ alkyl, wherein each R* is H, C_{1-6} alkyl or C_{3-6} cycloalkyl; and wherein –(optionally substituted) can also be C_{1-6} alkyl in the case of –(optionally substituted heterocyclyl) or –(optionally substituted carbocyclyl);

R^7 is selected from the group consisting of of –H and $–C_{1-6}$ alkyl;

R^8 is independently selected from the group consisting of –H, –Hal, –CN, –NR**R**, –(optionally substituted C_{1-6} alkyl), –OR**, –(optionally substituted heterocyclyl), and –(optionally substituted carbocyclyl), wherein R** is H, –(optionally substituted C_{1-6} 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, $–C_{1-6}$ alkyl, –Hal, –OR*, –NR*R*, –CN, and CF_3, wherein R* is –H or $–C_{1-6}$ alkyl;

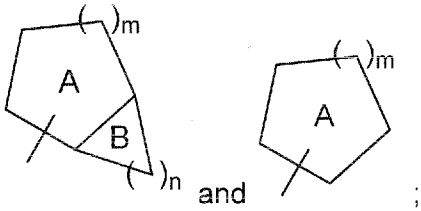
R^{10} is independently selected from the group consisting of –H, –Hal, –CN, $–NO_2$, –(optionally substituted C_{1-6} alkyl), –NR*R*, and –OR*, wherein R* is –H, or

–(optionally substituted C_{1-6} alkyl) and wherein the –(optionally substituted) may be halogen;

X^2 is selected from the group consisting of N and CR^9;

X^8 is selected from the group consisting of N and CR^{10};

T is selected from the group consisting of



;

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 ring A can be substituted in any available position by one or two substituents which are selected from the group consisting of $–L–R^5$; and

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 $–L–R^5$;

$–L–R^5$ is selected from $–L^a–R^{5a}$ and $–L^b–R^{5b}$, preferably $–L–R^5$ is $–L^b–R^{5b}$;

L^a is selected from the group consisting of $–(CH_2)_p–C(O)–$, $–(CH_2)_p–CR^7(OR^7)–$, $–(CH_2)_p–C(O)–N(R^7)–(CH_2)_p–$, $–(CH_2)_p–N(R^7)–C(O)–(CH_2)_p–$, $–(CH_2)_p–N(R^7)–S(O)_2–$, $–(CR^7R^7)_p–S(O)–$, $–(CR^7R^7)_p–S(O)_2–$, $–(CR^7R^7)_p–S(O)–(CR^7R^7)_p–$, $–(CR^7R^7)_p–S(O)_2–(CR^7R^7)_p–$, $–(CR^7R^7)_p–$(optionally substituted heterocyclylene)– and a bond; the optional substituent of the heterocyclyene is independently selected from one or more groups selected from –Hal, –CN, $–NO_2$, –OH and $–NH_2$;

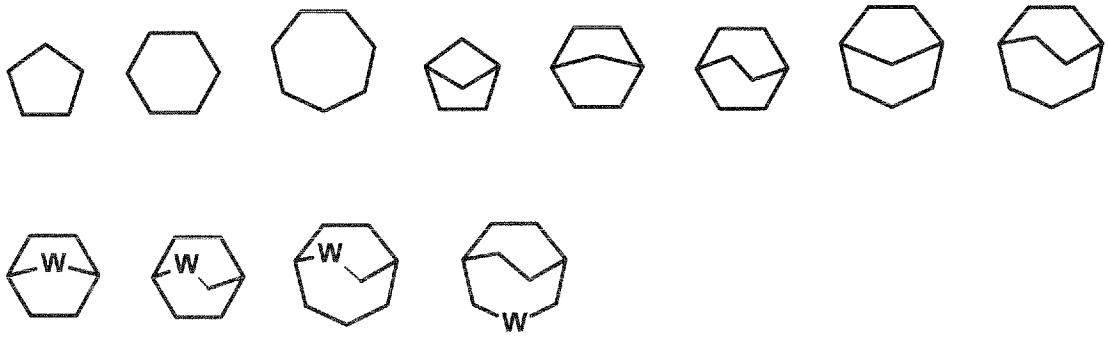
L^b is selected from the group consisting of $-(CH_2)_p-C(O)-O-$, $-(CH_2)_p-C(O)-$, $-(CH_2)_p-CR^7(OR^7)-$, $-(CH_2)_p-C(O)-N(R^7)-(CH_2)_p-$, $-(CH_2)_p-N(R^7)-$, $-(CH_2)_p-N(R^7)-C(O)-(CH_2)_p-$, $-(CH_2)_p-N(R^7)-C(O)-C(O)-$, $-(CH_2)_p-N(R^7)-C(O)-O-$, $-(CH_2)_p-N(R^7)-C(O)-N(R^7)-$, $-(CH_2)_p-N(R^7)-S(O)_2-$, $-N(R^7)-S(O)_2-N(R^7)-$, $-(CH_2)_p-O-C(O)-$, $-(CH_2)_p-O-C(O)-N(R^7)-$, $-(CR^7R^7)_p-O-$, $-(CR^7R^7)_p-S(O)-$, $-(CR^7R^7)_p-S(O)_2-$, $-(CR^7R^7)_p-S-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)_2-(CR^7R^7)_p-$, $-(CR^7R^7)_p-S(O)_2-N(R^7)-$, $-(CR^7R^7)_p-S(O)_2-N(R^7)-C(O)-$, $-(CR^7R^7)_p-P(O)(OR^7)O-$, $-O-P(O)(OR^7)O-$, $-P(O)_2O-$, $-(CR^7R^7)_p-$(optionally substituted heterocyclylene)– and a bond; the optional substituent of the heterocyclyene is independently selected from one or more groups selected from –Hal, –CN, $-NO_2$, –OH and $-NH_2$;

m is 1 to 3;

n is 1 to 4; and

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, and 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 any of the preceding claims, wherein R^3 is –halogen.

4. The compound according to any of the preceding claims, wherein R^9 is–H.

5. The compound according to any of the preceding claims, wherein R^2 is –H and/or R^4 is –H and/or R^7 is –H.

6. 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–.

7. 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.

8. The compound according to any of the preceding claims, wherein X^2 is N.

9. A pharmaceutical composition comprising:
a compound having the formula (I) as defined in any of claims 1 to 8, 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).

10. A compound having the formula (I) as defined in any of claims 1 to 8, 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.

11. 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 8, 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/CN2017/072839

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04(2006.01)i; A61K 31/519(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)

C07D 487/04; C07D 487/+; A61K 31/519

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)

DWPI, SIPOABS, CNKI, CNABS, CAPLUS, REGISTRY (STN) pyrrolopyrimidine, pyrazolopyrimidine, pyrrolo, pyrimidin, pyrazolo, influenza, structure search according to formula (I)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2016037953 A1 (JANSSEN SCIENCES IRELAND UC) 17 March 2016 (2016-03-17) See the whole document, especially tables 1-2 claims 1-9	1-7, 9-11
X	WO 2007041130 A2 (VERTEX PHARMAET AL.) 12 April 2007 (2007-04-12) See the whole document, especially description pp. 24, 26	1-6, 9
A	WO 2009143024 A3 (PLEXXIKON INCET AL.) 07 January 2010 (2010-01-07) See the whole document, especially claims 1, 17, description p. 141, line 6	1-11
A	WO 2004056830 A1 (PFIZER PROD INCET AL.) 08 July 2004 (2004-07-08) See the whole document, especially claim 1, description pp. 1-3	1-11

☐ 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	Date of mailing of the international search report
04 April 2017	**08 May 2017**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**FU,Wei**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62086335**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/072839

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.: **11**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 11 is directed to a method of treatment (Rule 39.1 (iv) PCT). Nonetheless, the search has been carried out based on the use of the compound of claims 1-8 in the manufacture of corresponding medicaments.

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/CN2017/072839

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2016037953 A1	17 March 2016	AU 2015314394 A1	02 March 2017
		SG 11201701621Y A	30 March 2017
WO 2007041130 A2	12 April 2007	WO 2007041130 A3	21 January 2010
		CA 2623032 A1	12 April 2007
		CN 101801971 A	11 August 2010
		EP 2532667 A1	12 December 2012
		IL 190249 D0	03 November 2008
		SG 151327 A1	30 April 2009
		NO 20082026 A	25 June 2008
		ES 2401192 T3	17 April 2013
		ZA 200802685 A	28 October 2009
		EP 1931674 A2	18 June 2008
		NO 20082026 B	25 June 2008
		ZA 200802685 B	28 October 2009
		RU 2008117151 A	10 November 2009
		NZ 567133 A	29 July 2011
		JP 2009513571 A	02 April 2009
		US 2007207995 A1	06 September 2007
		KR 20080063809 A	07 July 2008
		EP 1931674 B1	12 December 2012
		ES 2401192 T8	10 May 2013
		US 8580802 B2	12 November 2013
		AU 2006297351 A1	12 April 2007
WO 2009143024 A3	07 January 2010	WO 2009143024 A2	26 November 2009
		AR 071838 A1	21 July 2010
		US 2009286783 A1	19 November 2009
		TW 200948815 A	01 December 2009
		UY 31829 A	05 January 2010
		PE 18462009 A1	16 December 2009
		US 8153641 B2	10 April 2012
WO 2004056830 A1	08 July 2004	ZA 200504440 B	26 July 2006
		TW 200423939 A	16 November 2004
		NO 20052802 D0	09 June 2005
		GT 200300289 A	21 September 2004
		ZA 200504440 A	26 July 2006
		MX PA05006793 A	08 September 2005
		NL 1025068 C2	16 November 2004
		CA 2510853 C	28 April 2009
		US 2005037999 A1	17 February 2005
		EP 1578751 B1	15 June 2011
		MA 27568 A1	03 October 2005
		JP 4057013 B2	05 March 2008
		KR 20070087020 A	27 August 2007
		CA 2510853 A1	08 July 2004
		PA 8591701 A1	24 May 2005
		UA 80171 C2	27 August 2007
		PE 09142004 A1	08 January 2005
		US 7271262 B2	18 September 2007
		EC SP055867 A	20 September 2005
		OA 12976 A	13 October 2006

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2017/072839

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		AR	042509	A1	22 June 2005
		IS	7872	A	30 May 2005
		HN	2003000416	A	25 July 2006
		NZ	540456	A	30 November 2007
		KR	20050084402	A	26 August 2005
		BR	0317524	A	16 November 2005
		AU	2003286317	A1	14 July 2004
		AT	512965	T	15 July 2011
		EP	1578751	A1	28 September 2005
		AP	200503342	D0	30 June 2005
		HR	P20050560	A2	28 February 2006
		NO	20052802	A	19 July 2005
		JP	2006512356	A	13 April 2006
		NL	1025068	A1	22 June 2004
		RS	20050469	A	15 November 2007
		UY	28132	A1	30 July 2004
		PL	377774	A1	20 February 2006
		ES	2364649	T3	08 September 2011
		CN	1726218	A	25 January 2006