

TREM2 AGONISTS

Field of the Invention

The present invention relates to organic compounds useful for therapy or prophylaxis in a mammal, and in particular to Triggering Receptor Expressed on Myeloid cells 2 (TREM2) agonists for the treatment or prevention of Parkinson's disease, rheumatoid arthritis, Alzheimer's disease, amyotrophic lateral sclerosis, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, and stroke.

Background of the Invention

Microglia are immune cells resident in the central nervous system (CNS) which play a crucial role in the CNS development and maintenance of brain homeostasis through synaptic pruning and removal of apoptotic neurons (Paolicelli R.C. et al., Science 2011, 9;333(6048):1456-8 doi: 10.1126/science.1202529). Microglia are also key players in response to neurodegenerative conditions and neuropathological lesions, whereby they shift into an activated state characterized by cell proliferation, expression and secretion of cytokines and neuroprotective factors, migration to the lesion sites and phagocytosis of dead cells and debris. (Lue L.F. et al., Mol. Neurobiol. 2010, 41(2-3):115-28, doi: 10.1007/s12035-010-8106-8).

Microglia express a multitude of receptors on their surface, which play a key role in sensing the environmental changes and enabling the complex crosstalk regulating their physiological functions.

TREM2 (Triggering Receptor Expressed on Myeloid cells 2) is one of these cell surface receptors, which in brain is selectively expressed on microglia and plays a key role in their survival and activation (Colonna, M. et al., Nat Rev Immunol 3, 445–453 (2003). <https://doi.org/10.1038/nri1106>). TREM2 is a single-pass transmembrane receptor that belongs to the Immunoglobulin superfamily (Ig-SF). It is composed of a ligand binding extracellular immunoglobulin variable-like domain (IgV) followed by a long stalk domain, a single transmembrane helix and a short cytosolic tail that does not have signal transduction motifs.

Downstream signal transduction is mediated through its interaction with the effector protein DAP12, a transmembrane disulphide-linked adapter dimer which expression and cellular localization at the plasma membrane are dependent on TREM2, and which is associated to TREM2 transmembrane helix via lysine-aspartic acid interaction (K156-D50) forming a signaling complex (Zhong L. et al., J Biol Chem. 2015;290(25):15866–77). Given its short extracellular domain, DAP12 lacks ligand-binding capabilities. Endogenous ligands of TREM2 include a wide range of molecules, including phospholipids, glycolipids, lipoproteins, cellular debris, myelin and A β oligomers. Stimulation of the TREM2/DAP12 complex induces in the phosphorylation of two tyrosine residues within the immunoreceptor tyrosine-based activation motif (ITAM) in the cytoplasmic domain of DAP12, which results in recruitment of Syk kinase to activate downstream signaling molecules.

Activation of TREM2 plays a key role in microglia signaling and function, including survival, migration, amyloid plaque insulation, beta-amyloid phagocytosis, myelin debris clearance and the transition from the homeostatic to the disease-associated microglia (DAM) state in the context of a neurodegenerative environment (Condello, C. et al., Nat Commun 6, 6176, 2015, doi: org/10.1038/ncomms7176; Poliani et al., J Clin Invest, 2015 May;125(5):2161-70, doi: 10.1172/JCI77983; Zhao et al., Neuron, 2018 Mar 7;97(5):1023-1031.e7, doi: 10.1016/j.neuron.2018.01.031; Keren-Shaul H. et al., Cell, 2017 Jun 15;169(7):1276-1290.e17, doi: 10.1016/j.cell.2017.05.018).

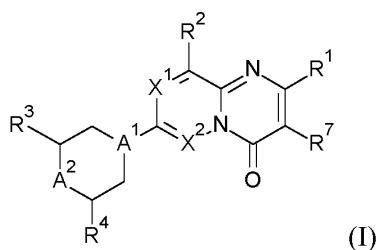
Genetic variants of TREM2 have been implicated in a multitude of neurodegenerative diseases (Hou J. et al. Molecular Neurodegeneration (2022) 17:84; doi: org/10.1186/s13024-022-00588-y). TREM2 variants resulting in lack of TREM2 expression were identified as the cause of the Nasu-Hakola Disease (NHD), or Polycystic lipomembranous osteodysplasia with sclerosis leukoencephalopathy (PLOS), a fatal condition manifesting with progressive pre-senile dementia and characterized by loss of myelin and bone abnormalities, consistent with TREM2 expression in myeloid cells microglia and osteoclasts (Paloneva, J. et al., Am J Hum Genet. 2002;71(3):656-62, doi: 10.1086/342259). Similarly, missense mutations of TREM2 have been associated with increased risk of Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Several of these TREM2 variants have been implicated with impaired microglia function and their reduced response to neurodegenerative diseases. (Kleinberger, G. et al., Sci. Transl. Med. 2014, 6, 243ra86).

Moreover, genomic-wide association studies (GWAS) showed a strong link between a number of rare loss of function (LoF) variants of TREM2 and an increased risk of late onset Alzheimer's disease (LOAD) (Guerreiro R. et al., N Engl J Med. 2013, 368(2):117–27; Jonsson T. et al., N Engl J Med. 2013, 368(2):107–16). Amongst those, the R47H variant, a LoF mutation associated with structural alterations within the extracellular domain of TREM2 resulting in impaired ability to bind endogenous ligands, was linked to a ca. 3 fold increased risk of LOAD (Sudom, A. et al., J Biol Chem. 2018 10;293(32):12634-12646; doi: 10.1074/jbc.RA118.002352). Studies are ongoing to elucidate the mechanism by which TREM2 LoF mutations contribute to AD. It is likely that patients carrying these mutations have impaired microglia function including reduced clearance of extracellular aggregates (e.g. amyloid and myelin debris) and apoptotic neurons, ultimately reducing their capacity to fight the disease and increasing their susceptibility to neurodegeneration. Indeed decreased microglia activation and failure to cluster around the amyloid plaque were observed in mouse models deficient for TREM2 or DAP12, confirming the central role of TREM2 signalling in microglia function and response to Alzheimer's pathological hallmarks.

In light of all this evidence, pharmacological activation of TREM2 appears to be a viable therapeutic intervention. The small molecules disclosed herein are potent and selective agonists of TREM2.

Summary of the Invention

In a first aspect, the present invention provides compounds of formula (I)



wherein A¹, A², X¹, X², R¹, R², R³, R⁴, and R⁷ are as defined herein.

In further aspects, the invention provides compositions including the compounds of formula (I), processes of manufacturing the compounds of formula (I) and methods of using the compounds of formula (I).

Detailed Description of the Invention**Definitions**

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be
5 understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of
10 any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The term “alkyl” refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched
15 saturated hydrocarbon group of 1 to 6 carbon atoms (“C₁₋₆-alkyl”), e.g., 1, 2, 3, 4, 5, or 6 carbon atoms. In some embodiments, the alkyl group contains 1 to 4 carbon atoms, e.g., 1, 2, 3, or 4 carbon atoms. In other embodiments, the alkoxy group contains 1 to 3 carbon atoms. Some non-limiting examples of alkyl include methyl, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, tert-butyl, and 2,2-dimethylpropyl. Particularly preferred, yet non-limiting examples
20 of alkyl are methyl, tert-butyl, and 2,2-dimethylpropyl.

The term “alkoxy” refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1 to 6 carbon atoms (“C₁₋₆-alkoxy”). In some embodiments, the alkoxy group contains 1 to 4 carbon atoms, e.g., 1, 2, 3, or 4 carbon atoms. In other embodiments, the alkoxy group contains 1
25 to 3 carbon atoms. Some non-limiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. A particularly preferred, yet non-limiting example of alkoxy is methoxy.

The term “halogen” or “halo” refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I). Preferably, the term “halogen” or “halo” refers to fluoro (F), chloro (Cl) or bromo (Br).
30 Particularly preferred, yet non-limiting examples of “halogen” or “halo” are fluoro (F) and chloro (Cl).

The term "cycloalkyl" as used herein refers to a saturated monocyclic or bicyclic hydrocarbon group of 3 to 10 ring carbon atoms ("C₃₋₁₀-cycloalkyl"). In some preferred embodiments, the cycloalkyl group is a monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. "Bicyclic cycloalkyl" refers to cycloalkyl moieties consisting of two saturated carbocycles having two
5 carbon atoms in common, i.e., the bridge separating the two rings is either a single bond or a chain of one or two ring atoms, and to spirocyclic moieties, i.e., the two rings are connected via one common ring atom. Preferably, the cycloalkyl group is a monocyclic hydrocarbon group of 3 to 6 ring carbon atoms, e.g., of 3, 4, 5 or 6 carbon atoms. Some non-limiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 1-
10 bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, norbornanyl, and 1-bicyclo[2.2.2]octanyl. Particularly preferred, yet non-limiting examples of cycloalkyl are cyclopropyl, bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl and cyclohexyl.

The term "aryl" refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of 6 to 10 ring members ("C₆-C₁₀-aryl"), wherein at least one ring in the system is aromatic.
15 Some non-limiting examples of aryl include phenyl and 9H-fluorenyl (e.g. 9H-fluoren-9-yl). A particularly preferred, yet non-limiting example of aryl is phenyl.

The term "heteroaryl" refers to a mono- or multivalent, monocyclic ring system having a total of 5 to 6 ring members, wherein the ring system is aromatic and contains one or more heteroatoms. Preferably, the heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S
20 and N. Most preferably, the heteroaryl comprises 1 to 2 heteroatoms independently selected from O, S and N. Some preferred, yet non-limiting examples of heteroaryl include thiazolyl (e.g. thiazol-2-yl); oxazolyl (e.g. oxazol-2-yl); oxadiazolyl; 1,2,4-oxadiazol-5-yl; pyridyl (e.g. 2-pyridyl); pyrazolyl (e.g. pyrazol-1-yl); triazolyl; tetrazolyl; pyrazinyl; and imidazolyl (e.g. imidazole-1-yl). Some preferred, yet non-limiting examples of heteroaryl include pyridyl and
25 pyrazolyl.

The term "heterocyclyl" refers to a saturated or partly unsaturated monocyclic ring system of 3 to 6 ring atoms, wherein 1, 2, or 3 of said ring atoms are heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Preferably, 1 to 2 of said ring atoms are selected from N and O, the remaining ring atoms being carbon. Some non-limiting examples of heterocyclyl
30 groups include azetidynyl, piperidyl, pyrrolidinyl, oxetanyl, piperidyl, 1,2-dihydropyridinyl, piperidyl, pyrrolidinyl, tetrahydrothiophenyl, and thietanyl. Preferred, yet non-limiting examples of heterocyclyl groups include 1,2-dihydropyridinyl and oxetanyl.

The term “haloalkyl” refers to an alkyl group as defined herein, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a halogen atom, preferably fluoro. Preferably, “haloalkyl” refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms of the alkyl group have been replaced by a halogen atom, most preferably fluoro. Particularly preferred, yet
5 non-limiting examples of haloalkyl are trifluoromethyl, difluoromethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl.

The term “alkoxyalkyl” refers to an alkyl group as defined herein, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxy group, preferably methoxy. Preferably, “alkoxyalkyl” refers to an alkyl group wherein 1 of the hydrogen atoms of the alkyl
10 group has been replaced by an alkoxy group, most preferably methoxy. A particularly preferred, yet non-limiting example of alkoxyalkyl is 2-methoxyethyl.

The term “cycloalkylalkyl” refers to an alkyl group as defined herein, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a cycloalkyl group, preferably cyclopropyl. Preferably, “cycloalkylalkyl” refers to an alkyl group wherein 1 of the hydrogen
15 atoms of the alkyl group has been replaced by a cycloalkyl group, most preferably cyclopropyl. A particularly preferred, yet non-limiting example of cycloalkylalkyl is cyclopropylmethyl.

The term “cycloalkylalkoxy” refers to an alkoxy group as defined herein, wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by a cycloalkyl group, preferably cyclopropyl. Preferably, “cycloalkylalkoxy” refers to an alkoxy group wherein 1 of the hydrogen
20 atoms of the alkoxy group has been replaced by a cycloalkyl group, most preferably cyclopropyl. A particularly preferred, yet non-limiting example of cycloalkylalkoxy is cyclopropylmethoxy.

The term “cycloalkoxy” refers to a cycloalkyl group as defined herein, wherein the cycloalkyl group is bound to the parent molecule through an oxygen atom. A particularly preferred, yet non-limiting example of cycloalkoxy is cyclobutyloxy.

25 The term “heterocyclalkyl” refers to an alkyl group as defined herein, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a heterocycl group, preferably oxetanyl. Preferably, “heterocyclalkyl” refers to an alkyl group wherein 1 of the hydrogen atoms of the alkyl group has been replaced by a heterocycl group, most preferably oxetanyl. A particularly preferred, yet non-limiting example of heterocyclalkyl is oxetanylmethyl.

The term “heterocyclylalkoxy” refers to an alkoxy group as defined herein, wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by a heterocyclyl group, preferably oxetanyl. Preferably, “heterocyclylalkoxy” refers to an alkoxy group wherein 1 of the hydrogen atoms of the alkoxy group has been replaced by a heterocyclyl group, most preferably oxetanyl.

5 A particularly preferred, yet non-limiting example of heterocyclylalkoxy is oxetanylmethoxy.

The term “heterocyclyloxy” refers to a heterocyclyl group as defined herein, wherein the heterocyclyl group is bound to the parent molecule through an oxygen atom. A particularly preferred, yet non-limiting example of heterocyclyloxy is oxetanyloxy.

The term “pharmaceutically acceptable salt” refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcysteine and the like. In addition these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like.

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The compounds of formula (I) can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

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The abbreviation “TREM2” refers to Triggering Receptor Expressed on Myeloid cells 2.

The term “treatment” as used herein includes: (1) inhibiting the state, disorder or condition (e.g. arresting, reducing or delaying the development of the disease, or a relapse thereof in case of maintenance treatment, of at least one clinical or subclinical symptom thereof); and/or (2)

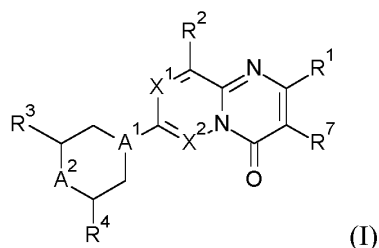
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relieving the condition (i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms). The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient or to the physician. However, it will be appreciated that when a medicament is administered to a patient to treat a disease, the outcome may not always be effective treatment.

The term “prophylaxis” as used herein includes: preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal and especially a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition.

10 Compounds of the Invention

In a first aspect, the present invention provides a compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

A^1 , X^1 and X^2 are each independently selected from N and CH;

15 A^2 is selected from O and CR^5R^6 ;

R^1 is selected from C_1 - C_6 -alkyl and halo- C_1 - C_6 -alkyl;

R^2 is selected from C_6 - C_{10} -aryl, 5- to 6-membered heteroaryl and C_3 - C_{10} -cycloalkyl, wherein said C_6 - C_{10} -aryl, 5- to 6-membered heteroaryl and C_3 - C_{10} -cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C_1 - C_6 -alkyl and halo- C_1 - C_6 -alkyl;

20 R^3 is selected from 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl, wherein said 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl are optionally substituted with 1-3 substituents independently selected from halogen, cyano, amino, hydroxy, oxo, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halo- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, halo-3- to 6-membered heterocyclyl,

3- to 6-membered heterocyclyl-C₁-C₆-alkyl, 3- to 6-membered heterocyclyl-C₁-C₆-alkoxy and 3- to 6-membered heterocyclyloxy;

R⁴ is selected from hydrogen and C₁-C₆-alkyl;

R⁵ and R⁶ are each independently selected from hydrogen and halogen; and

5 R⁷ is selected from hydrogen and C₁-C₆-alkyl.

In a further aspect, the present invention provides a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

A¹, X¹ and X² are each independently selected from N and CH;

A² is selected from O and CR⁵R⁶;

10 R¹ is selected from C₁-C₆-alkyl and halo-C₁-C₆-alkyl;

R² is selected from C₆-C₁₀-aryl and C₃-C₁₀-cycloalkyl, wherein said C₆-C₁₀-aryl and C₃-C₁₀-cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C₁-C₆-alkyl and halo-C₁-C₆-alkyl;

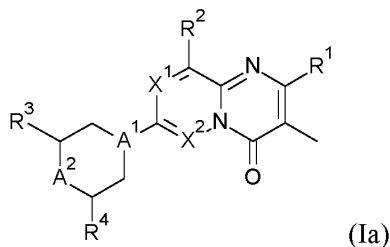
15 R³ is selected from 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl, wherein said 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl are optionally substituted with 1-3 substituents independently selected from halogen, cyano, amino, hydroxy, oxo, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyl, and 3- to 6-membered heterocyclyl;

R⁴ is selected from hydrogen and C₁-C₆-alkyl;

20 R⁵ and R⁶ are each independently selected from hydrogen and halogen; and

R⁷ is selected from hydrogen and C₁-C₆-alkyl.

In a further aspect, the present invention provides a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound of Formula (Ia)



25

wherein:

A¹, X¹ and X² are each independently selected from N and CH;

A² is selected from O and CR⁵R⁶;

- R¹ is selected from C₁-C₆-alkyl and halo-C₁-C₆-alkyl;
- R² is selected from C₆-C₁₀-aryl and C₃-C₁₀-cycloalkyl, wherein said C₆-C₁₀-aryl and C₃-C₁₀-cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C₁-C₆-alkyl and halo-C₁-C₆-alkyl;
- 5 R³ is a 5- to 6-membered heteroaryl that is optionally substituted with 1-3 substituents independently selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, and C₃-C₁₀-cycloalkyl;
- R⁴ is selected from hydrogen and C₁-C₆-alkyl; and
- R⁵ and R⁶ are each independently selected from hydrogen and halogen.

In one embodiment, the present invention provides a compound of formula (I) as described
10 herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X¹ and X² are both CH; or
- (ii) X¹ is CH and X² is N; or
- (iii) X¹ is N and X² is CH.

In one embodiment, the present invention provides a compound of formula (I) as described
15 herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X¹ is CH and X² is N; or
- (ii) X¹ is N and X² is CH.

In one embodiment, the present invention provides a compound of formula (I) as described
herein, or a pharmaceutically acceptable salt thereof, wherein X¹ is CH and X² is N.

20 In one embodiment, the present invention provides a compound of formula (I) as described
herein, or a pharmaceutically acceptable salt thereof, wherein X¹ is N and X² is CH.

In a preferred embodiment, the present invention provides a compound of formula (I) as
described herein, or a pharmaceutically acceptable salt thereof, wherein X¹ and X² are both CH.

In one embodiment, the present invention provides a compound of formula (I) as described
25 herein, or a pharmaceutically acceptable salt thereof, wherein A¹ is CH.

In one embodiment, the present invention provides a compound of formula (I) as described
herein, or a pharmaceutically acceptable salt thereof, wherein A¹ is N.

In one embodiment, the present invention provides a compound of formula (I) as described
herein, or a pharmaceutically acceptable salt thereof, wherein:

A^2 is selected from O and CR^5R^6 ;

R^5 and R^6 are both hydrogen or

R^5 and R^6 are both halogen.

In one embodiment, the present invention provides a compound of formula (I) as described
 5 herein, or a pharmaceutically acceptable salt thereof, wherein:

A^2 is selected from O and CR^5R^6 ;

R^5 and R^6 are both hydrogen or

R^5 and R^6 are both fluoro.

In a preferred embodiment, the present invention provides a compound of formula (I) as
 10 described herein, or a pharmaceutically acceptable salt thereof, wherein A^2 is O.

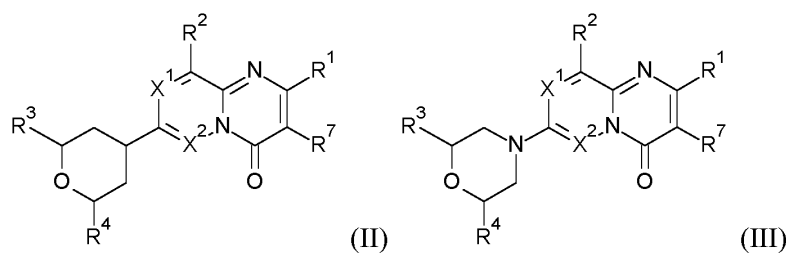
In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

A^2 is CR^5R^6 ;

R^5 and R^6 are both hydrogen or

15 R^5 and R^6 are both fluoro.

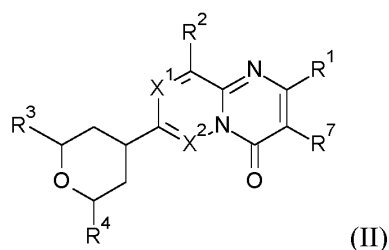
In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is a compound of formula (II) or (III):



20 wherein the variables are as defined herein.

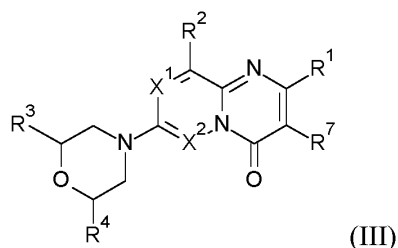
In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is a compound of formula (II):

- 12 -



wherein the variables are as defined herein.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is a
 5 compound of formula (III):



wherein the variables are as defined herein.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹ is C₁-C₆-alkyl.

10 In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from methyl and CHF₂.

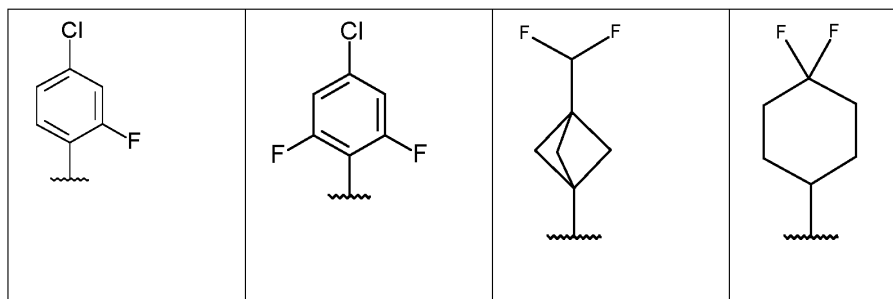
15 In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R² is selected from C₆-C₁₀-aryl, C₃-C₁₀-cycloalkyl, and 5- to 6-membered heteroaryl comprising 1-2 heteroatoms independently selected from N, O and S, wherein said C₆-C₁₀-aryl, C₃-C₁₀-cycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with 1-3 substituents independently selected from halogen
 20 and halo-C₁-C₆-alkyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, pyridyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF_2 , and CF_3 .

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from C_6 - C_{10} -aryl and C_3 - C_{10} -cycloalkyl, wherein said C_6 - C_{10} -aryl and C_3 - C_{10} -cycloalkyl are substituted with 1-3 substituents independently selected from halogen and halo- C_1 - C_6 -alkyl.

10 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, cyclohexyl, and bicyclo[1.1.1]pentane substituted with 1-3 substituents independently selected from fluoro, chloro, and CHF_2 .

In a further particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

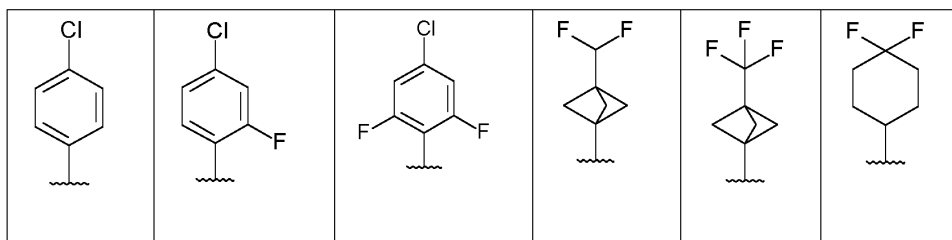


In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, cyclohexyl and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF_2 , and CF_3 .

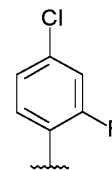
In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is phenyl substituted with 1-3 halogen substituents.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is phenyl substituted with 1-3 substituents selected from fluoro and chloro.

- In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



In a particularly preferred embodiment, the present invention provides a compound of formula



(I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^2 is

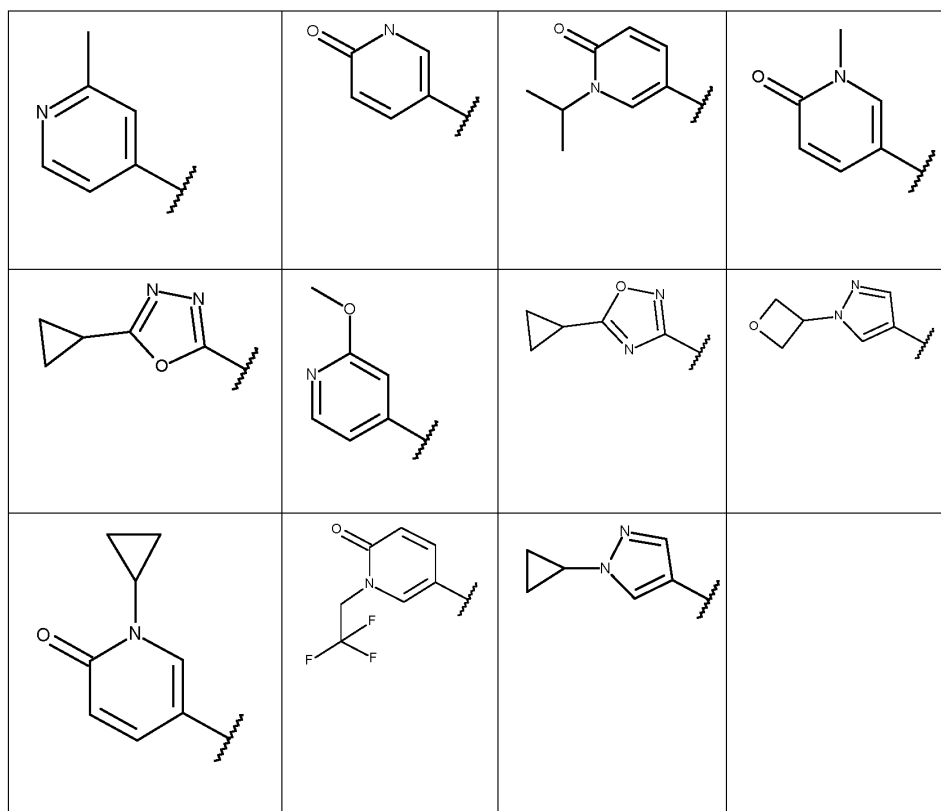
- In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is optionally substituted with 1-2 substituents independently selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkyl, and 3- to 6-membered heterocyclyl- C_1 - C_6 -alkoxy, and wherein said 3- to 6-membered heterocyclyl is optionally substituted with 1-2 substituents independently selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkoxy, and oxo.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF₂, CF₃, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, and oxetanylmethoxy, and wherein said 1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF₂, CF₃, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, oxetanylmethoxy, and oxo.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is substituted with 1 substituent selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyl, and 3- to 6-membered heterocyclyl, and wherein said 3- to 6-membered heterocyclyl is substituted with oxo and optionally one further substituent selected from C₁-C₆-alkyl, halo-C₁-C₆-alkyl, and C₃-C₁₀-cycloalkyl.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are substituted with 1 substituent selected from methyl, methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is substituted with oxo and optionally one further substituent selected from methyl, isopropyl, 2,2,2-trifluoroethyl, and cyclopropyl.

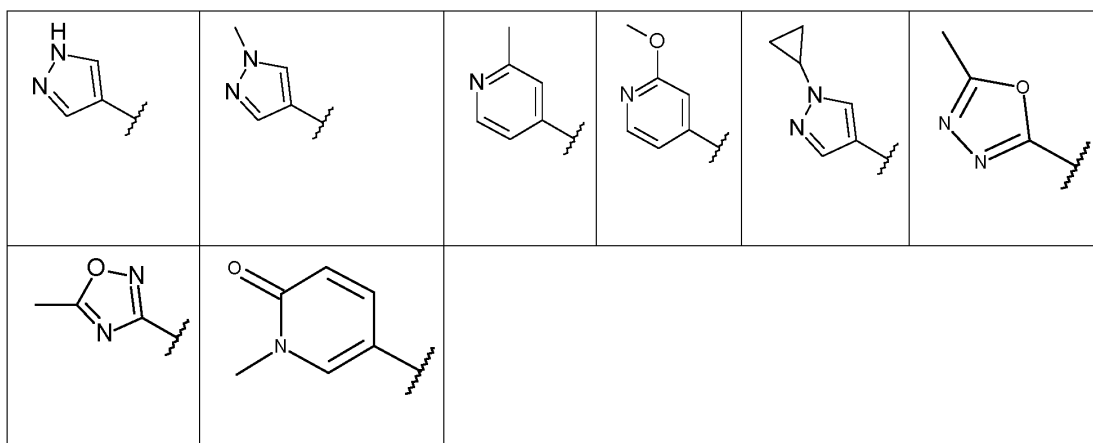
In a further particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is selected from:



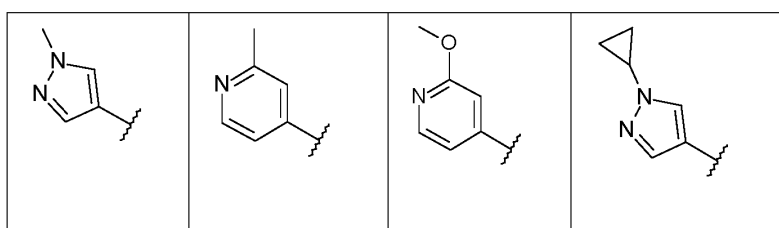
In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, CF_3 , methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, CF_3 , methoxy, cyclopropyl, oxetanyl, and oxo.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from pyridyl and pyrazolyl, wherein said pyridyl and pyrazolyl are substituted with 1 substituent selected from methyl, methoxy, and cyclopropyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:



In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:



- 5 In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen and methyl.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

- 10 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen and methyl.

- 15 In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_6 -alkyl.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁷ is methyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- 5 (i) X¹ and X² are both CH; or
- (ii) X¹ is CH and X² is N; or
- (iii) X¹ is N and X² is CH;
- A¹ is selected from N and CH;
- A² is selected from O and CR⁵R⁶;
- 10 R¹ is selected from C₁-C₆-alkyl and halo-C₁-C₆-alkyl;
- R² is selected from C₆-C₁₀-aryl, C₃-C₁₀-cycloalkyl, and 5- to 6-membered heteroaryl comprising 1-2 heteroatoms independently selected from N, O and S, wherein said C₆-C₁₀-aryl, C₃-C₁₀-cycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with 1-3 substituents independently selected from halogen and halo-C₁-
- 15 C₆-alkyl;
- R³ is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered
- 20 heteroaryl is optionally substituted with 1-2 substituents independently selected from C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyl, halo-C₃-C₁₀-cycloalkyl, C₃-C₁₀-cycloalkyl-C₁-C₆-alkyl, C₃-C₁₀-cycloalkyl-C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C₁-C₆-alkyl, and 3- to 6-membered heterocyclyl-C₁-C₆-alkoxy, and wherein said 3- to 6-membered heterocyclyl is optionally substituted with 1-2 substituents independently selected from C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyl, halo-C₃-C₁₀-cycloalkyl, C₃-C₁₀-cycloalkyl-C₁-C₆-alkyl, C₃-C₁₀-cycloalkyl-C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C₁-C₆-alkyl, 3- to 6-
- 25 membered heterocyclyl-C₁-C₆-alkoxy, and oxo;
- 30 R⁴ is selected from hydrogen and C₁-C₆-alkyl;
- R⁵ and R⁶ are both hydrogen or
- R⁵ and R⁶ are both halogen; and

R⁷ is selected from hydrogen and C₁-C₆-alkyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X¹ and X² are both CH; or
- 5 (ii) X¹ is CH and X² is N; or
- (iii) X¹ is N and X² is CH;
- A¹ is selected from N and CH;
- A² is selected from O and CR⁵R⁶;
- R¹ is selected from methyl and CHF₂;
- 10 R² is selected from phenyl, pyridyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF₂, and CF₃;
- R³ is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-
15 dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF₂, CF₃, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, and oxetanylmethoxy,
20 and wherein said 1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF₂, CF₃, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, oxetanylmethoxy, and oxo;
- 25 R⁴ is selected from hydrogen and methyl;
- R⁵ and R⁶ are both hydrogen or
- R⁵ and R⁶ are both fluoro; and
- R⁷ is selected from hydrogen and methyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as
30 described herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X¹ is CH and X² is N; or
- (ii) X¹ is N and X² is CH;
- A¹ is CH;

- A^2 is O;
 R^1 is selected from C₁-C₆-alkyl and halo-C₁-C₆-alkyl;
 R^2 is selected from C₆-C₁₀-aryl and C₃-C₁₀-cycloalkyl, wherein said C₆-C₁₀-aryl and C₃-C₁₀-cycloalkyl are substituted with 1-3 substituents independently selected from halogen and halo-C₁-C₆-alkyl;
 R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is substituted with 1 substituent selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyl, and 3- to 6-membered heterocyclyl, and wherein said 3- to 6-membered heterocyclyl is substituted with oxo and optionally one further substituent selected from C₁-C₆-alkyl, halo-C₁-C₆-alkyl, and C₃-C₁₀-cycloalkyl;
 R^4 is hydrogen; and
 R^7 is C₁-C₆-alkyl.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X^1 is CH and X^2 is N; or
 (ii) X^1 is N and X^2 is CH;
 A^1 is CH;
 A^2 is O;
 R^1 is selected from methyl and CHF₂;
 R^2 is selected from phenyl, cyclohexyl, and bicyclo[1.1.1]pentane substituted with 1-3 substituents independently selected from fluoro, chloro, and CHF₂;
 R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are substituted with 1 substituent selected from methyl, methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is substituted with oxo and optionally one further substituent selected from methyl, isopropyl, 2,2,2-trifluoroethyl, and cyclopropyl;
 R^4 is hydrogen; and
 R^7 is methyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X^1 and X^2 are both CH; or
- (ii) X^1 is CH and X^2 is N; or
- 5 (iii) X^1 is N and X^2 is CH;
- A^1 is selected from N and CH;
- A^2 is selected from O and CR^5R^6 ;
- R^1 is C_1 - C_6 -alkyl;
- R^2 is selected from phenyl, cyclohexyl and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF_2 , and CF_3 ;
- 10 R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, CF_3 , methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, CF_3 , methoxy, cyclopropyl, oxetanyl, and oxo;
- 15 R^4 is selected from hydrogen and C_1 - C_6 -alkyl;
- R^5 and R^6 are both hydrogen or
- 20 R^5 and R^6 are both halogen; and
- R^7 is selected from hydrogen and C_1 - C_6 -alkyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X^1 and X^2 are both CH; or
- 25 (ii) X^1 is CH and X^2 is N; or
- (iii) X^1 is N and X^2 is CH;
- A^1 is selected from N and CH;
- A^2 is selected from O and CR^5R^6 ;
- R^1 is C_1 - C_6 -alkyl;
- 30 R^2 is phenyl substituted with 1-3 halogen substituents;
- R^3 is selected from pyridyl and pyrazolyl, wherein said pyridyl and pyrazolyl are substituted with 1 substituent selected from methyl, methoxy, and cyclopropyl;
- R^4 is selected from hydrogen and methyl;

R⁵ and R⁶ are both hydrogen or
R⁵ and R⁶ are both halogen; and
R⁷ is C₁-C₆-alkyl.

In a particularly preferred embodiment, the present invention provides a compound of formula

5 (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- A¹, X¹ and X² are all CH;
A² is O;
R¹ is methyl;
R² is phenyl substituted with 1-3 substituents selected from fluoro and chloro;
10 R³ is selected from pyridyl and pyrazolyl, wherein said pyridyl and pyrazolyl are substituted with 1 substituent selected from methyl, methoxy, and cyclopropyl;
R⁴ is hydrogen; and
R⁷ is methyl.

In one embodiment, the present invention provides a compound of formula (Ia) as described

15 herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X¹ and X² are both CH; or
(ii) X¹ is CH and X² is N; or
(iii) X¹ is N and X² is CH;
A¹ is selected from N and CH;
20 A² is selected from O and CR⁵R⁶;
R¹ is C₁-C₆-alkyl;
R² is selected from phenyl, cyclohexyl and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF₂, and CF₃;
25 R³ is selected from pyridyl and pyrazolyl, wherein said pyridyl and pyrazolyl are substituted with 1 substituent selected from methyl, methoxy, and cyclopropyl;
R⁴ is selected from hydrogen and C₁-C₆-alkyl; and
R⁵ and R⁶ are both hydrogen or
R⁵ and R⁶ are both halogen.

30 In a preferred embodiment, the present invention provides a compound of formula (Ia) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- (i) X¹ and X² are both CH; or

- (ii) X^1 is CH and X^2 is N; or
- (iii) X^1 is N and X^2 is CH;
- A^1 is selected from N and CH;
- A^2 is selected from O and CR^5R^6 ;
- 5 R^1 is C_1 - C_6 -alkyl;
- R^2 is phenyl substituted with 1-3 halogen substituents;
- R^3 is selected from pyridyl and pyrazolyl, wherein said pyridyl and pyrazolyl are substituted with 1 substituent selected from methyl, methoxy, and cyclopropyl;
- R^4 is selected from hydrogen and methyl; and
- 10 R^5 and R^6 are both hydrogen or
- R^5 and R^6 are both halogen.

In a particularly preferred embodiment, the present invention provides a compound of formula (Ia) as described herein, or a pharmaceutically acceptable salt thereof, wherein:

- A^1 , X^1 and X^2 are all CH;
- 15 A^2 is O;
- R^1 is methyl;
- R^2 is phenyl substituted with 1-3 substituents selected from fluoro and chloro;
- R^3 is selected from pyridyl and pyrazolyl, wherein said pyridyl and pyrazolyl are substituted with 1 substituent selected from methyl, methoxy, and cyclopropyl; and
- 20 R^4 is hydrogen.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from:

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(3S)-3-(1-methylpyrazol-4-yl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-
- 10 dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(3S)-4,4-difluoro-3-(1-methylpyrazol-4-yl)-1-piperidyl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-
- 20 pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-
- 30 a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-
- 10 2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-
- 2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one formiate;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 5 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-
- 10 dimethylpyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methyl-6-oxopyridin-3-yl)oxan-4-
- 20 yl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-
- 30 dimethylpyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-
2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-
pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-
yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-
yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-
10 4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-
4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-
yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-
yl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-
bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-
20 bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-
bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-
dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-
dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-
(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-
30 bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-
bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-
(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

- 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- 10 tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- 20 tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- 30 tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-
- tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

- 7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-
- 10 (trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-
- (trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(trifluoromethyl)pyrazol-4-
- 20 yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-
- 30 yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]-9-[6-(trifluoromethyl)pyridin-3-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 15 7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(2-fluorophenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2,6-difluoro-phenyl)-7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 20 2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
2,3-dimethyl-7-[rac-(2R,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 25 7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

- 7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclobutoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[2-[2-(oxetan-3-ylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[6-keto-1-(trifluoromethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-
- 10 dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one; and
- 7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-
- 20 2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from:

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-
- 25 yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(3S)-3-(1-methylpyrazol-4-yl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-
- 10 dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(3S)-4,4-difluoro-3-(1-methylpyrazol-4-yl)-1-piperidyl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-
- 20 pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-
- 30 a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-
- 10 2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-
- 2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one formiate;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 5 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-
- 10 dimethylpyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methyl-6-oxopyridin-3-yl)oxan-4-
- 20 yl]pyrimido[1,2-b]pyridazin-4-one; and
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of

25 formula (I) is selected from:

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one; and

7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
5 formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-
10 2,3-dimethylpyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

15 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula
20 (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
25 formula (I) is 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-
30 yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

- 5 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

- In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.
- 10

- In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.
- 15

- In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.
- 20

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

- 25 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

- In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
- 30

formula (I) is 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
5 formula (I) is 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
10 formula (I) is 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
formula (I) is 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

15 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
formula (I) is 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula
20 (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
formula (I) is 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
25 formula (I) is 7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein said compound of
30 formula (I) is 7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

In a particular embodiment, the present invention provides pharmaceutically acceptable salts of the compounds according to formula (I) as described herein. In a further particular embodiment, the present invention provides compounds according to formula (I) as described herein as free bases or acids.

- 5 In some embodiments, the compounds of formula (I) are isotopically-labeled by having one or more atoms therein replaced by an atom having a different atomic mass or mass number. Such isotopically-labeled (i.e., radiolabeled) compounds of formula (I) are considered to be within the scope of this disclosure. Examples of isotopes that can be incorporated into the compounds of formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur,
10 fluorine, chlorine, and iodine, such as, but not limited to, ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Certain isotopically-labeled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e., ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready
15 means of detection. For example, a compound of formula (I) can be enriched with 1, 2, 5, 10, 25, 50, 75, 90, 95, or 99 percent of a given isotope.

Substitution with heavier isotopes, such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements. Therefore, deuterated versions of the compounds disclosed herein
20 are to be understood to be within the scope of the present invention.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the
25 Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Processes of Manufacturing

The preparation of compounds of formula (I) of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the invention are shown in the following
30 general schemes. The skills required for carrying out the reaction and purification of the resulting products are known to those persons skilled in the art. The substituents and indices used in the

following description of the processes have the significance given herein, unless indicated to the contrary.

- If one of the starting materials, intermediates or compounds of formula (I) contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protective groups (as described e.g., in “Protective Groups in Organic Chemistry” by T. W. Greene and P. G. M. Wuts, 5th Ed., 2014, John Wiley & Sons, N.Y.) can be introduced before the critical step applying methods well known in the art. Such protective groups can be removed at a later stage of the synthesis using standard methods described in the literature.
- 10 If starting materials or intermediates contain stereogenic centers, compounds of formula (I) can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art e.g., chiral HPLC, chiral SFC or chiral crystallization. Racemic compounds can e.g., be separated into their antipodes via diastereomeric salts by crystallization with optically pure acids or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent. It is equally possible to separate starting materials and intermediates containing stereogenic centers to afford diastereomerically/enantiomerically enriched starting materials and intermediates. Using such diastereomerically/enantiomerically enriched starting materials and intermediates in the synthesis of compounds of formula (I) will typically lead to the respective diastereomerically/enantiomerically enriched compounds of formula (I).
- 15
20

A person skilled in the art will acknowledge that in the synthesis of compounds of formula (I) - insofar not desired otherwise - an “orthogonal protection group strategy” will be applied, allowing the cleavage of several protective groups one at a time each without affecting other protective groups in the molecule. The principle of orthogonal protection is well known in the art and has also been described in literature (e.g. Barany and R. B. Merrifield, *J. Am. Chem. Soc.* **1977**, 99, 7363; H. Waldmann et al., *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2056).

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A person skilled in the art will acknowledge that the sequence of reactions may be varied depending on reactivity and nature of the intermediates.

In more detail, the compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Also, for reaction

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conditions described in literature affecting the described reactions see for example:

Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). It was found convenient to carry out the reactions in the presence or absence of a solvent. There is no particular

- 5 restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. The described reactions can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the described reactions in a temperature range between -78 °C to reflux. The time required for the reaction may
- 10 also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 hours to several days will usually suffice to yield the described intermediates and compounds. The reaction sequence is not limited to the one displayed in the schemes, however, depending on the starting materials and their respective reactivity, the sequence of reaction steps can be freely altered.

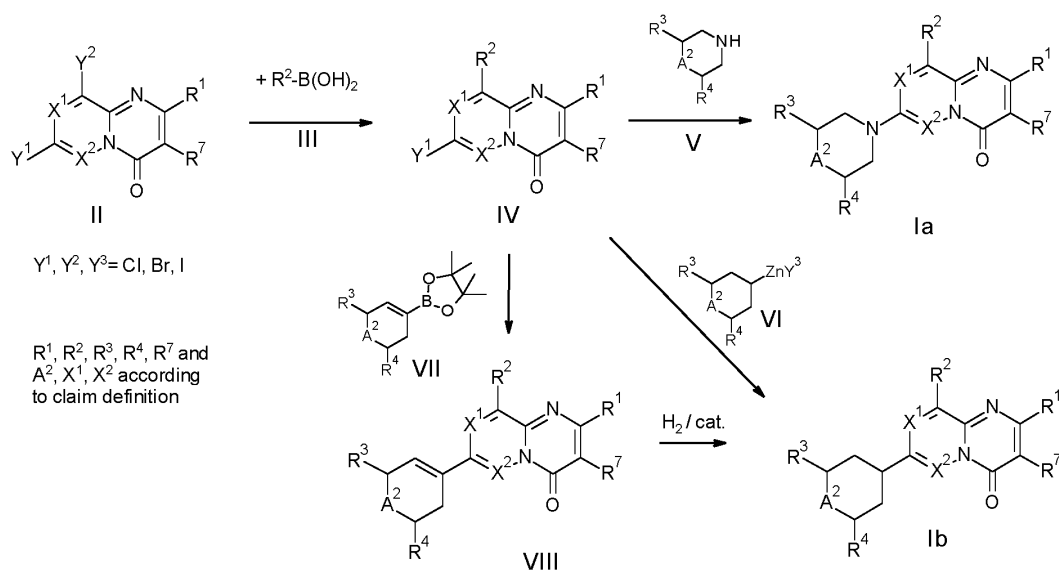
- 15 If starting materials or intermediates are not commercially available or their synthesis not described in literature, they can be prepared in analogy to existing procedures for close analogues or as outlined in the experimental section.

The following abbreviations are used in the present text:

	°C	degrees celsius
20	¹ H	proton
	Å	ångström
	Alk	alkyl
	c	concentration
	CAS	Chemical Abstracts Service registry number
25	CH ₃ CN	acetonitrile
	CO ₂	carbon dioxide
	DIPEA	N,N-Diisopropylethylamine
	DMEM	Dulbecco's modified eagle medium
	DMF	N,N-Dimethylformamide
30	DMSO	dimethylsulfoxide
	DMSO-d ₆	hexadeuterodimethylsulfoxide
	EC ₅₀	half maximal effective concentration
	eq	equivalent

	ESI	electron spray ionization
	Ex.	example
	FBS	fetal bovine serum
	g	gram
5	g/L	gram per liter
	h	hour
	HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
	HBTU	hexafluorophosphate benzotriazole tetramethyl uronium
	HCOOH	formic acid
10	HEK	human embryonic kidney
	HPLC	high performance liquid chromatography
	J	coupling constant
	kg	kilogram
	M	molar
15	m/z	mass-to-charge ratio
	MeOH	methanol
	mg	milligram
	MgSO ₄	magnesium sulfate
	MHz	megahertz
20	min	minute
	ml	milliliter
	mm	millimeter
	mmol	millimole
	MPLC	medium pressure liquid chromatography
25	MS	mass spectrometry
	Na ₂ SO ₃	sodium sulfite
	Na ₂ SO ₄	sodium sulfate
	NaHCO ₃	sodium bicarbonate
	neg.	negative
30	NH ₄ Cl	ammonium chloride
	nm	nanometer
	NMR	nuclear magnetic resonance spectroscopy
	pH	potential of hydrogen
	pos.	positive

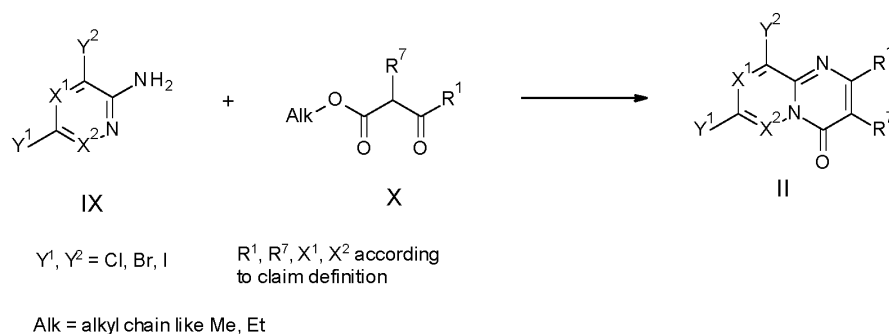
	psi	pounds per square inch
	R	<i>Rectus</i> according to the Cahn–Ingold–Prelog priority rules
	RP	reverse phase
	RPM	revolutions per minute
5	s	second
	S	<i>Sinister</i> according to the Cahn–Ingold–Prelog priority rules
	SFC	supercritical fluid chromatography
	TLC	thin layer chromatography
	μl	microliter
10	μm	micrometer
	μmol	micromoles
	Xantphos	(9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)
	α D	specific rotation at 589 nm
	δ	chemical shift in parts per million

15 Scheme 1

- Compounds of general formula Ia and Ib can be prepared as described in Scheme 1 by reacting intermediate II first with a boronic acid (or a boronic acid derivative) III under palladium catalysed conditions (a palladium source such as (1,1'-bis(diphenylphosphino)-
- 20 ferrocene)palladium(II) dichloride or tetrakis(triphenylphosphine)palladium(0) and a base such as cesium carbonate or sodium carbonate) to form compound IV. This intermediate can be

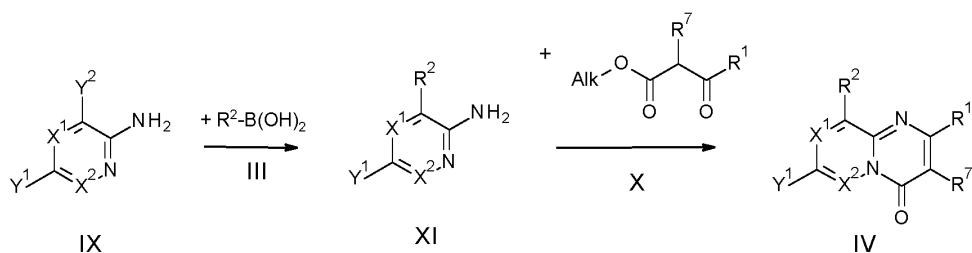
reacted with amine V in presence of a base like N,N-diisopropyl ethylamine, triethylamine or the like in a dipolar aprotic solvent such as dimethylformamide, dimethyl sulfoxide or N-methylpyrrolidone to form Ia (nucleophilic substitution). In addition, compound IV can be reacted with amine V using palladium-catalysed coupling conditions (a palladium source such as tris(dibenzylideneacetone) dipalladium(0), a suitable ligand such as Xantphos and a base such as cesium carbonate or sodium tert.-butoxide to form compound Ia (metal-catalysed coupling). For the synthesis of C-linked derivatives Ib, intermediate IV can either be directly reacted with an organozinc reagent VI using palladium-catalysed conditions, or first with boronic acid derivative VII using a palladium catalyst and a base to form intermediate VIII, which can then be reduced by treatment with a suitable agent like hydrogen and a catalyst to form compound Ib. Preferred catalysts are palladium on charcoal or platinum oxide in ethyl acetate, ethanol or methanol with or without the addition of further reagents like magnesium oxide or triethylamine.

Scheme 2



Compounds of general formula II can be prepared as described in Scheme 2 by reacting heterocyclic compound IX with ketoester X in presence of an acid like polyphosphoric acid or a Lewis acid such as bismuth trichloride at elevated temperatures.

Scheme 3



$Y^1, Y^2 = \text{Cl, Br, I}$

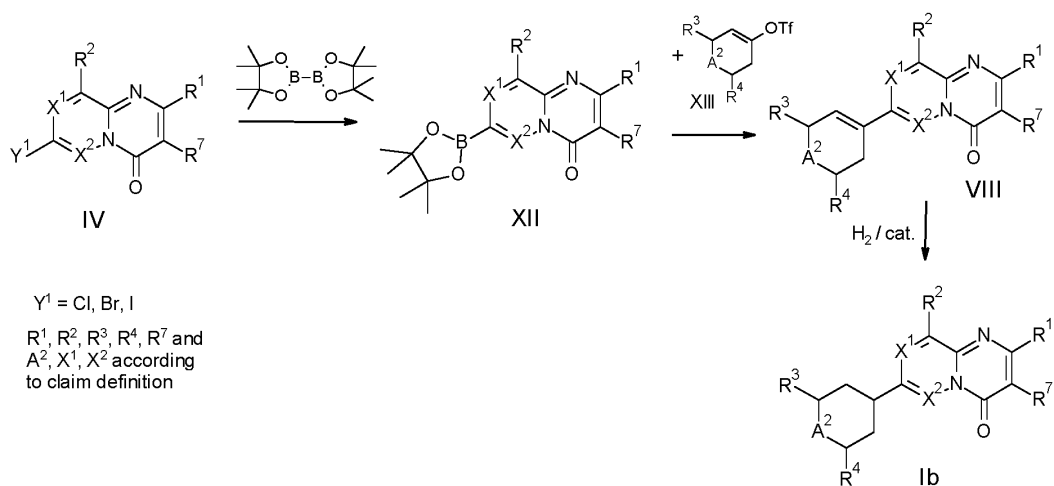
R^1, R^2, R^7 and
 X^1, X^2 according
to claim definition

Alk = alkyl chain like Me, Et

Furthermore compounds of general formula IV can be prepared as described in Scheme 3 by first reacting heterocyclic compound IX with a boronic acid (or a boronic acid derivative, R^2 is preferably aromatic or heteroaromatic) III under palladium catalysed coupling conditions (a

5 palladium source such as (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride or tetrakis(triphenylphosphine)palladium(0) and a base such as cesium carbonate or sodium carbonate) to form compound XI. This intermediate can then react with ketoester X in presence of an acid like polyphosphoric acid or a Lewis acid such as bismuth trichloride at elevated temperatures to form compound IV.

10 Scheme 4



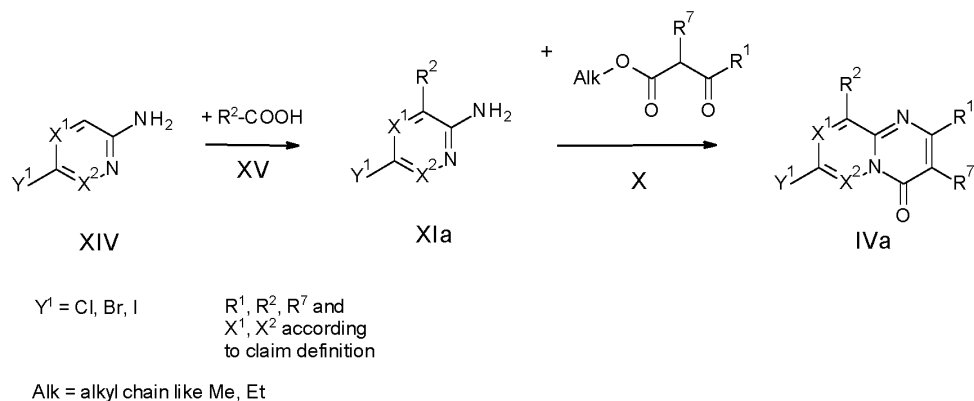
$Y^1 = \text{Cl, Br, I}$

R^1, R^2, R^3, R^4, R^7 and
 A^2, X^1, X^2 according
to claim definition

Furthermore, compounds of general formula Ib can be prepared as described in Scheme 4 by reacting intermediate IV first with bis(pinacolato)diboron under palladium catalysed conditions (a palladium source such as (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride or

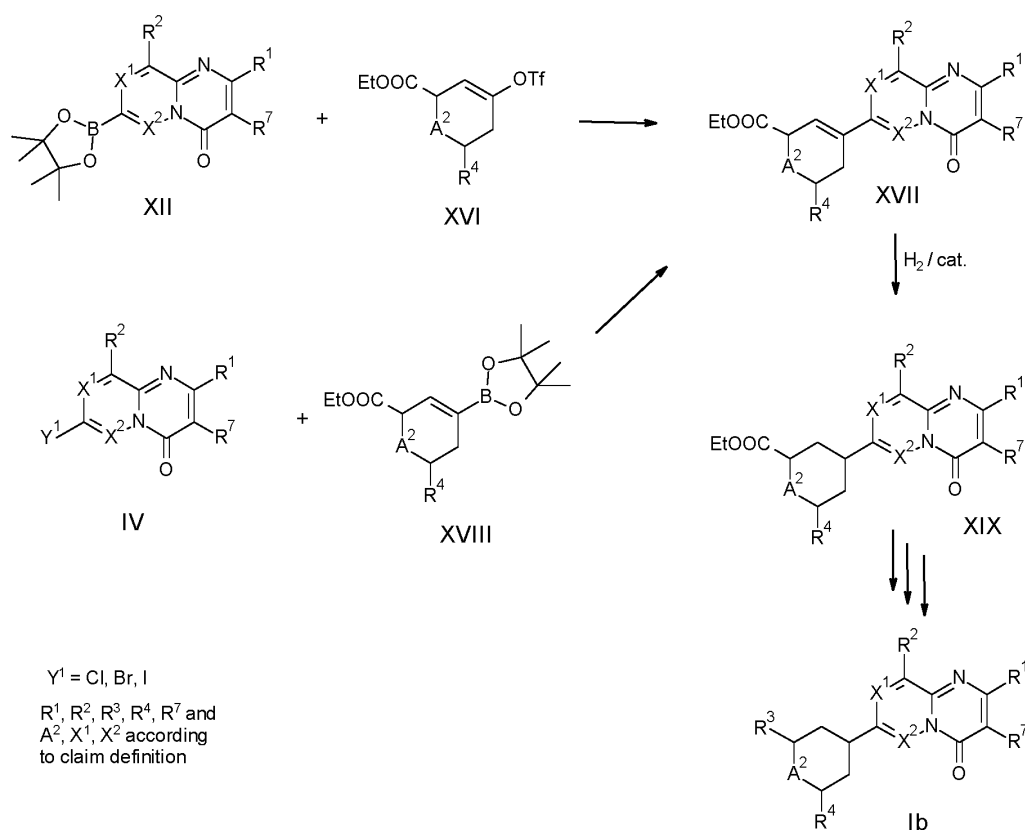
tetrakis(triphenylphosphine)palladium(0) and a base such as cesium carbonate or sodium carbonate) to form compound XII. This intermediate can be reacted with triflate XIII using a palladium catalyst and a base to form intermediate VIII, which can then be reduced by treatment with a suitable agent like hydrogen and a catalyst to form compound Ib.

5 Scheme 5



- Furthermore compounds of general formula IVa (R^2 is preferably cycloaliphatic) can be prepared as described in Scheme 5 by first reacting heterocyclic compound XIV with a carboxylic acid XV under oxydative coupling conditions (using for example ammonium persulfate in dimethylsulfoxide at temperatures of 0 °C to 50 °C, Minisci reaction) to form compound XIa. This intermediate can then react with ketoester X in presence of an acid like polyphosphoric acid or a Lewis acid such as bismuth trichloride at elevated temperatures to form compound IVa.

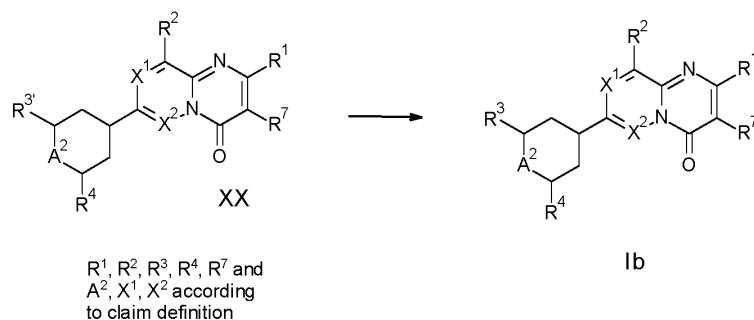
Scheme 6



Furthermore, compounds of general formula Ib can be prepared as described in Scheme 6.

Intermediate XII is first reacted with triflate XVI under palladium catalysed conditions (a palladium source such as (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride or

- 5 tetrakis(triphenylphosphine)palladium(0) and a base such as cesium carbonate or sodium carbonate) to form compound XVII. Likewise, intermediate IV can be reacted with boronic ester derivative XVIII under palladium catalysed conditions (a palladium source such as (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride or tetrakis(triphenylphosphine)-palladium(0) and a base such as cesium carbonate or sodium carbonate) to form as well
- 10 compound XVII. In the next step this intermediate is reduced by treatment with a suitable agent like hydrogen and a catalyst to form compound XIX. The ester functionality can then be transformed into various heterocyclic residues R³ by multi-step reactions known to people skilled in the art and published in various literature reviews such as J. Chem. Rev., 2022, 4(3), 255-271.



Furthermore, compounds of general formula Ib can be prepared as described in Scheme 7 by late stage modification of compound XX. Such transformations of residue R3' to residue R3 include removal of a protecting group, halogen-carbon-exchange reactions (such as bromine to methyl) or alkylation reactions (for instance on NH-pyrazoles or NH-pyridones) and can be performed according to known conditions for related compounds published in the literature.

In one aspect, the present invention provides a process of manufacturing a compound of formula (I) described herein, or a pharmaceutically acceptable salt thereof, wherein the process is as described in any one of schemes 1 to 7.

- 10 In one aspect, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, when manufactured according to any one of the processes described herein.

TREM2 Agonistic Activity

- 15 Compounds of the present invention are TREM2 agonists. Thus, in one aspect, the present invention provides the use of compounds of formula (I) as described herein for restoring the function of human TREM2 in a subject in need thereof.

In a further aspect, the present invention provides compounds of formula (I) as described herein for use in a method of restoring the function of human TREM2 in a subject in need thereof.

- 20 In a further aspect, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for restoring the function of human TREM2 in a subject in need thereof.

In a further aspect, the present invention provides a method for restoring the function of human TREM2 in a subject in need thereof, which method comprises administering an effective amount of a compound of formula (I) as described herein to the subject.

TREM2 agonist potency of the compounds of formula (I) according to the invention was measured using a HEK cell line expressing human TREM2 and DAP12. Upon binding of small molecule ligands to the TREM2 receptor, Syk kinase is recruited and activated by DAP12. The resulting increased levels of phosphorylated Syk were measured in lysed cells with a commercial
5 AlphaLisa reagent kit.

To perform the assay, frozen HEK293-TREM2/DAP12 cells were thawed, adjusted and plated by using Certus at 20,000 cells per well in a 384 well plate, in 10 μ L of DMEM media without Phenolred and supplemented with 5% FBS.

Compounds in dose response (1:3) were diluted in DMSO (highest concentration 10mM) and
10 added to the cells from a Low Dead Volume plate using the ECHO (0-20 μ M), diluting 500x (20 nL in 10 μ L cell suspension; highest concentration 20 μ M, DMSO concentration 0.2% in all wells). Neutral (DMSO) and stimulator (1 μ M tool compound) controls were also added.

Cells were incubated for 30 minutes at 37°C, 5% CO₂ and 95% humidity. After compound addition and incubation, 2.5 μ L of lysis buffer was added by using the Certus. After a quick spin,
15 plates were shaken for 30 minutes at 450 RPM, at room temperature and in the dark. After complete lysis, AlphaLisa reagents were added by Certus to the lysate, and fluorescence intensity was measured using a Pherastar plate reader (Excitation: 680nm/Emission: 615nm). EC₅₀ values were calculated by using Genedata Screener, normalized to DMSO and 100% activity to the tool compound.

20 TREM2 agonistic potencies of the compounds of formula (I) according to the invention as measured in the assay described above are presented in table 1. TREM2 agonistic potencies of reference compounds as measured in the assay described above are presented in table 2.

Table 1

Ex.	hTREM2 EC ₅₀ (μ M)
1	0.327
2	1.01
3	0.078

Ex.	hTREM2 EC ₅₀ (μ M)
4	0.086
5	1.27
6	0.729

Ex.	hTREM2 EC ₅₀ (μM)
7	2.33
8	0.042
9	0.193
10	0.570
11	0.218
12	0.074
13	0.639
14	2.29
15	0.355
16	0.489
17	1.17
18	0.339
19	0.128
20	0.297
21	0.712
22	0.024
23	0.117
24	0.680
25	2.06
26	0.100
27	0.141

Ex.	hTREM2 EC ₅₀ (μM)
28	3.25
29	0.617
30	0.228
31	0.073
32	0.095
33	0.045
34	0.046
35	0.392
36	0.452
37	0.536
38	0.172
39	0.608
40	0.144
41	0.134
42	1.53
43	1.63
44	0.264
45	0.092
46	0.432
47	1.08
48	0.885

Ex.	hTREM2 EC ₅₀ (μM)
49	0.801
50	1.370
51	0.121
52	2.33
53	3.67
54	3.40
55	3.175
56	4.700
57	1.640
58	0.229
59	0.043
60	0.673
61	0.211
62	0.755
63	0.947
64	0.367
65	4.88
66	0.586
67	0.027
68	0.979
69	0.027

Ex.	hTREM2 EC ₅₀ (μM)
70	0.033
71	1.410
72	0.194
73	2.42
74	0.114
75	0.057
76	0.517
77	0.810
78	0.446
79	0.602
80	0.024
81	0.740
82	0.149
83	3.87
84	0.020
85	0.356
86	0.016
87	0.022
88	0.094
89	0.070
90	0.436

Ex.	hTREM2 EC ₅₀ (μM)
91	0.030
92	0.015
93	0.260
94	0.004
95	0.071
96	1.160
97	0.893
98	0.777
99	0.086
100	0.598
101	0.171
102	0.007
103	0.050
104	1.605
105	1.863
106	0.006
107	0.028
108	4.253
109	1.950
110	0.011
111	4.624

Ex.	hTREM2 EC ₅₀ (μM)
112	0.012
113	0.105
114	0.074
115	0.005
116	0.054
117	0.010
118	0.021
119	0.165
120	0.037
121	0.024
122	0.565
123	0.145
124	0.154
125	0.029
126	0.013
127	0.214
128	0.109
129	0.003
130	0.034
131	0.003
132	0.044

Ex.	hTREM2 EC ₅₀ (μM)
133	0.006
134	0.131
135	0.021
136	0.005
137	0.111
138	0.003
139	0.129
140	0.236
141	0.302
142	0.022
143	0.047
144	0.004
145	0.019
146	0.145
147	0.020
148	0.010
149	0.032
150	0.008
151	0.051
152	0.010
153	0.083

Ex.	hTREM2 EC ₅₀ (μM)
154	0.115
155	0.027
156	0.004
157	0.072
158	0.012
159	0.103
160	0.010
161	0.013
162	0.063
163	0.005
164	0.006
165	1.272
166	0.009
167	0.094
168	0.063
169	0.039
170	0.131
171	1.372
172	0.043
173	0.065
174	0.040

Ex.	hTREM2 EC ₅₀ (μM)
175	0.024
176	0.003
177	0.150
178	0.081
179	0.013
180	0.063
181	0.142
182	0.037
183	0.006
184	0.014
185	0.068
186	0.011
187	0.002
188	1.911
189	0.009
190	0.003
191	0.006
192	0.002
193	0.004
194	0.032
195	0.017

Ex.	hTREM2 EC ₅₀ (μM)
196	0.003
197	0.283
198	0.171
199	0.005
200	0.388
201	0.450
202	0.095
203	0.077
204	0.006
205	0.123
206	0.204
207	0.286
208	0.093
209	5.500
210	0.025
211	0.045
212	0.215
213	0.027
214	0.381
215	0.016
216	2.617

Ex.	hTREM2 EC ₅₀ (μM)
217	0.180
218	0.048
219	0.228
220	0.046
221	0.126
222	0.047
223	0.078
224	0.371
225	0.231
226	0.013
227	0.003
228	0.069
229	0.016
230	0.011
231	0.006
232	0.004
233	0.006
234	0.008
235	0.008
236	0.823
237	0.007

Ex.	hTREM2 EC ₅₀ (μM)
238	0.005
239	0.022
240	0.013
241	0.002
242	1.974
243	0.005
244	0.038
245	0.006
246	0.020
247	0.014
248	0.010
249	0.007
250	0.078
251	0.005
252	0.007
253	0.008
254	0.007
255	0.008
256	0.003
257	0.005
258	0.015

Ex.	hTREM2 EC ₅₀ (μM)
259	0.004
260	0.018
261	0.005
262	0.042
263	0.008
264	0.011
265	0.022
266	0.004
267	0.005
268	0.008
269	0.010
270	0.092
271	0.195
272	0.012
273	0.094

Ex.	hTREM2 EC ₅₀ (μM)
274	N.a.
275	0.044
276	0.002
277	0.224
278	0.042
279	0.003
280	0.874
281	N.a.
282	0.219
283	0.007
284	0.284
285	0.005
286	0.018
287	0.002

Using the Compounds of the Invention

In one aspect, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described herein for use as a therapeutically active substance.

- 5 In a further aspect, the present invention provides a method of treating or preventing a condition associated with a loss of function of human TREM2 in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In a further aspect, the present invention provides a compound of formula (I) described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein, for use in a method of treating or preventing a condition associated with a loss of function of human TREM2 in a subject in need thereof.

- 5 In a further aspect, the present invention provides the use of a compound of formula (I) described herein, or of a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein, in a method of treating or preventing a condition associated with a loss of function of human TREM2 in a subject in need thereof.

- 10 In a further aspect, the present invention provides the use of a compound of formula (I) described herein, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in a method of treating or preventing a condition associated with a loss of function of human TREM2 in a subject in need thereof.

- In one embodiment, said condition associated with a loss of function of human TREM2 is selected from Parkinson's disease, rheumatoid arthritis, Alzheimer's disease, amyotrophic lateral sclerosis, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, and stroke.
- 15

In a preferred embodiment, said condition associated with a loss of function of human TREM2 is Parkinson's disease.

- In a preferred embodiment, said condition associated with a loss of function of human TREM2 is rheumatoid arthritis.
- 20

In a preferred embodiment, said condition associated with a loss of function of human TREM2 is Alzheimer's disease.

In a preferred embodiment, said condition associated with a loss of function of human TREM2 is amyotrophic lateral sclerosis.

- 25 In a preferred embodiment, said condition associated with a loss of function of human TREM2 is Nasu-Hakola disease.

In a preferred embodiment, said condition associated with a loss of function of human TREM2 is frontotemporal dementia.

In a preferred embodiment, said condition associated with a loss of function of human TREM2 is multiple sclerosis.

In a preferred embodiment, said condition associated with a loss of function of human TREM2 is prion disease.

- 5 In a preferred embodiment, said condition associated with a loss of function of human TREM2 is stroke.

Pharmaceutical Compositions and Administration

In one aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) as described herein and a therapeutically inert carrier.

- 10 In one embodiment, there is provided a pharmaceutical composition according to Example 288 or 289.

The compounds of formula (I) and their pharmaceutically acceptable salts can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées,
15 hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I) and their pharmaceutically acceptable salts can be processed with
20 pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-
25 solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants,
5 salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about
10 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should be appropriate. It will, however, be clear that the upper limit given herein can be exceeded when this is shown to be indicated.

Examples

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

In case the preparative examples are obtained as a mixture of enantiomers, the pure enantiomers can be separated by methods described herein or by methods known to the man skilled in the art, such as e.g., chiral chromatography (e.g., chiral SFC) or crystallization.

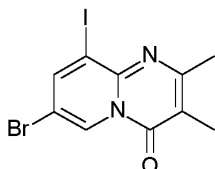
The compounds of formula I can contain several asymmetric centers and can be present in the
20 form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers or mixtures of diastereoisomers. According to the Cahn-Ingold-Prelog Convention the asymmetric carbon atom can be of the "R" or "S" configuration. For the compounds described in the patent the absolute stereochemistry was arbitrarily assigned.

All reaction examples and intermediates were prepared under an argon atmosphere if not
25 specified otherwise.

The compounds disclosed and described herein have been named using the IUPAC naming function of Biovia Draw 22.1. If there is a discrepancy between a depicted structure and a name given to that structure, then the depicted structure controls.

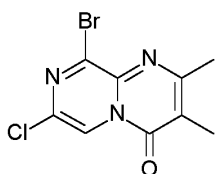
The following intermediates were prepared according to the procedures provided herein, are commercially available or can be prepared according to literature procedures.

Intermediate A1: 7-bromo-9-iodo-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one



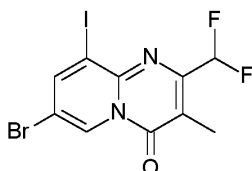
- 5 A mixture of 5-bromo-3-iodo-pyridin-2-amine (CAS 381233-96-1, 2.0 g, 6.69 mmol), ethyl 2-methylacetoacetate (CAS 609-14-3, 965 mg, 0.97 ml, 6.69 mmol) and polyphosphoric acid (1.0 g, 6.69 mmol) was stirred for 90 min at 120 °C. The reaction mixture was taken up with water, basified with saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The residue
- 10 was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-100%) to give the title compound (1.07 g, 40% yield) as off-white solid, MS m/z: 378.8 [M+H]⁺, ESI pos.

Intermediate A2: 9-bromo-7-chloro-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



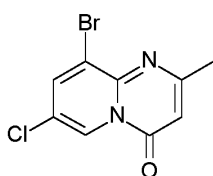
- The title compound was prepared in analogy to Intermediate A1 from 3-bromo-5-chloro-pyrazin-2-amine (CAS 76537-18-3) instead of 5-bromo-3-iodo-pyridin-2-amine. Yellow solid, MS m/z:
- 15 290.0 [M+H]⁺, ESI pos.

Intermediate A3: 7-bromo-2-(difluoromethyl)-9-iodo-3-methyl-pyrido[1,2-a]pyrimidin-4-one



Polyphosphoric acid (31.8 g, 132 mmol) was added to a mixture of ethyl 4,4-difluoro-2-methyl-3-oxo-butanoate (5.3 g, 26.5 mmol) and 2-amino-5-bromo-3-iodopyridine (3.17 g, 10.6 mmol, 0.4 eq). After stirring at 120 °C for 1.5 h, the mixture was cooled to room temperature, quenched with saturated NaHCO₃ aqueous solution (300 ml), and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo. The crude material was purified by flash chromatography (silica gel, acetonitrile in chloroform from 0-50%,) to obtain 7-bromo-2-(difluoromethyl)-9-iodo-3-methyl-pyrido[1,2-a]pyrimidin-4-one (0.34 g, 3% yield). MS m/z: 414.8 [M+H]⁺, ESI pos.

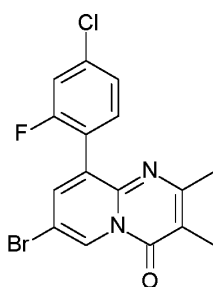
Intermediate A4: 9-bromo-7-chloro-2-methyl-pyrido[1,2-a]pyrimidin-4-one



10

The title compound was prepared in analogy to Intermediate A1 using 3-bromo-5-chloro-pyridin-2-amine instead of 5-bromo-3-iodo-pyridin-2-amine and 3-ketobutyric acid ethyl ester (CAS 141-97-9) instead of ethyl 2-methylacetoacetate. Yellow solid, MS m/z: 273.0 [M+H]⁺, ESI pos.

15 **Intermediate B1:** 7-bromo-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one

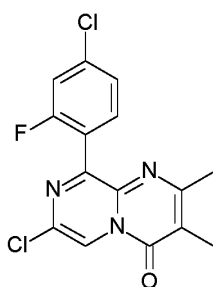


To a solution of 7-bromo-9-iodo-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (Intermediate A1, 260 mg, 0.68 mmol) in dioxane (7 ml) were added (4-chloro-2-fluoro-phenyl)boronic acid (179 mg, 1.03 mmol) and 2 M aqueous cesium carbonate solution (1.03 ml, 2.06 mmol) at room temperature. The mixture was degassed with argon before 1,1'-bis(diphenylphosphino)ferrocene-

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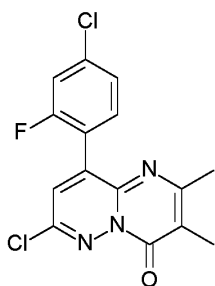
palladium(II)dichloride dichloromethane complex (56 mg, 0.069 mmol, 0.100 eq) was added. The mixture was stirred over night at 60 °C, then diluted with water and extracted two times with ethyl acetate. The organic layers were dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (on silica, ethyl acetate in heptane 0-50%) to obtain the title compound (221 mg, 81% yield) as white solid, MS m/z: 383.0 [M+H]⁺, ESI pos.

Intermediate B2: 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

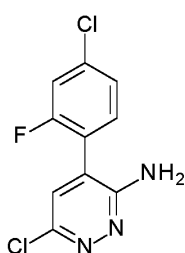


To a solution of 9-bromo-7-chloro-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (Intermediate A2, 290 mg, 1.01 mmol) in 1,4-dioxane (6 ml) was added (4-chloro-2-fluoro-phenyl)boronic acid (263 mg, 1.51 mmol) and aqueous cesium carbonate solution (1.51 ml, 3.02 mmol) at room temperature. The mixture was degassed with argon before 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (82 mg, 0.10 mmol, 0.10 eq) was added. The mixture was stirred for 3 h at 60 °C, then diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-100%) and the obtained material was triturated with methyl tert-butyl ether to obtain the title compound (177 mg, 49% yield) as yellow solid, MS m/z: 338.0 [M+H]⁺, ESI pos.

Intermediate B3: 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

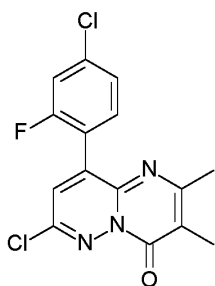


Step 1: 6-chloro-4-(4-chloro-2-fluoro-phenyl)pyridazin-3-amine



To a solution of 4-bromo-6-chloro-pyridazin-3-amine (CAS 446273-59-2, 1.00 g, 4.8 mmol) in
5 1,4-dioxane (20 ml) were added (4-chloro-2-fluoro-phenyl)boronic acid (836 mg, 4.8 mmol) and
cesium carbonate (4.69 g, 14.4 mmol). The mixture was degased with argon, 1,1'-
bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane (392 mg, 0.48 mmol,
0.10 eq) was added and the reaction mixture was stirred for 2 h at room temperature. The
mixture was diluted with water and extracted two times with ethyl acetate. The combined
10 organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to
dryness. The residue was purified by flash chromatography (silica gel, dichloromethane /
methanol 0-10%) to yield 6-chloro-4-(4-chloro-2-fluoro-phenyl)pyridazin-3-amine as dark
brown solid (852 mg, 69% yield), MS m/z: 258.0 [M+H]⁺, ESI pos.

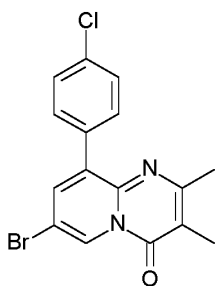
Step 2: 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



To a suspension of 6-chloro-4-(4-chloro-2-fluoro-phenyl)pyridazin-3-amine (100 mg, 0.388 mmol) in ethyl 2-methylacetoacetate (559 mg, 564 μ l, 3.87 mmol) was added bismuth trichloride (12 mg, 0.038 μ mol, 0.10 eq) at room temperature and the mixture was stirred for 16 h at 120 °C.

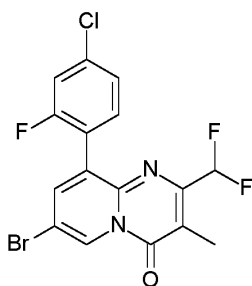
- 5 The reaction mixture was diluted with saturated NaHCO_3 -solution and extracted two times with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-50%) to yield the title compound as light yellow solid (62 mg, 43% yield), MS m/z : 338.1 $[\text{M}+\text{H}]^+$, ESI pos.

- 10 **Intermediate B4:** 7-bromo-9-(4-chlorophenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one



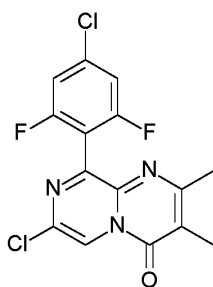
The title compound was prepared in analogy to Intermediate B1 using (4-chlorophenyl)boronic acid instead of (4-chloro-2-fluoro-phenyl)boronic acid. White solid, MS m/z : 365.1 $[\text{M}+\text{H}]^+$, ESI pos.

- 15 **Intermediate B5:** 7-bromo-9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-pyrido[1,2-a]pyrimidin-4-one



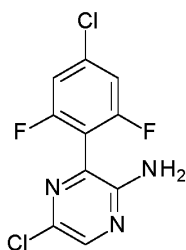
To a stirred solution of 4-chloro-2-fluorophenylboronic acid (75 mg, 0.43 mmol) and 7-bromo-2-(difluoromethyl)-9-iodo-3-methyl-pyrido[1,2-a]pyrimidin-4-one (Intermediate A3, 320 mg, 0.62 mmol) in a mixture of 1,4-dioxane (17 ml) and water (1.7 ml) was added cesium carbonate (603 mg, 1.85 mmol). The mixture was degassed, filled with argon, and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (50 mg, 0.06 mmol, 0.1 eq) was added. After stirring at 60 °C for 18 h, the mixture was evaporated in vacuo. The residue was diluted with water (100 ml) and extracted with ethyl acetate (2 x 100 ml), then the combined organic layers were filtered through anhydrous sodium sulfate and evaporated in vacuo. The residue was purified by preparative HPLC (column XBridge 19 x 100 mm, 60% water-acetonitrile, 4 ml/min acetonitrile) to obtain the title compound (103 mg, 40% yield) as a light brown solid. MS m/z: 417.0 [M+H]⁺, ESI pos.

Intermediate B6: 7-chloro-9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



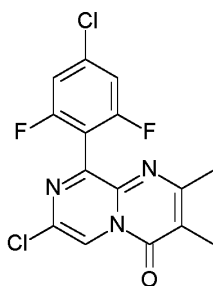
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Step 1: 5-chloro-3-(4-chloro-2,6-difluoro-phenyl)pyrazin-2-amine



In a glove box, to a solution of (3-bromo-5-chloro-pyrazin-2-yl)amine (500 mg, 2.4 mmol) in toluene (7.5 ml) was added (4-chloro-2,6-difluoro-phenyl)boronic acid (600 mg, 3.12 mmol) and diisopropyl ethylamine (930 mg, 7.2 mmol). The mixture was degassed with argon before
 5 chloro(crotyl)(tri-tert-butylphosphine)palladium(II) (CAS 1334497-00-5, 48 mg, 0.12 mmol) was added and the mixture was stirred at 80 °C for 2 h. The reaction mixture was diluted with water and extracted three times with ethyl acetate followed by five times with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The crude material was purified by flash chromatography (C18, acetonitrile in water 10-100%) to yield 5-
 10 chloro-3-(4-chloro-2,6-difluoro-phenyl)pyrazin-2-amine as yellow solid (193 mg, 29% yield). MS m/z: 276.0 [M+H]⁺, ESI pos.

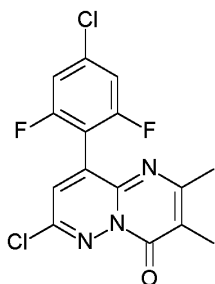
Step 2: 7-chloro-9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



5-Chloro-3-(4-chloro-2,6-difluoro-phenyl)pyrazin-2-amine (170 mg, 0.616 mmol), ethyl 2-
 15 methylacetoacetate (888 mg, 897 µl, 6.16 mmol) and polyphosphoric acids (85 mg) were mixed at room temperature and the mixture was stirred for 6 h at 120 °C. The reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The crude material was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-50%). The obtained material was
 20 suspended with tert-butyl methyl ether and stirred for 5 min before filtering it off. The solids

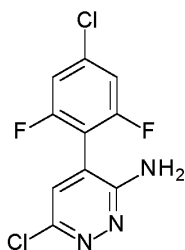
were washed with tert-butyl methyl ether, then dried in vacuum to obtain the title compound (156 mg, 71% yield) as yellow solid. MS m/z: 356.1 [M+H]⁺, ESI pos.

Intermediate B7: 7-chloro-9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



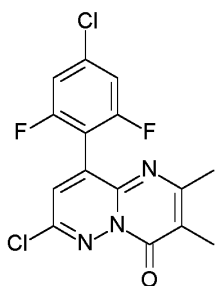
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Step 1: 6-chloro-4-(4-chloro-2,6-difluoro-phenyl)pyridazin-3-amine



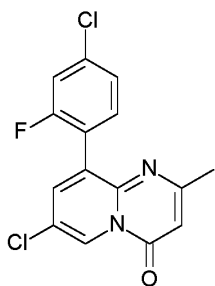
To a solution of (4-bromo-6-chloro-pyridazin-3-yl)amine (491 mg, 2.36 mmol) in t-amyl alcohol (7.5 ml) was added (4-chloro-2,6-difluoro-phenyl)boronic acid (680 mg, 3.53 mmol) and diisopropyl ethylamine (913 mg, 7.07 mmol). The mixture was degassed with argon before PdCl₂(amphos) (CAS 887919-35-9, 250 mg, 0.15 mmol) was added and the mixture was stirred at 50 °C for 2.5 h. The reaction mixture was diluted with water and extracted three times with ethyl acetate followed by five times with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The crude material was purified by flash chromatography (C18, acetonitrile in water 10-70%) to yield 6-chloro-4-(4-chloro-2,6-difluoro-phenyl)pyridazin-3-amine as light brown solid (214 mg, 33% yield). MS m/z: 276.1 [M+H]⁺, ESI pos.

Step 2: 7-chloro-9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



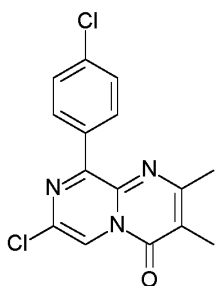
To a mixture of 6-chloro-4-(4-chloro-2,6-difluoro-phenyl)pyridazin-3-amine (210 mg, 0.76 mmol) and ethyl 2-methylacetoacetate (1.1 g, 1.11 ml, 7.61 mmol) was added bismuth trichloride (24 mg, 0.076 mmol, 0.10 eq) at room temperature and the mixture was stirred over
 5 night at 120 °C. The reaction mixture was diluted with saturated NaHCO₃ solution and extracted two times with ethyl acetate. The organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude material was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-40%) to obtain the title compound (152 mg, 55% yield) as brown solid, MS m/z: 356.1 [M+H]⁺, ESI pos.

10 **Intermediate B8:** 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2-methyl-pyrido[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Intermediate B1 using Intermediate A4 instead of Intermediate A1. White solid, MS m/z: 323.1 [M+H]⁺, ESI pos.

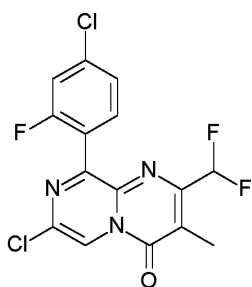
Intermediate B9: 7-chloro-9-(4-chlorophenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



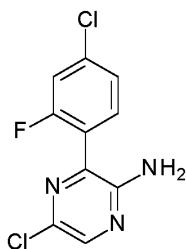
The title compound was prepared in analogy to Intermediate B3 using 3-bromo-5-chloro-pyrazin-2-amine instead of 4-bromo-6-chloro-pyridazin-3-amine and (4-chlorophenyl)boronic acid instead of (4-chloro-2-fluoro-phenyl)boronic acid instep a). Yellow solid, MS m/z: 320.0

5 [M+H]⁺, ESI pos.

Intermediate B10: 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one



Step 1: 5-chloro-3-(4-chloro-2-fluoro-phenyl)pyrazin-2-amine

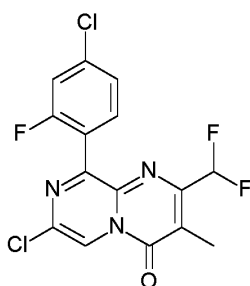


10

To a solution of (3-bromo-5-chloro-pyrazin-2-yl)amine (2.5 g, 12.0 mmol) in 1,4-dioxane (50 ml) (4-chloro-2-fluoro-phenyl)boronic acid (2.51 g, 14.4 mmol) and 3 M cesium carbonate solution (12 ml, 36 mmol) were added at room temperature. The mixture was degassed with argon, 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex

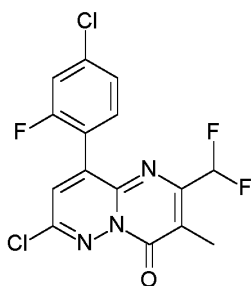
(980 mg, 1.2 mmol, 0.10 eq) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to dryness. The crude material was triturated with tert-butyl methyl ether to yield 5-chloro-3-(4-chloro-2-fluoro-phenyl)pyrazin-2-amine as light brown solid (2.2 g, 64% yield, 90% purity), MS m/z: 258.1 [M+H]⁺, ESI pos.

Step 2: 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one



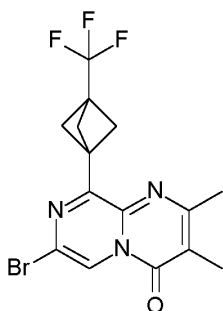
10 In a vial, 4,4-difluoro-3-keto-2-methyl-butyric acid ethyl ester (CAS 425394-84-9, 3.49 g, 19.4 mmol), polyphosphoric acid (250 mg) 5-chloro-3-(4-chloro-2-fluoro-phenyl)pyrazin-2-amine (500 mg, 1.94 mmol) were mixed. The vial was sealed and the reaction was heated overnight to 140 °C. Another portion of 4,4-difluoro-3-keto-2-methyl-butyric acid ethyl ester (3.49 g, 19.37 mmol) and polyphosphoric acid (250 mg) were added. The reaction was sealed and stirred for
15 another 6 h at 140 °C. The reaction mixture was cooled to room temperature, diluted with water and ethyl acetate. The organic layers were washed with water and brine, dried over Na₂SO₄ and the volatiles evaporated. The residue was purified by flash column chromatography (silica, 0-50 % ethyl acetate in heptane) to afford the title compound (197 mg, 26% yield) as yellow solid. MS m/z: 374.2 [M+H]⁺, ESI pos. ¹H NMR (300 MHz, DMSO-d₆): δ = 8.86 (s, 1H), 7.77 - 7.70 (m, 1H), 7.68 (dd, J = 2.0, 10.1 Hz, 1H), 7.51 (td, J = 1.0, 8.3 Hz, 1H), 7.30 - 6.82 (m, 1H), 2.31 (t, J = 1.9 Hz, 3H).

Intermediate B11: 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one

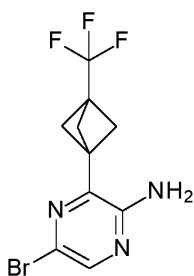


The title compound was prepared in analogy to Intermediate B3 using 4,4-difluoro-3-keto-2-methyl-butiric acid ethyl ester instead of ethyl 2-methylacetoacetate. Light brown solid, MS m/z : 374.0 $[M+H]^+$, ESI pos.

- 5 **Intermediate B12**: 7-bromo-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]-pyrazino[1,2-a]pyrimidin-4-one



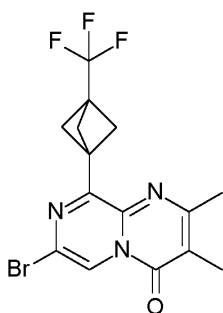
Step 1: 5-bromo-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazin-2-amine



- 10 To a solution of (5-bromopyrazin-2-yl)amine (300 mg, 1.72 mmol) in dimethylsulfoxide / water (600/1), 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (3.11 g, 17.2 mmol) was added. The reaction mixture was degassed while bubbling argon through it. A freshly prepared solution of ammonium persulfate (2.36 g, 10.3 mmol) in purged dimethylsulfoxide / water

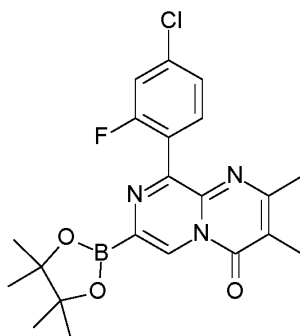
(600/1) was added under argon and the mixture was stirred at 40 °C for 20 h. The reaction mixture was quenched with a saturated solution of NaHCO₃ and extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by column chromatography (silica gel, 0-35% ethyl acetate in heptane) to give 5-bromo-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazin-2-amine (190 mg, 31% yield) as yellow solid, MS m/z: 308.2 / 310.2 [M+H]⁺, ESI pos.

Step 2: 7-bromo-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one



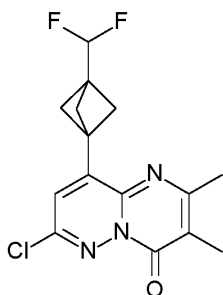
To a mixture of 5-bromo-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazin-2-amine (170 mg, 0.55 mmol) and ethyl 2-methylacetoacetate (796 mg, 805 μ l, 5.52 mmol) was added bismuth trichloride (17 mg, 0.055 mmol, 0.10 eq) at room temperature and the mixture was stirred at 100 °C for 18 h. The reaction mixture was diluted with saturated NaHCO₃ solution and extracted two times with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-10%) to afford the title compound (111 mg, 52% yield) as light yellow solid, MS m/z: 388.2 / 390.2 [M+H]⁺, ESI pos.

Intermediate B13: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one

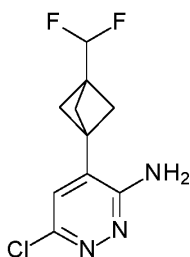


To a solution of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (Intermediate B2, 1.5 g, 4.44 mmol) in 1,4-dioxane (27 ml) were added under argon bis(pinacolato)diboron (1.35 g, 5.32 mmol), potassium acetate (1.31 g, 13.3 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (367 mg, 0.445 mmol, 0.10 eq). The reaction mixture was heated to 80 °C and stirred for 20 h. After cooling to room temperature the reaction mixture was filtered over Celite and washed with ethyl acetate. The filtrate was concentrated and purified by flash chromatography (silica gel, 0% to 100% ethyl acetate in heptane) to afford 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one (1.8 g, 85% yield) as orange oil.

Intermediate B14: 7-chloro-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

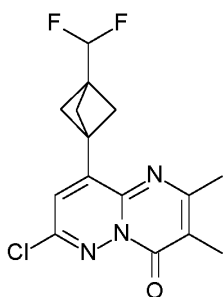


Step 1: 6-chloro-4-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyridazin-3-amine



To a solution of 3-amino-6-chloropyridazine (600 mg, 4.63 mmol) in 9 dimethylsulfoxide / water (600/1; 9 ml) was added 3-(difluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid (7.5 g, 46.3 mmol). The reaction mixture was degassed while bubbling nitrogen through it. A freshly
 5 prepared solution of ammonium persulfate (6.34 g, 27.79 mmol) in purged dimethylsulfoxide / water (600/1) was added under nitrogen and the mixture was stirred at 40 °C for 20 h. The reaction mixture was quenched with a saturated solution of NaHCO₃, the pH was adjusted to 8-9 and extracted with ethyl acetate (200 ml x 3). The combined organic layers were washed with
 10 brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was first purified by preparative HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 µm, mobile phase: water + 0.25% formic acid / acetonitrile 10-15%, flow rate 25 ml/min) to give a crude product which was purified further by column chromatography (silica gel, petroleum ether / ethyl acetate = 100 : 1 to 1 : 1) to afford 6-chloro-4-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyridazin-3-amine (190 mg, 17% yield) as light yellow solid, MS m/z: 246.1 [M+H]⁺, ESI pos.

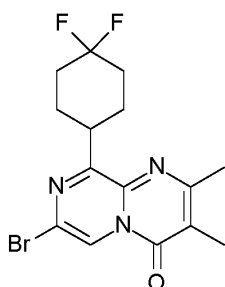
15 Step 2: 7-chloro-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



To a solution of 6-chloro-4-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyridazin-3-amine (190 mg, 0.77 mmol) in toluene (5 ml) was added ethyl 2-methylacetoacetate (556 mg, 3.87
 20 mmol) and p-toluene sulfonic acid (27 mg, 0.15 mmol) and the mixture was stirred at 110 °C for

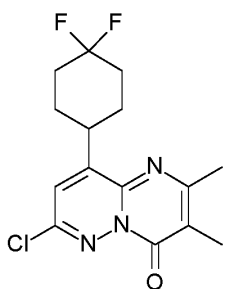
- 16 h under nitrogen atmosphere. The reaction mixture was poured into water (150 ml), neutralized with saturated sodium bicarbonate aqueous solution to pH=8, then extracted with ethyl acetate (100 ml x 3). The combined organic layers were washed with brine (100 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by
- 5 chromatography (silica, petroleum ether / ethyl acetate = 1/1) to give the title compound (200 mg, 79% yield) as light yellow solid, MS m/z: 326.1 [M+H]⁺, ESI pos.

Intermediate B15: 7-bromo-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



- 10 The title compound was prepared in analogy to Intermediate B12 using 4,4-difluorocyclohexane carboxylic acid instead of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid in step 1). Light yellow solid, MS m/z: 372.1 / 374.1 [M+H]⁺, ESI pos.

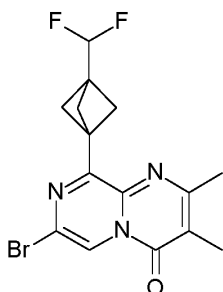
Intermediate B16: 7-chloro-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



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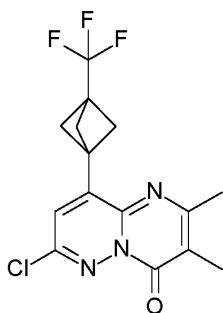
The title compound was prepared in analogy to Intermediate B14 using 4,4-difluorocyclohexane carboxylic acid instead of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid in step 1). Yellow solid, MS m/z: 328.1 [M+H]⁺, ESI pos.

Intermediate B17: 7-bromo-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



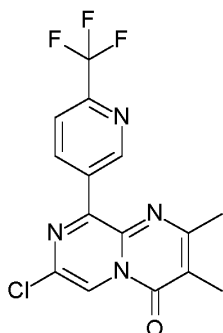
The title compound was prepared in analogy to Intermediate B12 using 3-(difluoromethyl)-
5 bicyclo[1.1.1]pentane-1-carboxylic acid instead of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid in step 1). Light yellow solid, MS m/z: 370.1 [M+H]⁺, ESI pos.

Intermediate B18: 7-chloro-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one



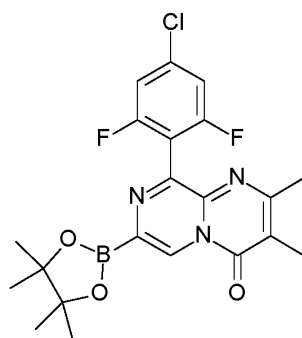
10 The title compound was prepared in analogy to Intermediate B14 using 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid instead 3-(difluoromethyl)-bicyclo[1.1.1]pentane-1-carboxylic acid of in step 1). Light yellow solid, MS m/z: 344.1 [M+H]⁺, ESI pos.

Intermediate B19: 7-chloro-2,3-dimethyl-9-[6-(trifluoromethyl)-3-pyridyl]pyrazino[1,2-
15 a]pyrimidin-4-one



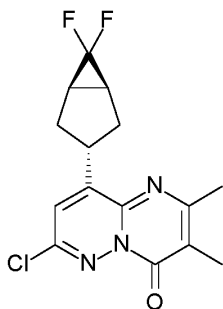
The title compound was prepared in analogy to Intermediate B2 using [6-(trifluoromethyl)-3-pyridyl]boronic acid instead of (2,4-difluorophenyl)boronic acid in step 1. Yellow solid, MS m/z : 355.1 $[M+H]^+$, ESI pos.

- 5 **Intermediate B20**: 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Intermediate B13 using Intermediate B6 instead of Intermediate B2. Orange oil, MS m/z : 366.0 $[M+H]^+$ (corresponds to boronic acid), ESI pos.

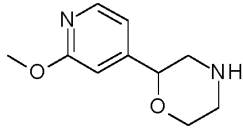
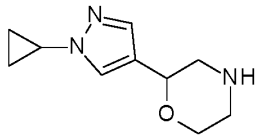
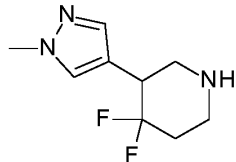
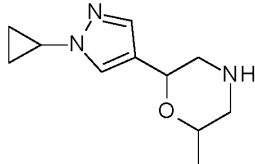
- 10 **Intermediate B21**: 7-chloro-2,3-dimethyl-9-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]pyrimido[1,2-b]pyridazin-4-one



The title compound was prepared in analogy to Intermediate B14 using 6,6-difluorobicyclo[3.1.0]hexane-3-carboxylic acid instead of 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylic acid in step 1). Yellow oil, MS m/z: 326.0

5 $[M+H]^+$, ESI pos.

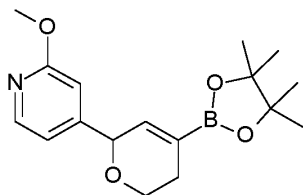
Intermediate	Name	Structure	Source
C1	2-(1-methylpyrazol-4-yl)morpholine		commercial, CAS 1375963- 52-2
C2	2-(2-methyl-4-pyridyl)morpholine		commercial, CAS 1211523- 01-1
C3	3-(1-methylpyrazol-4-yl)piperidine		commercial, CAS 1340528- 88-2

C4	2-(2-methoxy-4-pyridyl)morpholine		commercial, CAS 2091599-93-6
C5	2-(1-cyclopropylpyrazol-4-yl)morpholine		known, CAS 1780917-09-0
C6	4,4-difluoro-3-(1-methylpyrazol-4-yl)piperidine		known, CAS 2738350-76-8
C7	2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholine		known, CAS 2738496-25-6

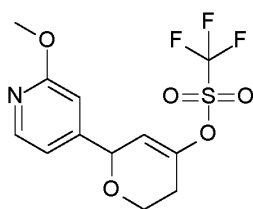
Chiral Separation of Intermediate C1:

2-(1-Methylpyrazol-4-yl)morpholine (Intermediate C1) was separated by chiral SFC (column AD-H, 5 μ m, 100 x 4.6 mm, 20-40% MeOH + 0,2% diethylamine) to yield (+)- 2-(1-methylpyrazol-4-yl)morpholine (+)-C1 as the first eluting enantiomer and (-)- 2-(1-methylpyrazol-4-yl)morpholine (-)-C1 as the second eluting enantiomer. (+)- 2-(1-methylpyrazol-4-yl)morpholine: yellow oil, $\alpha_D(589\text{nm})$ 20 °C = +13.36° (c = 0.1 g/l, MeOH).

Intermediate C8: 2-methoxy-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine

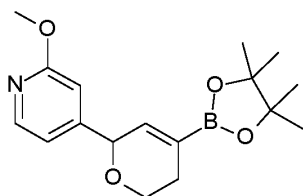


Step 1: [6-(2-methoxy-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



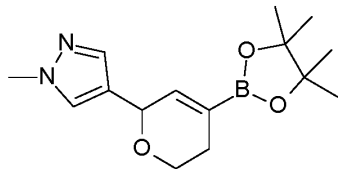
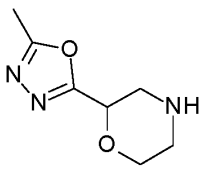
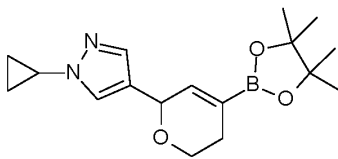
- To a solution of 2-methoxyisonicotinaldehyde (1.0 g, 7.29 mmol) in dichloromethane (10 ml)
- 5 was added at 3-buten-1-ol (767 mg, 0.833 ml, 10.94 mmol) under argon. Then the mixture was cooled to -10 °C and trifluoromethanesulfonic acid (3.28 g, 1.92 ml, 21.9 mmol) was added. After stirring for 30 min at -10 °C the mixture was warmed to room temperature and stirring was continued overnight. The reaction mixture was diluted with saturated NaHCO₃-solution and extracted two times with ethyl acetate. The combined organic layers were washed with water and
- 10 brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-100%) to afford [6-(2-methoxy-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (870 mg, 32% yield) as colorless oil, MS m/z: 340.1 [M+H]⁺, ESI pos.

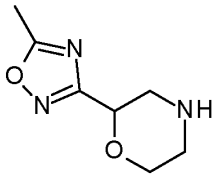
- Step 2: 2-methoxy-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine
- 15



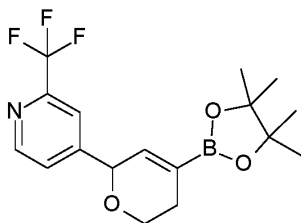
To a solution of [6-(2-methoxy-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (870 mg, 2.31 mmol) in 1,4-dioxane (15 ml) were added bis(pinacolato)diboron (1.17 g, 4.62

mmol), potassium acetate (906 mg, 9.23 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (189 mg, 0.231 mmol, 0.10 eq). The mixture was purged and backfilled with argon three times, then stirred at 90 °C for 2 h. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-80%) to afford 2-methoxy-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine (656 mg, 81% yield) as colorless oil, MS m/z: 318.3 [M+H]⁺, ESI pos.

Intermediate	Name	Structure	Source
C9	1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole		known, CAS 2738350-63-3
C10	2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholine		commercial, CAS 1509286-40-1
C11	1-cyclopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole		known, CAS 2738495-81-1

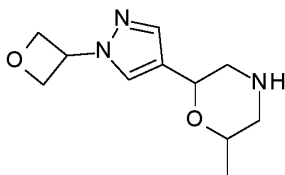
C12	2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholine		commercial, CAS 1444103- 32-5
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Intermediate C13: 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]-2-(trifluoromethyl)pyridine

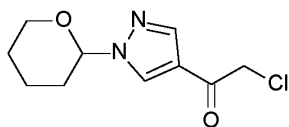


- 5 The title compound was prepared in analogy to Intermediate C8 from 2-(trifluoromethyl)-isonicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow oil, MS m/z: 356.3 [M+H]⁺, ESI pos.

Intermediate C14: 2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine



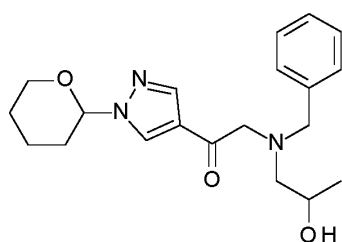
- 10 Step 1: 2-chloro-1-(1-tetrahydropyran-2-yl)pyrazol-4-yl)ethanone



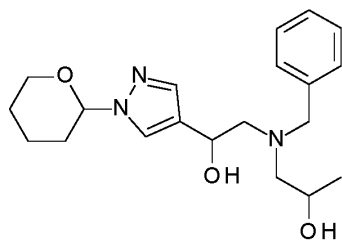
To a solution of 4-iodo-1-tetrahydropyran-2-yl-pyrazole (CAS 938066-17-2, 32.0 g, 115 mmol) in tetrahydrofuran (350 ml) was added isopropylmagnesium chloride lithium chloride complex

(1.3 M in tetrahydrofuran, 133 ml, 173 mmol) at -70 °C under nitrogen atmosphere and the mixture was stirred at -70 °C for 0.5 h. Then a solution of 2-chloro-N-methoxy-N-methylacetamide (CAS 67442-07-3, 19 g, 138 mmol) in tetrahydrofuran (100 ml) was added dropwise at -70 °C under nitrogen and stirred at 0 °C for 1.5 h. The reaction mixture was poured
5 into saturated aqueous ammonium chloride solution (500 ml) and the aqueous phase was extracted with ethyl acetate (300 ml x 3). The combined organic layers were washed with brine (300 ml x 3), dried with anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 100:1 to 2:1) to afford 2-chloro-1-(1-tetrahydropyran-2-ylpyrazol-4-yl)ethanone (25.0 g, 95% yield) as light yellow oil.
10 MS m/z: 145.0 [M+H]⁺, ESI pos.

Step 2: 2-[benzyl(2-hydroxypropyl)amino]-1-(1-tetrahydropyran-2-ylpyrazol-4-yl)ethanone

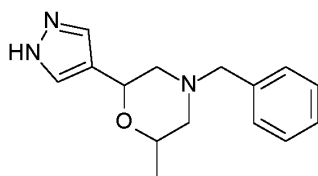


To a light yellow solution of 2-chloro-1-(1-tetrahydropyran-2-ylpyrazol-4-yl)ethanone (25.0 g, 109.32 mmol) in dimethylsulfoxide (250 ml) was added potassium carbonate (30.2 g, 219
15 mmol), potassium iodide (18.15 g, 109.3 mmol) and 1-(benzylamino)propan-2-ol (CAS 27159-32-6, 18.06 g, 109.32 mmol) and the mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into water (500 ml) and extracted with ethyl acetate (300 ml x 3). The combined organic layers were washed with brine (300 ml x 3), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative MPLC (column: Spherical C18, 20-45 μm, 100
20 Å; mobile phase: water + 0.1% formic acid / acetonitrile 10-15%, flow rate 200 ml/min). The eluent was adjusted the pH to 8 with ammonium hydroxide and extracted with ethyl acetate (500 ml x 3), the combined organic layers were washed with brine (500 ml), dried over Na₂SO₄ and concentrated in vacuo to give 2-[benzyl(2-hydroxypropyl)amino]-1-(1-tetrahydropyran-2-ylpyrazol-4-yl)ethanone (26.0 g, 66% yield) as light yellow oil. MS m/z: 358.2 [M+H]⁺, ESI pos.
25 Step 3: 1-[benzyl-[2-hydroxy-2-(1-tetrahydropyran-2-ylpyrazol-4-yl)ethyl]amino]propan-2-ol



To a solution of 2-[benzyl(2-hydroxypropyl)amino]-1-(1-tetrahydropyran-2-yl)pyrazol-4-yl)ethanone (26.0 g, 72.7 mmol) in methanol (260 ml) was added sodium borohydride (8.26 g, 218 mmol, multiple times in batches) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was slowly poured into aqueous saturated ammonium chloride solution (1000 ml) at 0-5 °C, stirred for 0.5 h and the aqueous layer was extracted with dichloromethane (300 ml x 3). The combined organic layers were washed with brine (300 ml), dried over Na₂SO₄, and concentrated in vacuo to give 1-[benzyl-[2-hydroxy-2-(1-tetrahydropyran-2-yl)pyrazol-4-yl]ethyl]amino]propan-2-ol (24.0 g, 92% yield) as light yellow oil. The product was used directly in the next step without further purification. MS m/z: 360.2 [M+H]⁺, ESI pos.

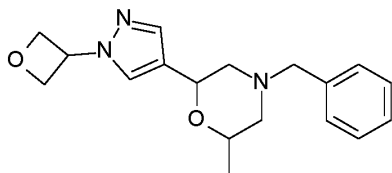
Step 4: 4-benzyl-2-methyl-6-(1H-pyrazol-4-yl)morpholine



To a solution of 1-[benzyl-[2-hydroxy-2-(1-tetrahydropyran-2-yl)pyrazol-4-yl]ethyl]amino]propan-2-ol (24.0 g, 66.8 mmol) in 1,4-dioxane (96 ml) at 20 °C was slowly added water (48 ml) and hydrochloric acid (37% in water, 48 ml, 576 mmol). The reaction mixture was stirred at 110 °C for 2 h, then cooled to room temperature and the pH was adjusted to 8 by aqueous saturated NaHCO₃ solution. The aqueous layer (1000 ml) was extracted with dichloromethane (300 ml x 3). The combined organic layers were washed with brine (500 ml x 3), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative MPLC (column: Spherical C18, 20-45 μm, 100 Å; mobile phase: water + 0.1% formic acid / acetonitrile 10-15%, flow rate 150 ml/min) to give a product 4-benzyl-2-methyl-6-(1H-pyrazol-4-yl)morpholine (14.0 g, 82% yield) as light yellow oil, MS m/z: 258.2 [M+H]⁺, ESI pos., ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (s, 1H), 7.56 (s, 1H), 7.40 - 7.27 (m, 5H), 4.99 - 4.64 (m,

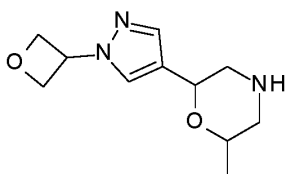
1H), 3.95 - 3.76 (m, 1H), 3.55 (s, 1H), 3.48 (s, 1H), 2.94 - 2.79 (m, 1H), 2.72 - 2.54 (m, 1H), 2.21 - 1.80 (m, 2H), 1.17 (dd, J = 6.4, 15.8 Hz, 3H).

Step 5: 4-benzyl-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine



- 5 To a solution of 4-benzyl-2-methyl-6-(1H-pyrazol-4-yl)morpholine (1.0 mg, 3.89 mmol) in dimethylformamide (20 ml) was added cesium carbonate (3.17 g, 9.71 mmol) and 3-iodooxetane (1.07 g, 5.83 mmol) and the mixture was stirred at 50 °C for 16 h. The reaction mixture was poured into water (200 ml) and extracted with ethyl acetate (100 ml x 3). The combined organic layers were washed with brine (100 ml x 3), dried over Na₂SO₄, and concentrated in vacuum.
- 10 The residue was purified by preparative MPLC (column: Spherical C18, 20-45 μm, 100 Å; mobile phase: water + 0.1% formic acid / acetonitrile 40-60%, flow rate 70 ml/min) to give 4-benzyl-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine (850 mg, 70% yield) as light yellow oil. MS m/z: 314.2 [M+H]⁺, ESI pos.

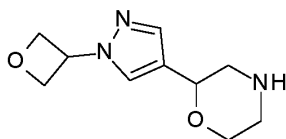
Step 6: 2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine



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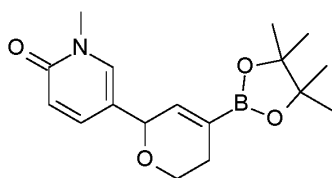
- A suspension of 4-benzyl-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine (1.0 g, 3.19 mmol) in methanol (20 ml) was degassed with argon for 3 times, then palladium on charcoal (10%, 340 mg) was added to the reaction and the gas phase was exchanged to hydrogen 3 times. The reaction was stirred at 50 °C for 12 h under hydrogen atmosphere (15 Psi), then cooled to
- 20 room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give 2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine (680 mg, 96% yield) as light yellow oil. MS m/z: 224.2 [M+H]⁺, ESI pos.

Intermediate C15: 2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholine



The title compound was prepared in analogy to Intermediate C14 from 2-(benzylamino)ethanol instead of 1-(benzylamino)propan-2-ol in step 2). Light yellow oil, MS m/z : 210.1 $[M+H]^+$, ESI pos.

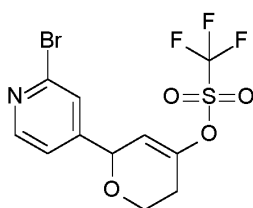
- 5 **Intermediate C16:** 1-methyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridin-2-one



The title compound was prepared in analogy to Intermediate C8 from 1-methyl-6-oxo-pyridine-3-carbaldehyde (CAS 98279-50-6) instead of 2-methoxyisonicotinaldehyde. Brown oil, MS m/z :

- 10 318.2 $[M+H]^+$, ESI pos.

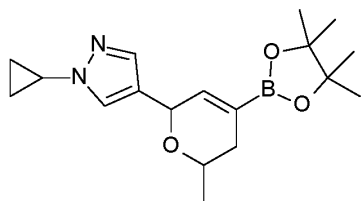
Intermediate C17: [6-(2-bromo-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



- In a 100 ml three-necked flask was introduced under argon 2-bromoisonicotinaldehyde (2.0 g, 10.75 mmol), 3-buten-1-ol (1.13 g, 1.23 ml, 40.87 mmol) and dichloromethane (23 ml) at 25 °C. The reaction mixture was cooled down to 0 °C, trifluoromethane sulfonic acid (4.84 g, 2.86 ml, 32.26 mmol) was added in portions and the mixture was stirred 30 min at 0 °C and then 4 h at room temperature. The reaction mixture was poured into saturated NaHCO_3 solution and extracted two times with dichloromethane. The combined organic layers were washed with water

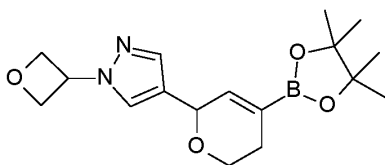
and brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 40% ethyl acetate in heptane) to afford the title compound (1.2 g, 23% yield) as colorless liquid.

- Intermediate C18:** 1-cyclopropyl-4-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole

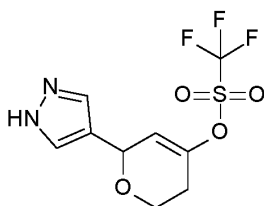


The title compound was prepared in analogy to Intermediate C8 from 1-cyclopropylpyrazole-4-carbaldehyde (CAS 1082066-00-9) instead of 2-methoxyisonicotinaldehyde and 4-pentyn-2-ol instead of 3-butyn-1-ol. Brown oil MS m/z: 331.2 [M+H]⁺, ESI pos.

- Intermediate C19:** 1-(oxetan-3-yl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole



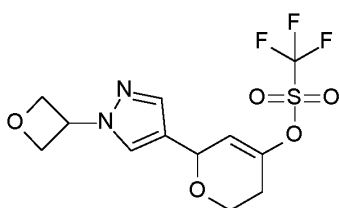
Step 1: [6-(1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



- 15 A 500 ml-three necked flask was charged with 1H-pyrazole-4-carbaldehyde (20.0 g, 208 mmol), and under a flow of nitrogen 3-butyn-1-ol (21.9 g, 312 mmol) was added at 25 °C. While being stirred, trifluoromethane sulfonic acid (55.2 ml, 624 mmol) was added in portions at -10 °C and

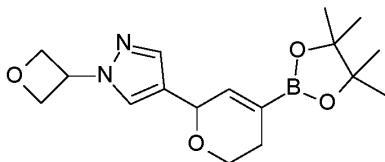
the mixture was stirred at -10 °C for 2 h. The reaction mixture was poured into aqueous NaHCO₃ solution (400 ml) and extracted with dichloromethane (200 ml x 3). The combined layers were washed with brine (200 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Unisil C18, 250 x 100 mm x 10 µm, water + 0.1% formic acid / acetonitrile, flow rate 350 ml/min) to give [6-(1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (24.0 g, 39% yield), MS m/z: 299.1 [M+H]⁺, ESI pos.

Step 2: [6-[1-(oxetan-3-yl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



To a solution of [6-(1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (4.0 g, 13.41 mmol) in dimethylformamide (32 ml) was added 3-iodooxetane (12.3 g, 67.1 mmol) and cesium carbonate (8.74 g, 26.8 mmol) and the reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was added into water (160 ml) and extracted with ethyl acetate (160 ml x 3). The combined organic layers were washed with brine (160 ml x 3), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by preparative HPLC (Phenomenex Luna C18, 150 x 40 mm x 15 µm, water + 0.225% formic acid / acetonitrile, flow rate 60 ml/min) and to give [6-[1-(oxetan-3-yl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (440 mg, 9% yield) as yellow oil. MS m/z: 355.0 [M+H]⁺, ESI pos.

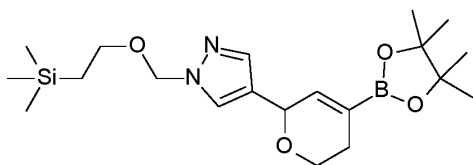
Step 3: 1-(oxetan-3-yl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole



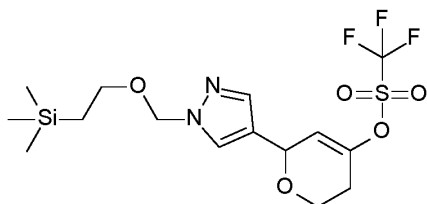
To a suspension of [6-[1-(oxetan-3-yl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (325 mg, 0.81 mmol) and bis(pinacolato)diboron (246 mg, 0.97

mmol) in 1,4-dioxane (5 ml) was added potassium acetate (965 mg, 2.42 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (66 mg, 0.08 mmol, 0.1 eq). After being degassed with nitrogen three times, the resulting mixture was stirred at 90 °C for 1 h under nitrogen. The reaction mixture was added into water (20 ml) and
 5 extracted with ethyl acetate (10 ml x 3). The combined organic layers were washed with brine (10 ml), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by chromatography (silica, petroleum ether, ether = 1:1) to give the title compound (108 mg, 36% yield) as light yellow oil. MS m/z: 333.1 [M+H]⁺, ESI pos.

Intermediate C20: trimethyl-[2-[[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazol-1-yl]methoxy]ethyl]silane
 10



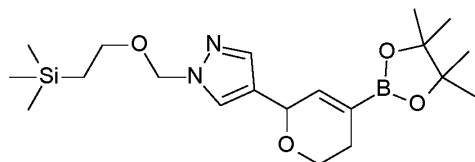
Step 1: [6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



15 To a solution of [6-(1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (see Intermediate C19 step 1, 2.0 g, 6.71 mmol) in tetrahydrofuran (20 ml) was added lithium tert-butoxide (1.075 g, 13.4 mmol) at 0 °C and the solution was stirred at 0 °C for 0.5 h. Then 2-(trimethylsilyl)ethoxymethyl chloride (1.78 ml, 10.06 mmol) was added dropwise and the mixture was stirred at 20 °C for 2 h under nitrogen atmosphere. The reaction mixture was poured
 20 into water (500 ml), the aqueous layer was separated and extracted with ethyl acetate (300 ml x 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 3 : 1 to 1 : 1) to give [6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]-3,6-dihydro-

2H-pyran-4-yl] trifluoromethanesulfonate (2.0 g, 70% yield) as yellow oil, MS m/z: 429.3 [M+H]⁺, ESI pos.

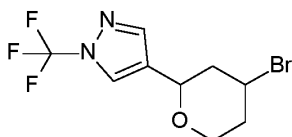
Step 2: trimethyl-[2-[[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazol-1-yl]methoxy]ethyl]silane



5

To a solution of [6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (2.1 g, 4.9 mmol) in 1,4-dioxane (20 ml) was added bis(pinacolato)diboron (1.49 g, 5.88 mmol), potassium acetate (1.44 g, 14.7 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (200 mg, 0.25 mmol, 0.05 eq), the mixture was degassed by nitrogen three times, and stirred for 2 h at 90 °C. After cooling to room temperature, the mixture was poured into water (200 ml) and extracted with ethyl acetate (200 ml x 3). The combined organic layers were washed with brine (200 ml), dried over Na₂SO₄ and concentrated in vacuo to afford the title compound (2.1 g, 63% yield) as brown oil, used directly without further purification, MS m/z: 407.3 [M+H]⁺, ESI pos.

15 **Intermediate C21:** 4-(4-bromotetrahydropyran-2-yl)-1-(trifluoromethyl)pyrazole

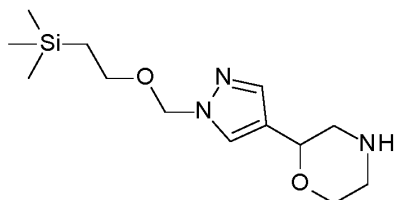


1-(Trifluoromethyl)pyrazole-4-carbaldehyde (870 mg, 5.3 mmol) was combined with 3-buten-1-ol (401 mg, 0.48 ml, 5.57 mmol) in dichloromethane (7.5 ml) under argon atmosphere. Then hydrobromic acid (33% in acetic acid, 1.29 g, 0.91 ml, 15.91 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The mixture was carefully poured into saturated NaHCO₃ solution (100 ml) and the resulting solution was extracted with dichloromethane (3 x 100ml), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0-25% ethyl acetate in heptane) to

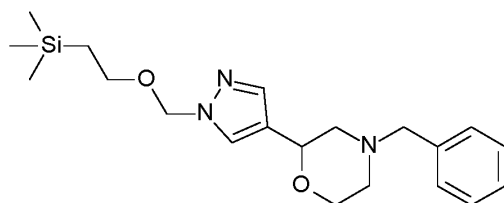
20

afford 4-(4-bromotetrahydropyran-2-yl)-1-(trifluoromethyl)pyrazole (1.25 g, 79%) as light yellow oil. MS m/z: 299.0 [M+H]⁺, ESI pos.

Intermediate C22: trimethyl-[2-[(4-morpholin-2-yl)pyrazol-1-yl)methoxy]ethyl]silane

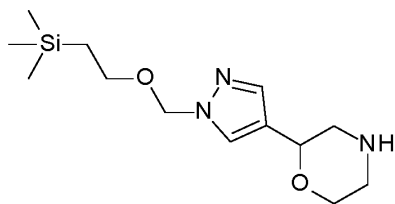


5 **Step 1:** 2-[[4-(4-benzylmorpholin-2-yl)pyrazol-1-yl]methoxy]ethyl-trimethyl-silane



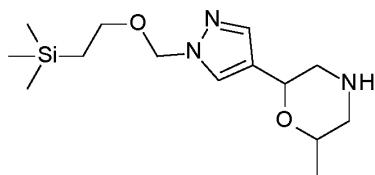
To a solution of 4-benzyl-2-(1H-pyrazol-4-yl)morpholine (CAS 2228909-51-9, 930 mg, 3.82 mmol) in tetrahydrofuran (10 ml) was added lithium tert-butoxide (1.02 g, 7.64 mmol) at 0 °C and the solution was stirred at 0 °C for 1 h. Then 2-(trimethylsilyl)ethoxymethyl chloride (1.01 ml, 5.73 mmol) was slowly added dropwise and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured to aqueous ammonium chloride solution (50 ml) and extracted by ethyl acetate (50 ml x 3). The combined organic layers were washed with saturated sodium chloride solution (10 ml x 3) and dried over anhydrous sodium sulfate, filtered and concentrated under vacuo. The residue was purified by reversed phase chromatography (column: spherical C18 20-45 mm, 100 Å, mobile phase: water / 0.1% formic acid - acetonitrile, 0-100%, flow rate 80 ml/min) to give 2-[[4-(4-benzylmorpholin-2-yl)pyrazol-1-yl]methoxy]ethyl-trimethyl-silane (1.2 g, 84% yield) as colorless oil. MS m/z: 374.2 [M+H]⁺, ESI pos.

Step 2: trimethyl-[2-[(4-morpholin-2-yl)pyrazol-1-yl)methoxy]ethyl]silane



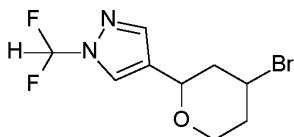
- To a solution of 2-[[4-(4-benzylmorpholin-2-yl)pyrazol-1-yl]methoxy]ethyl-trimethyl-silane (820 mg, 2.2 mmol) in methanol (5 ml) was added palladium on charcoal (10%, 233 mg) under nitrogen atmosphere. Then reaction was degassed in vacuo and hydrogen was added (3 times).
- 5 The mixture was stirred at 50 °C for 12 h under a hydrogen atmosphere of 45 Psi. The reaction mixture was cooled to room temperature, filtered through a pad of celite and the filtrate was concentrated in vacuo to give the trimethyl-[2-[(4-morpholin-2-yl)pyrazol-1-yl]methoxy]ethyl]silane (610 mg, 98% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.55 (s, 1H), 7.52 (s, 1H), 5.39 (s, 2H), 4.51 (dd, J = 2.4, 10.1 Hz, 1H), 3.96 (dd, J = 1.8, 11.4
- 10 Hz, 1H), 3.74 (dt, J = 2.8, 11.3 Hz, 1H), 3.60 - 3.50 (m, 2H), 3.07 (dd, J = 2.1, 12.2 Hz, 1H), 3.01 - 2.93 (m, 1H), 2.92 - 2.84 (m, 2H), 1.87 (s, 1H), 0.94 - 0.87 (m, 2H), 0.00 - 0.04 (m, 9H).

Intermediate C23: trimethyl-[2-[[4-(6-methylmorpholin-2-yl)pyrazol-1-yl]methoxy]ethyl]silane

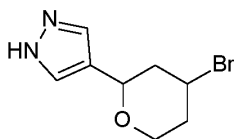


- The title compound was prepared in analogy to Intermediate C22 using 4-benzyl-2-methyl-6-(1H-pyrazol-4-yl)morpholine (see Intermediate C14) instead of 4-benzyl-2-(1H-pyrazol-4-yl)morpholine in step 1). Light yellow oil, MS m/z: 298.2 [M+H]⁺, ESI pos.
- 15

Intermediate C24: 4-(4-bromotetrahydropyran-2-yl)-1-(difluoromethyl)pyrazole

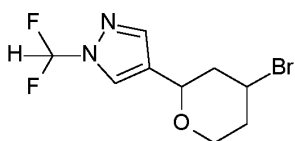


Step 1: 4-(4-bromotetrahydropyran-2-yl)-1H-pyrazole



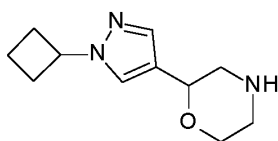
To a solution of 1H-pyrazole-4-carbaldehyde (3.0 g, 31.2 mmol) in dichloromethane (43 ml) was added 3-buten-1-ol (2.46 g, 2.94 ml, 32.8 mmol) under argon. The mixture was sonicated for 5 min at 40 °C, then hydrobromic acid (33% in acetic acid, 23.0 g, 16.2 ml, 93.6 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. A saturated aqueous solution of NaHCO₃ was carefully added until neutral pH and the mixture was extracted several times with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography (silica gel, 0-50 % ethyl acetate / ethanol 3:1 in heptane) to yield 4-(4-bromotetrahydropyran-2-yl)-1H-pyrazole (4.6 g, 64% yield) as white solid. MS m/z: 231.1 / 233.0 [M+H]⁺, ESI pos.

Step 2: 4-(4-bromotetrahydropyran-2-yl)-1-(difluoromethyl)pyrazole

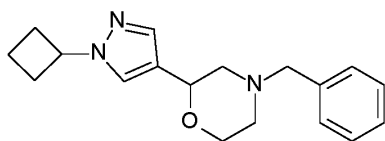


To a solution of diethyl (bromodifluoromethyl)phosphonate (CAS 65094-22-6, 1.73 g, 1.15 ml, 6.49 mmol) in acetonitrile (40 ml) was added potassium fluoride (754 mg, 13 mmol) and 4-(4-bromotetrahydropyran-2-yl)-1H-pyrazole (1.0 g, 4.33 mmol) under argon at room temperature. The reaction mixture was sonicated for 5 min and then stirred at 40 °C for 8 h. After cooling to room temperature the mixture was filtered and the liquid was concentrated to dryness. The crude material was purified by flash chromatography (silica gel, 0-50% ethyl acetate in heptane) to give 4-(4-bromotetrahydropyran-2-yl)-1-(difluoromethyl)pyrazole (1.3 g, 98% yield) as yellow oil. MS m/z: 281.1 / 283.1 [M+H]⁺, ESI pos.

Intermediate C25: 2-(1-cyclobutylpyrazol-4-yl)morpholine

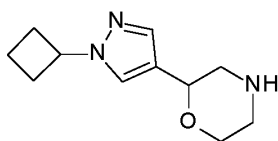


Step 1: 4-benzyl-2-(1-cyclobutylpyrazol-4-yl)morpholine



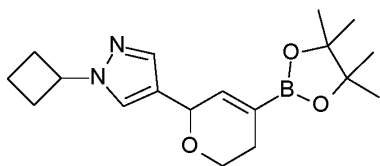
To a solution of 4-benzyl-2-(1H-pyrazol-4-yl)morpholine (CAS 2228909-51-9, 500 mg, 2.05 mmol) in dimethylformamide (5 ml) was added bromocyclobutane (832 mg, 6.16 mmol) and potassium carbonate (568 mg, 4.11 mmol) and the mixture was stirred at 120 °C for 48 h. The mixture was filtered and evaporated. The residue was purified by preparative HPLC (column: Phenomenex Luna C18, 150 x 25 mm x 10 µm, water + 0.1% formic acid / acetonitrile, flow rate 60 ml/min) to give 4-benzyl-2-(1-cyclobutylpyrazol-4-yl)morpholine (400 mg, 65% yield) as yellow oil. MS m/z: 298.2 [M+H]⁺, ESI pos.

Step 2: 2-(1-cyclobutylpyrazol-4-yl)morpholine

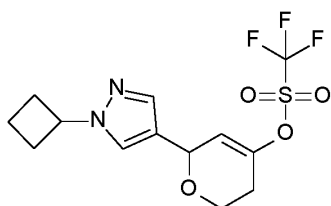


To a solution of 4-benzyl-2-(1-cyclobutylpyrazol-4-yl)morpholine (400 mg, 1.34 mmol) in methanol (5 ml) was added palladium on charcoal (10%, 143 mg) under nitrogen. The reaction was degassed with hydrogen 3 times and stirred at a hydrogen atmosphere of 45 Psi at 50 °C for 12 h. The reaction mixture was cooled down to room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give the title compound (260 mg, 93% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.51 - 7.48 (m, 1H), 7.47 - 7.44 (m, 1H), 4.77 - 4.68 (m, 1H), 4.48 (dd, J = 2.6, 10.1 Hz, 1H), 3.98 - 3.92 (m, 1H), 3.78 - 3.70 (m, 1H), 3.12 - 3.02 (m, 1H), 3.00 - 2.93 (m, 1H), 2.92 - 2.84 (m, 2H), 2.58 - 2.50 (m, 1H), 2.49 - 2.42 (m, 2H), 1.95 - 1.76 (m, 3H).

Intermediate C26: 1-cyclobutyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole

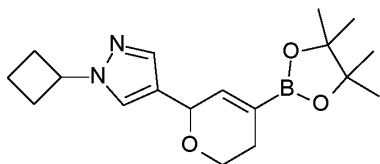


Step 1: [6-(1-cyclobutylpyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



- To a solution of [6-(1H-pyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (see
- 5 Intermediate C19 step 1, 1.0 g, 3.35 mmol) in dimethylformamide (15 ml) was added iodocyclobutane (3.05 g, 16.77 mmol) and cesium carbonate (2.18 g, 6.71 mmol) and the reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was added into water (40 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (20 ml x 3) and dried over Na₂SO₄, then concentrated in vacuum. The residue was purified
- 10 preparative HPLC (column: Phenomenex Luna C18, 150 x 40 mm x 15 μm, water + 0.225% formic acid / acetonitrile, flow rate 60 ml/min) to give [6-(1-cyclobutylpyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (0.35 g, 30% yield) as light yellow oil. MS m/z: 353.1 [M+H]⁺, ESI pos.

- Step 2: 1-cyclobutyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-
- 15 6-yl]pyrazole

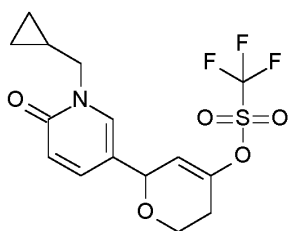


To a solution of [6-(1-cyclobutylpyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (350 mg, 0.99 mmol) in 1,4-dioxane (10 ml) was added bis(pinacolato)diboron (303 mg, 1.19 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane

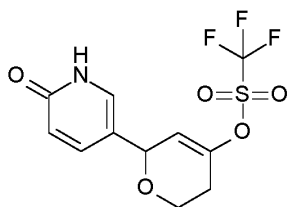
complex (40 mg, 0.05 mmol, 0.05 eq) and potassium acetate (292 mg, 2.98 mmol). The mixture was degassed with nitrogen three times and the reaction was stirred at 90 °C for 2 h under nitrogen. The reaction mixture was poured into water (30 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (20 ml x 3), dried over

5 Na₂SO₄ and concentrated in vacuum to give the title compound (328 mg, 99% yield) as light yellow oil. MS m/z: 331.1 [M+H]⁺, ESI pos.

Intermediate C27: [6-[1-(cyclopropylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



10 Step 1: [6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate

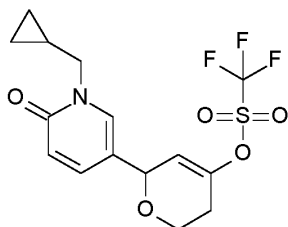


Under inert atmosphere 6-keto-1H-pyridine-3-carbaldehyde (3 g, 24.4 mmol) and 3-butyn-1-ol (2.56 g, 2.78 ml, 36.6 mmol) were dissolved in dichloromethane (65 ml) at room temperature. The resulting solution was cooled to -10 °C and trifluoromethane sulfonic acid (11.0 g, 6.5 ml,

15 73.1 mmol) was carefully added dropwise. The reaction mixture was stirred at -10 °C for 30 min and then at room temperature for 4 h. The reaction mixture was quenched with saturated NaHCO₃ solution and extracted three times with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-10%) to obtain [6-(6-oxo-1H-

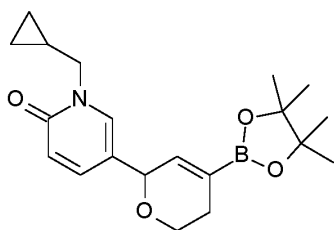
20 pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (4.85 g, 60% yield) as light yellow gum, MS m/z: 326.0 [M+H]⁺, ESI pos.

Step 2: [6-[1-(cyclopropylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



- To a solution of [6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (1.5 g, 4.61 mmol) in acetonitrile (20 ml) were added
- 5 bromomethylcyclopropane (934 mg, 671 μ l, 6.92 mmol) and potassium carbonate (1.27 g, 9.22 mmol) at room temperature and the mixture was stirred for 18 h at 90 °C. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated to dryness. The residue was purified by flash
- 10 chromatography (silica gel, methanol in dichloromethane 0-4%) to obtain the title compound (1.24 g, 67% yield) as light yellow solid, MS m/z : 380.1 $[\text{M}+\text{H}]^+$, ESI pos.

Intermediate C28: 1-(cyclopropylmethyl)-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridin-2-one

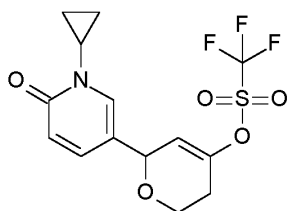


- 15 To a solution of [6-[1-(cyclopropylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (Intermediate C27, 800 mg, 2.11 mmol) in 1,4-dioxane (12 ml) were added potassium acetate (828 mg, 8.44 mmol) and bis(pinacolato)diboron (803 mg, 3.16 mmol) at room temperature. The mixture was degassed with argon before 1,1'-bis(diphenylphosphino)-ferrocene-palladium(II)dichloride dichloromethane complex (172 mg, 0.211 mmol, 0.10 eq) was
- 20 added. The reaction mixture was stirred for 2 h at 90 °C, then it was diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over MgSO_4 and

concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-3%) to obtain the title (585 mg, 58% yield) as brown liquid, MS m/z: 358.2 [M+H]⁺, ESI pos.

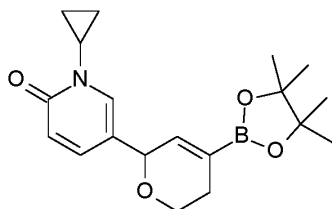
Intermediate C29: [6-(1-cyclopropyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]

5 trifluoromethanesulfonate



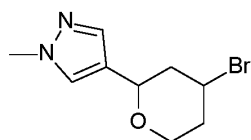
To a solution of [6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (see Intermediate C27 step 1, 1.75 g, 5.38 mmol) in 1,2-dichloroethane (30 ml) were added cyclopropylboronic acid (1.02 g, 11.84 mmol), 2,2'-bipyridine (924 mg, 5.92 mmol), copper(II) acetate monohydrate (1.18 g, 5.92 mmol) and sodium carbonate (1.31 g, 12.4 mmol) at room temperature and air was bubbled through for 3 min. The mixture was stirred overnight at 70 °C under air atmosphere. The reaction mixture was diluted with water and extracted two times with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-40%) to obtain [6-(1-cyclopropyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (1.37 g, 61% yield) as light yellow oil, MS m/z: 366.0 [M+H]⁺, ESI pos.

Intermediate C30: 1-cyclopropyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridin-2-one



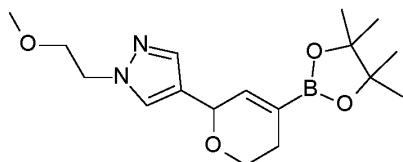
To a solution of [6-(1-cyclopropyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (Intermediate C29, 950 mg, 2.6 mmol) in 1,4-dioxane (13 ml) was added potassium acetate (1.02 g, 10.4 mmol) and bis(pinacolato)diboron (991mg, 3.9 mmol) at room temperature. The mixture was degassed with argon before 1,1'-bis(diphenylphosphino)-ferrocene-palladium(II)dichloride dichloromethane complex (212 mg, 0.26 mmol, 0.10 eq) was added. The mixture was stirred for 1 h at 90 °C, then it was diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-40%) to obtain the title compound (775 mg, 61% yield, 705 purity) as brown oil, MS m/z: 344.2 [M+H]⁺, ESI pos.

Intermediate C31: 4-(4-bromotetrahydropyran-2-yl)-1-methyl-pyrazole



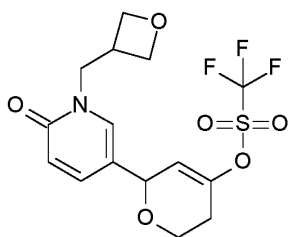
To a solution of 1-methylpyrazole-4-carbaldehyde (2 g, 18.2 mmol) in dichloromethane (25 ml) was added 3-buten-1-ol (1.38 g, 1.64 ml, 19.1 mmol) under argon. Hydrobromic acid (33% solution in acetic acid (13.4 g, 9.9 mL, 54.5 mmol) was added at room temperature in one portion and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was carefully quenched with saturated NaHCO₃ solution and washed with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography (silica gel, 0-50% ethyl acetate / ethanol = 3:1 in heptane) to afford 4-(4-bromotetrahydropyran-2-yl)-1-methyl-pyrazole (2.87 g, 62% yield) as light yellow oil, 245.1 [M+H]⁺, ESI pos.

Intermediate C32: 1-(2-methoxyethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazole



The title compound was prepared in analogy to Intermediate C26 using 2-bromoethyl methyl ether instead of iodocyclobutane in step 1. Yellow solid, MS m/z: 335.1 [M+H]⁺, ESI pos.

Intermediate C33: [6-[1-(oxetan-3-ylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



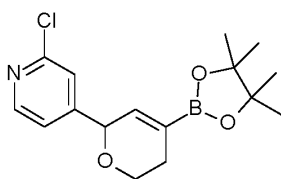
5

To a solution of [6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (see Intermediate C27 step 1, 1.25 g, 3.84 mmol) in acetonitrile (17 ml) was added 3-(bromomethyl)oxetane (871 mg, 625 μ l, 5.76 mmol) and potassium carbonate (1.06 g, 7.69 mmol) at room temperature and the mixture was stirred for 4 h at 90 °C. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-10%) to obtain the title compound (1.06 g, 66% yield) as light yellow oil, MS m/z: 396.1 [M+H]⁺, ESI pos.

10

Intermediate C34: 2-chloro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine

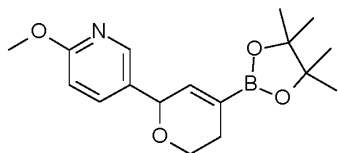
15



The title compound was prepared in analogy to Intermediate C8 from 2-chloroisonicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow oil, MS m/z: 322.2 [M+H]⁺, ESI pos.

Intermediate C35: 2-methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine

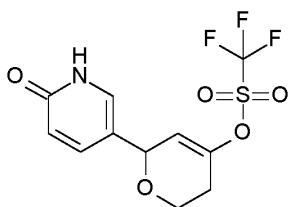
20



The title compound was prepared in analogy to Intermediate C8 from 6-methoxynicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Yellow oil, MS m/z : 318.3 $[M+H]^+$, ESI pos.

Intermediate C36: [6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl]

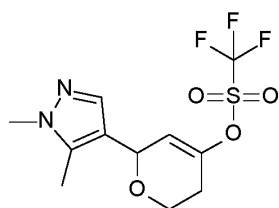
5 trifluoromethanesulfonate



The title compound was prepared in analogy to Intermediate C8 (step 1) from 6-keto-1H-pyridine-3-carbaldehyde instead of 2-methoxyisonicotinaldehyde. Brown oil, MS m/z : 326.1 $[M+H]^+$, ESI pos.

10 **Intermediate C37:** [6-(1,5-dimethylpyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl]

trifluoromethanesulfonate

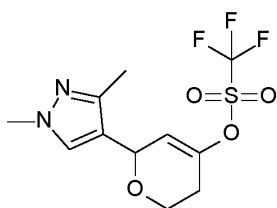


The title compound was prepared in analogy to Intermediate C8 (step 1) from 1,5-dimethylpyrazole-4-carbaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow liquid,

15 MS m/z : 327.4 $[M+H]^+$, ESI pos.

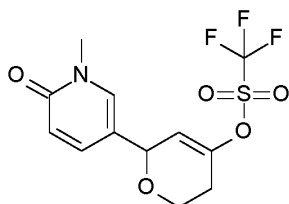
Intermediate C38: [6-(1,3-dimethylpyrazol-4-yl)-3,6-dihydro-2H-pyran-4-yl]

trifluoromethanesulfonate



The title compound was prepared in analogy to Intermediate C8 (step 1) from 1,3-dimethylpyrazole-4-carbaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow liquid, MS m/z: 327.5 [M+H]⁺, ESI pos.

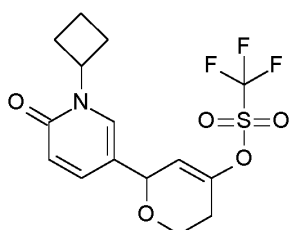
- 5 **Intermediate C39:** [6-(1-methyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



The title compound was prepared in analogy to Intermediate C8 (step 1) from 2-keto-1-methyl-isonicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow oil, MS m/z: 340.1

- 10 [M+H]⁺, ESI pos.

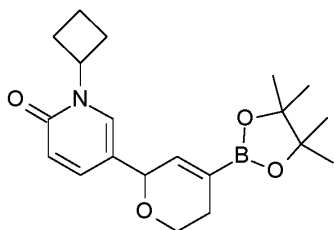
- Intermediate C40:** [6-(1-cyclobutyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



The title compound was prepared in analogy to Intermediate C8 (step 1) from 1-cyclobutyl-6-keto-nicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow oil, MS m/z: 358.3 [M+H]⁺, ESI pos.

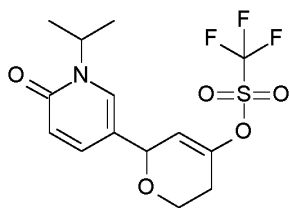
- 15

Intermediate C41: 1-cyclobutyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridin-2-one



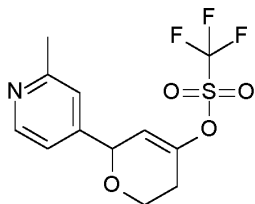
The title compound was prepared in analogy to Intermediate C8 from 1-cyclobutyl-6-keto-
5 nicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Light yellow oil, MS m/z: 358.3
[M+H]⁺, ESI pos.

Intermediate C42: [6-(1-isopropyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]
trifluoromethanesulfonate



10 The title compound was prepared in analogy to Intermediate C8 (step 1) from 1-isopropyl-6-
keto-nicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Brown oil, MS m/z: 368.1
[M+H]⁺, ESI pos.

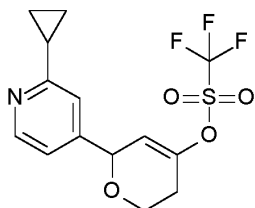
Intermediate C43: [6-(2-methyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]
trifluoromethanesulfonate



The title compound was prepared in analogy to Intermediate C8 (step 1) from 2-methylisonicotinaldehyde instead of 2-methoxyisonicotinaldehyde. Orange oil, MS m/z: 324.1 $[M+H]^+$, ESI pos.

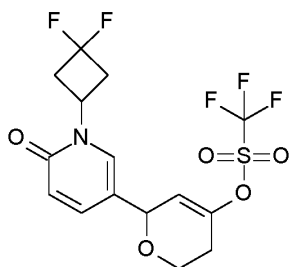
Intermediate C44: [6-(2-cyclopropyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]

5 trifluoromethanesulfonate

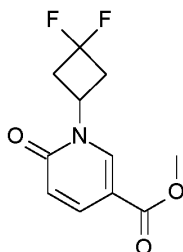


The title compound was prepared in analogy to Intermediate C8 (step 1) from 2-cyclopropylpyridine-4-carbaldehyde instead of 2-methoxyisonicotinaldehyde. Yellow oil, MS m/z: 350.0 $[M+H]^+$, ESI pos.

10 **Intermediate C45:** [6-[1-(3,3-difluorocyclobutyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



Step 1: methyl 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carboxylate

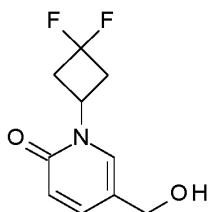


To solution of 6-ketopyran-3-carboxylic acid methyl ester (CAS 6018-41-3, 3.3 g, 21.4 mmol) in N,N-dimethylformamide (30 ml) was added (3,3-difluorocyclobutyl)amine hydrochloride (CAS 637031-93-7, 3.38 g, 23.6 mmol) and N,N-diisopropyl ethylamine (3.04 g, 4.1 ml, 23.6 mmol) at 0 °C. After stirring at 0 °C for 30 min the mixture was allowed to warm to room temperature and

5 4-(dimethylamino)pyridine (523 mg, 4.28 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.34 g, 27.8 mmol) were added, and stirring at room temperature was continued overnight. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue purified by flash chromatography (silica gel, 10 -100% ethyl acetate in

10 heptane) to give methyl 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carboxylate (1.44 g, 28% yield) as yellow solid. MS m/z: 244.1 [M+H]⁺, ESI pos.

Step 2: 1-(3,3-difluorocyclobutyl)-5-(hydroxymethyl)pyridin-2-one

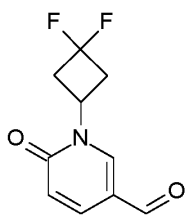


To a solution of methyl 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carboxylate (1 g, 4.11 mmol) in toluene (30 ml) was added diisobutylaluminum hydride solution (1.2 M in toluene

15 (10.28 ml, 12.34 mmol) dropwise under argon at -78 °C and the mixture was stirred at -78 °C for 3 h. Then diethylether was added and the mixture was allowed to warm to 0 °C. Water (10 µl), 1 M sodium hydroxide solution (0.5 ml) and again water (20 µl) were added and the resulting mixture was stirred for 10 min at room temperature. Na₂SO₄ was added and the mixture was

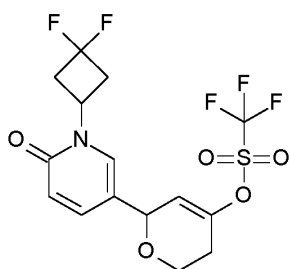
20 stirred for another 10 min at room temperature. The suspension was filtered, the solid was rinsed with dichloromethane / methanol and the resulting solution was concentrated to dryness and used for the next step without further purification. Orange solid, MS m/z: 216.1 [M+H]⁺, ESI pos.

Step 3: 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carbaldehyde



To a solution of 1-(3,3-difluorocyclobutyl)-5-(hydroxymethyl)pyridin-2-one (880 mg, 4.09 mmol) in dichloromethane (25 ml) was added manganese dioxide (3.56 g, 40.9 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was filtrated over
 5 dicalite and the solvent was evaporated under reduced pressure to yield 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carbaldehyde as an orange solid which was used for the subsequent reaction without further purification. MS m/z: 214.1 [M+H]⁺, ESI pos.

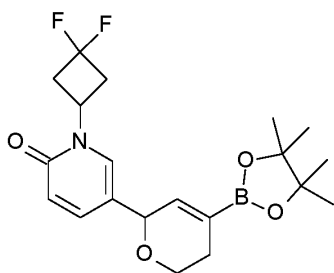
Step 4: [6-[1-(3,3-difluorocyclobutyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



10

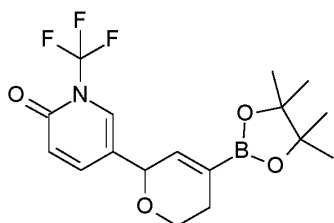
To a solution of 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carbaldehyde (590 mg, 1.38 mmol) in dichloromethane (8 ml) was added 3-buten-1-ol (146 mg, 158 µl, 2.08 mmol) at room temperature under argon atmosphere. The reaction was cooled down to -10 °C and trifluoromethane sulfonic acid (623 mg, 366 µl, 4.15 mmol) was added dropwise. The mixture
 15 was stirred at -10 °C for 1 h, then stirred at room temperature for 3.5 h. The reaction mixture was diluted with saturated NaHCO₃ solution and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to dryness. The crude material was used for subsequent reactions without further purification (662 mg, 35% yield, 30% purity), red gum, MS m/z: 416.1 [M+H]⁺, ESI pos.

20 **Intermediate C46:** 1-(3,3-difluorocyclobutyl)-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridin-2-one

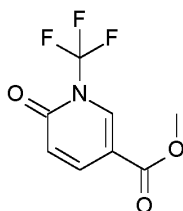


The title compound was prepared in analogy to Intermediate C28 from Intermediate C45 instead of Intermediate C27. Red solid, MS m/z : 394.3 $[M+H]^+$, ESI pos.

Intermediate C47: 5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]-1-(trifluoromethyl)pyridin-2-one



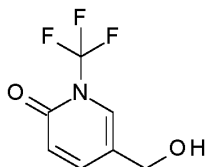
Step 1: methyl 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carboxylate



In a 185 ml-carbonylation reactor, 5-bromo-1-(trifluoromethyl)-2-pyridone (1.5 g, 6.2 mmol) was dissolved in methanol (50 ml). Then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (177 mg, 0.217 mmol) and triethylamine (1.78 g, 2.45 ml, 17.85 mmol) were added. The reactor was flushed 3 times with 7 bar of argon and five times with 10 bar of carbon monoxide. The reactor was then filled with 8 bar of carbon monoxide, heated to 70 °C and stirred overnight for 18 h. The reaction mixture was concentrated under reduced pressure and the obtained crude product was purified by column chromatography

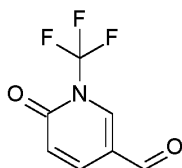
(silica, 0-50% ethyl acetate in heptane) to afford methyl 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carboxylate (1.23 g, 90% yield) as white solid, MS m/z: 222.1 $[M+H]^+$, ESI pos.

Step 2: 5-(hydroxymethyl)-1-(trifluoromethyl)pyridin-2-one



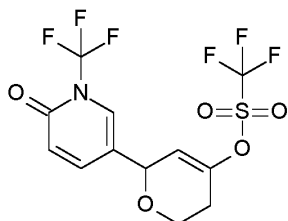
- 5 To a solution of methyl 1-(3,3-difluorocyclobutyl)-6-oxo-pyridine-3-carboxylate (750 mg, 3.39 mmol) in toluene (22 ml) was added under argon diisobutylaluminum hydride solution (1.2 M in toluene, 8.5 ml, 10.2 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 1.5 h, then diluted with diethyl ether. At 0 °C, water (7 mg, 7 μ l, 386 μ mol), sodium hydroxide (1 M, 386 μ L, 386 μ mol) and again water (17 mg, 17 μ l, 956 μ mol) were added and the resulting mixture
- 10 was stirred for 10 min warming to room temperature. Na_2SO_4 was added to dry. The suspension was stirred for another 10 min at room temperature and was then filtered. The filter residue was rinsed with dichloromethane and methanol, the filtrate was concentrated to dryness to obtain the crude product which was used for the next step without further purification. Red solid, MS m/z: 194.1 $[M+H]^+$, ESI pos.

15 Step 3: 6-oxo-1-(trifluoromethyl)pyridine-3-carbaldehyde



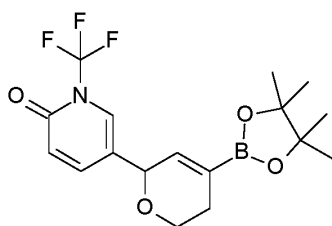
- To a solution of 5-(hydroxymethyl)-1-(trifluoromethyl)pyridin-2-one (520 mg, 2.69 mmol) in dichloromethane (20 ml) was added manganese dioxide (2.34 g, 26.9 mmol) and the reaction mixture was stirred at room temperature for 96 h. The mixture was filtered over dicalite and the
- 20 resulting filtrate was concentrated under reduced pressure to yield 6-oxo-1-(trifluoromethyl)pyridine-3-carbaldehyde as red oil (175 mg, 14%, 40 % purity) which was used for the subsequent reaction without further purification, MS m/z: 192.1 $[M+H]^+$, ESI pos.

Step 4: [6-[6-oxo-1-(trifluoromethyl)-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate



To a solution of 6-oxo-1-(trifluoromethyl)pyridine-3-carbaldehyde (175 mg, 0.458 mmol) in dichloromethane (3 ml) was added 3-buten-1-ol (48 mg, 52 μ l, 0.688 μ mol) at room temperature under argon atmosphere. The reaction was cooled down to -10 °C and trifluoromethane sulfonic acid (206 mg, 121 μ l, 1.37 mmol) was added dropwise via a syringe. The mixture was stirred at -10 °C for 60 min, then allowed to come to room temperature and stirred at ambient temperature for 3 h. Upon completion, the reaction mixture was diluted with a saturated NaHCO₃ solution and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0-5 % methanol in dichloromethane) to yield [6-[6-oxo-1-(trifluoromethyl)-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate as light yellow liquid (35 mg, 14%, 70% purity), MS m/z: 394.1 [M+H]⁺, ESI pos.

Step 5: 5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]-1-(trifluoromethyl)pyridin-2-one

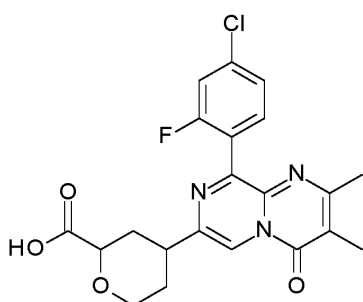


To a solution of [6-[6-oxo-1-(trifluoromethyl)-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (35 mg, 89 μ mol) in 1,4-dioxane (1 ml) was added potassium acetate (35 mg, 0.356 mmol) and bis(pinacolato)diboron (29 mg, 0.116 mmol). The mixture was degassed with argon before adding 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (7.3 mg, 8.9 μ mol, 0.100 eq) and the reaction mixture was stirred for 2

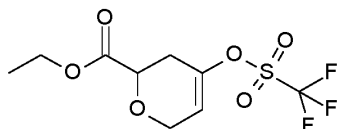
h at 80 °C. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to dryness to yield the title compound as brown liquid (59 mg, 89% yield, 50% purity), which was used for the subsequent step without additional purification. MS m/z: 372.3

5 [M+H]⁺, ESI pos.

Intermediate D1: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylic acid



Step 1: ethyl 4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyran-2-carboxylate

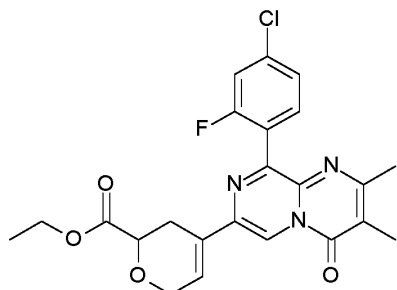


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To a mixture of 4-ketotetrahydropyran-2-carboxylic acid ethyl ester (CAS 287193-07-1, 2.32 g, 2 ml, 13.5 mmol) and 2,6-di-tert-butyl-4-methylpyridine (3.33 g, 16.2 mmol) in dichloromethane (46 ml) was added trifluoromethanesulfonyl anhydride (7.62 g, 4.56 ml, 27.0 mmol) at 0 °C. The ice bath was removed after the addition and the mixture was stirred at 35 °C overnight. The

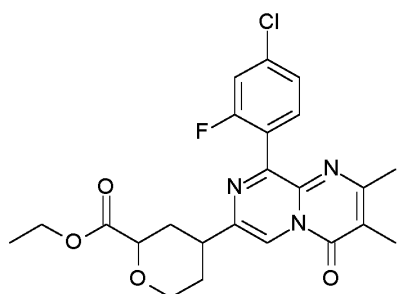
15 reaction mixture was poured into ice cold sodium hydrogencarbonate solution (60 ml) under stirring, then diluted with water. The aqueous layer was separated and back extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 0% to 50% ethyl acetate in heptane) to afford ethyl 4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-
20 pyran-2-carboxylate (1.67 g, 41%) as colorless liquid.

Step 2: ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylate



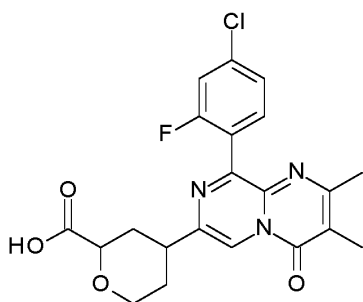
To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one (Intermediate B13, 2.33 g, 5.42 mmol) in 1,4-dioxane (108 ml) and water (18 ml) were added under argon stream ethyl 4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyran-2-carboxylate (1.65 g, 5.42 mmol), potassium carbonate (2.25 g, 16.3 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (402 mg, 0.542 mmol, 0.10 eq) and the reaction mixture was stirred at 60 °C for 2.5 h. The reaction mixture was filtered over dicalite. The filtrate was poured into water and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0% to 10% methanol in dichloromethane). The product was suspended in ethyl acetate then filtered to afford ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylate (2.07 g, 79%) as yellow solid. MS m/z: 458.2 [M+H]⁺, ESI pos.

Step 3: ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylate



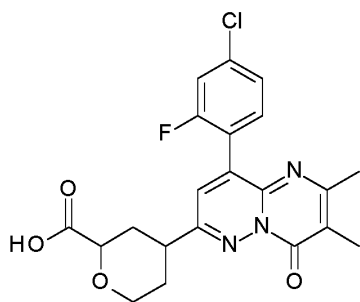
To a solution of 4-[9-(4-chloro-2-fluoro-phenyl)-4-keto-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (400 mg, 0.874 mmol) in ethyl acetate (60 ml) were added under argon triethylamine (106 mg, 146 μ l, 1.05 mmol), magnesium oxide (352 mg, 8.74 mmol) and palladium on charcoal (10%, 186 mg). The mixture was degassed with
 5 argon several times then stirred under hydrogen gas atmosphere (balloon pressure) at room temperature for 40 min. The reaction mixture was filtered over dicalite and washed with ethyl acetate. The filtrate was concentrated and the crude material was purified by flash chromatography (HP C18 RediSep Gold,, 0% to 70% acetonitrile in water) to afford ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-
 10 2-carboxylate (230 mg, 52%) as yellow foam. MS m/z: 460.2 [M+H]⁺, ESI pos.

Step 4: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylic acid

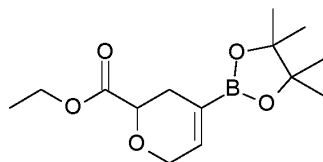


To a solution of ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-
 15 a]pyrimidin-7-yl]tetrahydropyran-2-carboxylate (246 mg, 0.535 mmol) in tetrahydrofuran (2 ml) and ethanol (1 ml) was added aqueous lithium hydroxide solution (1 M, 1.6 ml, 1.6 mmol) and the reaction mixture was stirred at room temperature. Then aqueous hydrochloric acid (1M, 1.6 ml, 1.6 mmol) was added and the mixture was poured into water and extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄ and
 20 concentrated in vacuo to afford the title compound (248 mg, 97%) as yellow foam. MS m/z: 432.2 [M+H]⁺, ESI pos.

Intermediate D2: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]tetrahydropyran-2-carboxylic acid

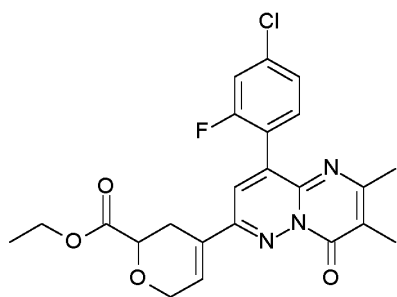


Step 1: ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-2-carboxylate



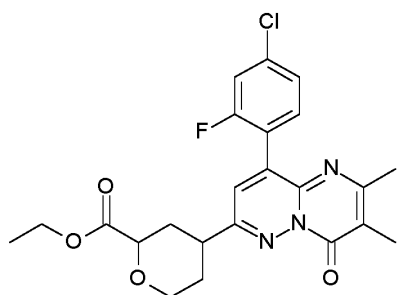
- 5 To a solution of ethyl 4-(trifluoromethylsulfonyloxy)-3,6-dihydro-2H-pyran-2-carboxylate (see Intermediate D1 step 1, 24.3 g, 79.87 mmol) in 1,4-dioxane (240 ml) was added bis(pinacolato)diboron (21.3 g, 83.9 mmol), potassium acetate (23.52 g, 240 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (1.96 g, 2.4 mmol, 0.03 eq). Then the mixture was degassed with nitrogen three times and the reaction was stirred at 90 °C for 2 h
- 10 under nitrogen atmosphere. The mixture was poured into water (500 ml) and extracted with ethyl acetate (300 ml x 3). The combined organic layers were washed with brine (300 ml) and dried over Na₂SO₄, then concentrated in vacuum. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 100 : 1 to 3 : 1) to afford ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-2-carboxylate (14.0 g, 62% yield) as light
- 15 yellow oil. MS m/z: 283.2 [M+H]⁺, ESI pos.

Step 2: ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylate



To a solution of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B3, 2.1 g, 6.21 mmol) in 1,4-dioxane (50 ml) and water (5 ml) was added ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-2-carboxylate (2.45 g, 8.69 mmol), cesium carbonate (6.07 g, 18.63 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (254 mg, 0.31 mmol, 0.05 eq). Then the reaction was degassed with nitrogen three times and stirred at 25 °C for 2 h under nitrogen atmosphere. The mixture was poured into water (200 ml) and extracted with ethyl acetate (100 ml x 3). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 100 : 1 to 1 : 3) to afford ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylate (2.6 g, 91% yield) as light yellow solid. MS m/z: 458.1 [M+H]⁺, ESI pos.

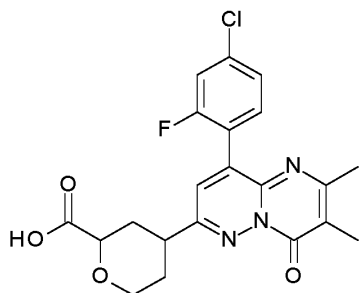
Step 3: ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]tetrahydropyran-2-carboxylate



To a suspension of platinum oxide (198 mg, 0.87 mmol, 0.2 eq) in ethyl acetate (25 ml) under nitrogen was added a solution of ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylate (2.0 g, 4.37 mmol) in ethyl acetate (25 ml) and dimethylformamide (10 mL), magnesium oxide (1.76 g, 43.7 mmol) and

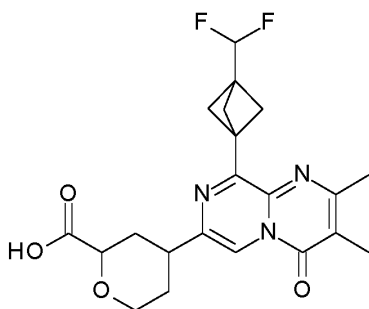
triethylamine (530 mg, 5.24 mmol). The reaction was degassed with hydrogen three times, then stirred at 25 °C for 4 h under hydrogen (15 Psi). The reaction mixture was filtered through a pad of diatomaceous earth, then poured into water (150 ml) and extracted with ethyl acetate (100 ml x 3). The combined organic layers were washed with brine (50 ml x 3) and dried over Na₂SO₄, then concentrated in vacuum. The residue was purified by preparative HPLC (Phenomenex Luna C18, 250 x 70 mm x 10 µm, water + 0.225% formic acid / acetonitrile, flow rate 140 ml/min) to give ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]tetrahydropyran-2-carboxylate (1.3 g, 65% yield) as light yellow solid. MS m/z: 460.2 [M+H]⁺, ESI pos.

10 Step 4: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]tetrahydropyran-2-carboxylic acid



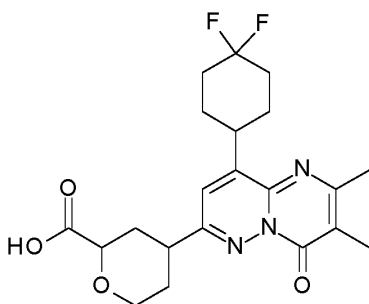
To a solution of ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]tetrahydropyran-2-carboxylate (1.3 g, 2.83 mmol) in tetrahydrofuran (12 ml) and water (4 ml) was added lithium hydroxide monohydrate (178 mg, 4.24 mmol) and the reaction was stirred at 20 °C for 1 h. The mixture was poured into water (100 ml), the pH was adjusted to 6 with 1M hydrochloric acid, then extracted with ethyl acetate (80 ml x 3). The combined organic layers were washed with brine (80 ml), dried over Na₂SO₄, then concentrated in vacuum to give the title compound (1.2 g, 98% yield) as yellow solid. MS m/z: 432.1 [M+H]⁺, ESI pos.

Intermediate D3: 4-[9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylic acid



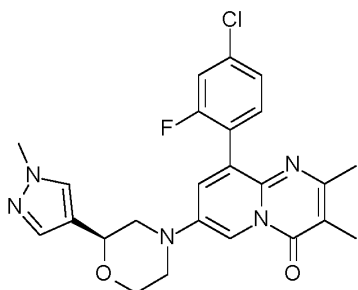
The title compound was prepared in analogy to Intermediate D2 using Intermediate B17 instead of Intermediate B3 in step 2. Light yellow solid, MS m/z: 420.2 $[M+H]^+$, ESI pos.

Intermediate D4: 4-[9-(4,4-difluorocyclohexyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]tetrahydropyran-2-carboxylic acid



The title compound was prepared in analogy to Intermediate D2 using Intermediate B16 instead of Intermediate B3 in step 2. White solid, MS m/z: 422.1 $[M+H]^+$, ESI pos.

Example 1: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one

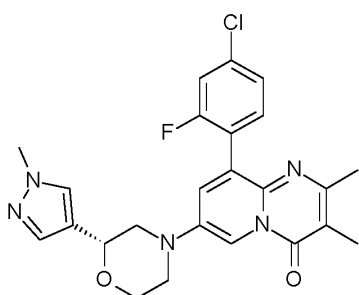


To a suspension of 7-bromo-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (Intermediate B1, 75 mg, 0.196 mmol) in 1,4-dioxane (2 ml) was added (2S)-2-(1-methylpyrazol-4-yl)morpholine (Intermediate (+)-C1, 39 mg, 0.235 mmol), cesium carbonate (192 mg, 0.589 mmol) at room temperature. The mixture was degassed with argon before

5 tris(dibenzylideneacetone)dipalladium (9 mg, 0.0098 mmol, 0.05 eq) and Xantphos (11 mg, 0.0196 mmol, 0.10 eq) was added. The reaction mixture was stirred overnight at 100 °C, then it was diluted with water and extracted two times with ethyl acetate. The combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-5%) to obtain

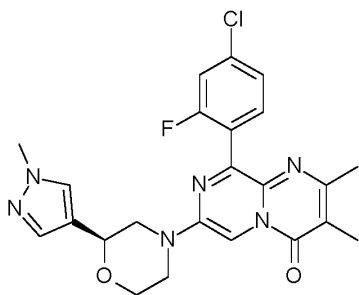
10 the title compound (38 mg, 41% yield) as light yellow solid, MS m/z: 468.1 [M+H]⁺, ESI pos., absolute stereochemistry arbitrarily assigned.

Example 2: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one



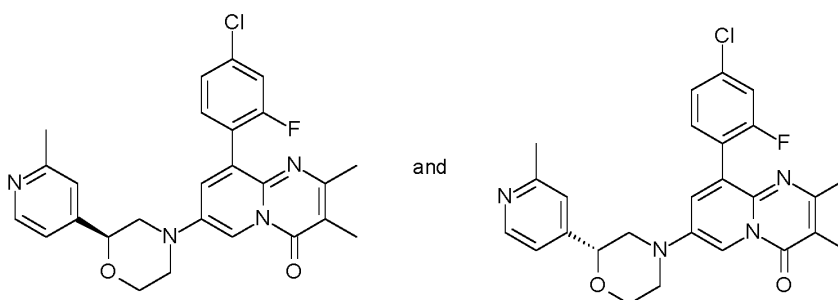
15 The title compound was prepared in analogy to Example 1 from Intermediate (-)-C1 instead of Intermediate (+)-C1. Light brown solid, MS m/z: 468.2 [M+H]⁺, ESI pos., absolute stereochemistry arbitrarily assigned.

Example 3: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Example 1 from Intermediate B2 instead of Intermediate B1. Orange solid, MS m/z : 469.1 $[M+H]^+$, ESI pos., absolute stereochemistry arbitrarily assigned.

- 5 **Example 4 and Example 5:** 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one

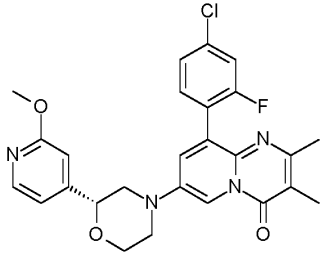
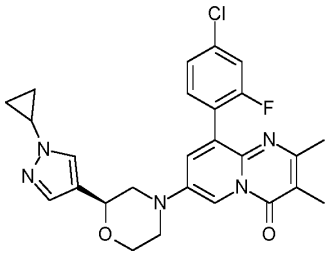
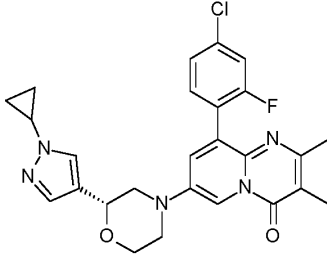
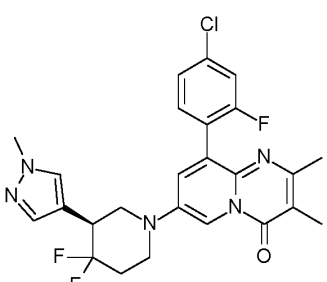


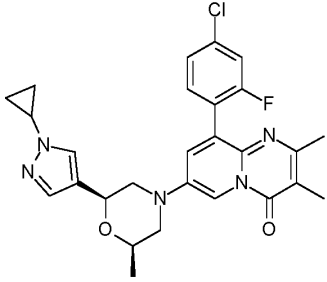
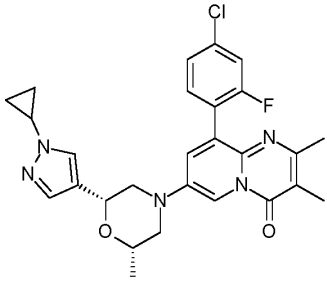
- To a suspension of 7-bromo-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (Intermediate B1, 50 mg, 0.13 mmol) in 1,4-dioxane (3 ml) was added 2-(2-methyl-4-pyridyl)morpholine (Intermediate C2, 28 mg, 0.16 mmol), cesium carbonate (128 mg, 0.39 mmol), tris(dibenzylideneacetone)dipalladium (6.0 mg, 0.01 mmol, 0.05 eq) and Xantphos (7.5 mg, 0.01 mmol, 0.1 eq) and the mixture was stirred at 100 °C for 16 h under nitrogen. The reaction mixture was poured into water (40 ml) and extracted with ethyl acetate (20 ml $\times$ 2). The combined original layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative MPLC (column: Spherical C18, 20-45 μm , 100 Å ; water with 0.1% formic acid / acetonitrile, flow rate 50 ml/min) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (40 mg). This racemate was separated by chiral SFC (column Daicel Chiralpak AD 250 mm $\times$ 30

mm, 10 μ m, acetonitrile / isopropanol / 0.1% ammonium hydroxide, flow rate 70 ml/min) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 0.848 min, white solid, MS m/z: 479.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one as second eluting enantiomer with retention time 1.289 min), white solid, MS m/z: 479.1 [M+H]⁺, ESI pos., absolute stereochemistry arbitrarily assigned.

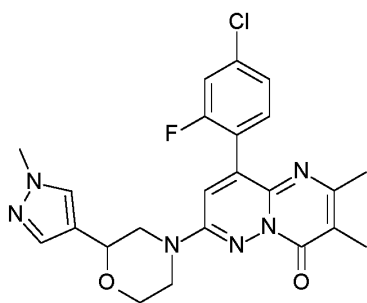
The following **Examples 6 to 13** were prepared in analogy to Examples 4 and 5 by starting from the indicated intermediates instead of intermediate C2. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediate	MS (ESI): m/z
6		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(3S)-3-(1-methylpyrazol-4-yl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one	C3	466.2 [M+H] ⁺
7		9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C4	495.2 [M+H] ⁺

8		9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C4	495.2 [M+H] ⁺
9		9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C5	494.2 [M+H] ⁺
10		9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C5	494.2 [M+H] ⁺
11		9-(4-chloro-2-fluorophenyl)-7-[(3S)-4,4-difluoro-3-(1-methylpyrazol-4-yl)-1-piperidyl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C6	502.1 [M+H] ⁺

12		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C7	508.2 [M+H] ⁺
13		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	C7	508.2 [M+H] ⁺

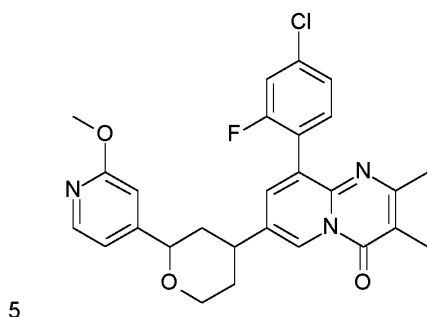
Example 14: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one



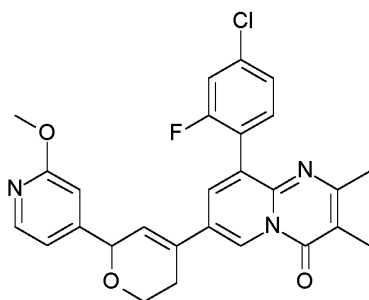
- 5 To a solution of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B3, 100 mg, 0.30 mmol) in acetonitrile (3 ml) was added 2-(1-methylpyrazol-4-yl)morpholine (Intermediate C1, 49 mg, 0.30 mmol) and potassium carbonate (191 mg, 0.90 mmol) and the mixture was stirred at 80 °C for 4 h. The reaction mixture was
- 10 washed with water and brine, dried over Na₂SO₄ and concentrated to dryness. The residue was

purified by flash chromatography (silica gel, methanol in dichloromethane 0-10%) to yield the title compound (19 mg, 14% yield) as light brown solid, MS m/z : 469.2 $[M+H]^+$, ESI pos.

Example 15: 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one



Step 1: 9-(4-chloro-2-fluoro-phenyl)-7-[6-(2-methoxy-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one



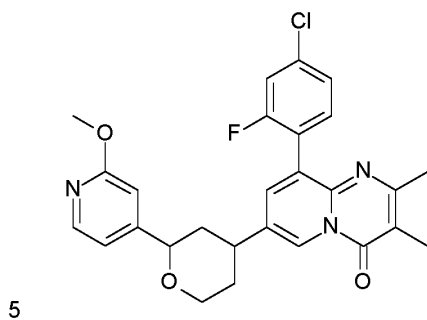
To a solution of 7-bromo-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (Intermediate B1, 50 mg, 0.131 mmol) in 1,4-dioxane (1.5 ml) was added 2-methoxy-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine (Intermediate C8, 54 mg, 0.170 mmol) followed by a solution of potassium carbonate (54 mg, 0.393 mmol) in water (0.30 ml). The mixture was flushed with argon for 5 min followed by addition of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (11 mg, 0.013 mmol, 0.10 eq). Flushing with argon was continued for 5 min, then the tube was sealed and warmed to 60 °C for 1 h. Saturated NaHCO_3 solution (10 ml) was added and the mixture was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0-70% ethyl acetate in heptane) to give 9-(4-chloro-2-fluoro-

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phenyl)-7-[6-(2-methoxy-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (51 mg, 79% yield) as light brown solid, MS m/z: 492.3 [M+H]⁺, ESI pos.

Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one

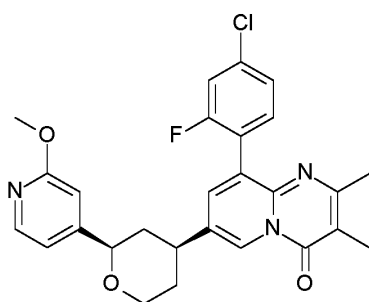


A solution of 9-(4-chloro-2-fluoro-phenyl)-7-[6-(2-methoxy-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (47 mg, 0.096 mmol) in ethyl acetate (2 ml) was purged and backfilled with nitrogen (3 x). Then palladium (10% on activated carbon, 10 mg, 0.0096 mmol, 0.10 eq) was added. The mixture was purged and backfilled with hydrogen and stirred at 22 °C overnight with a balloon filled with hydrogen attached. The catalyst was filtered off, washed with ethyl acetate (3 x 5 ml) and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0-100% ethyl acetate in heptane) to give the title compound (44 mg, 93% yield) as light yellow oil, MS m/z: 494.3 [M+H]⁺, ESI pos.

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Example 16: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one

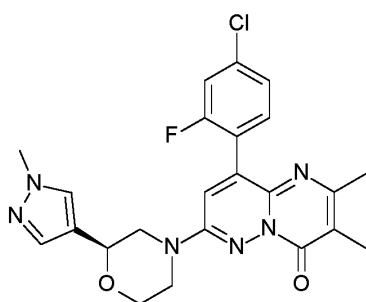
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Racemic 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one was separated by chiral SFC (column IB, 250 mm × 20

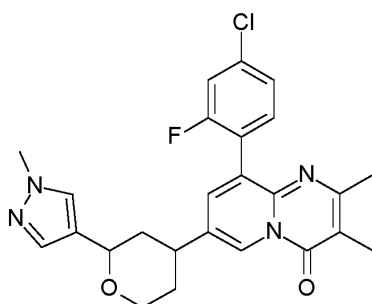
mm, 5 μ m, 30% methanol) to give 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 2.582 min, white powder, MS m/z: 494.4 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

- 5 **Example 17:** 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one



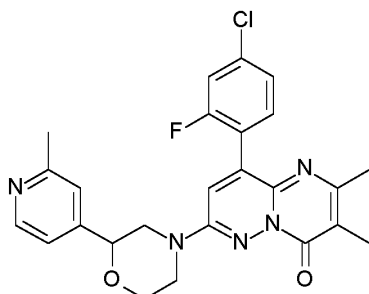
- Racemic 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one was separated by chiral SFC (column OD-H, 250 mm $\times$ 20 mm, 5 μ m, 25% methanol + 0.2% diethylamine) to give 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one as second eluting enantiomer with retention time 4.033 min, light yellow solid, MS m/z: 469.2 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

- Example 18:** 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one



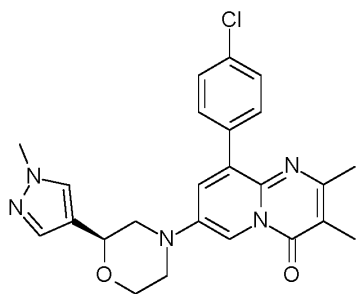
The title compound was prepared in analogy to Example 15 from Intermediate C9 instead of Intermediate C8. Light yellow powder, MS m/z: 467.3 $[M+H]^+$, ESI pos.

Example 19: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one



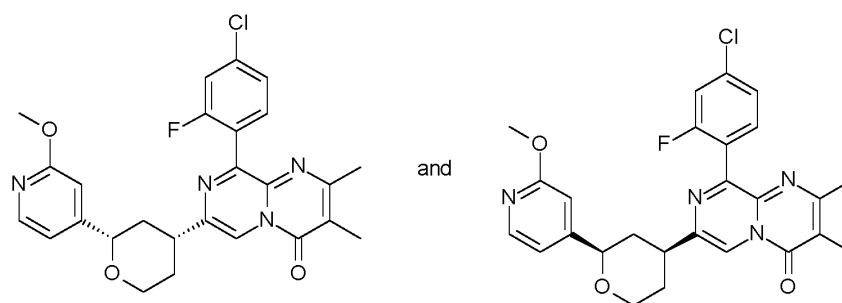
The title compound was prepared in analogy to Example 14 from Intermediate C2 instead of
5 Intermediate C1. Light brown solid, MS m/z: 480.2 [M+H]⁺, ESI pos.

Example 20: 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Example 1 from Intermediate B4 instead of
10 Intermediate B1. Light yellow powder, MS m/z: 450.4 [M+H]⁺, ESI pos.

Example 21 and Example 22: 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



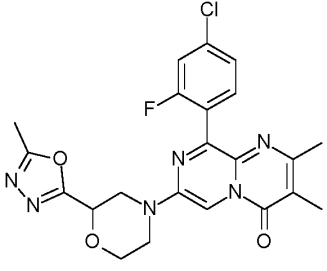
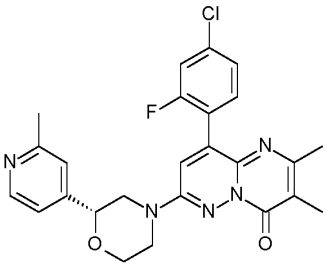
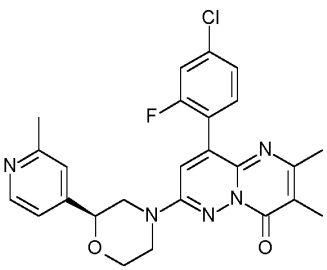
The title compounds was prepared in analogy to Example 15 from Intermediate B2 instead of Intermediate B1. The formed racemic 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one was separated by

5 chiral SFC (column Chiralpak Cel-SZ, 250 mm × 20 mm, 5 μm, 40% methanol) to give 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 3.63 min, white powder, MS m/z: 495.4 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one as

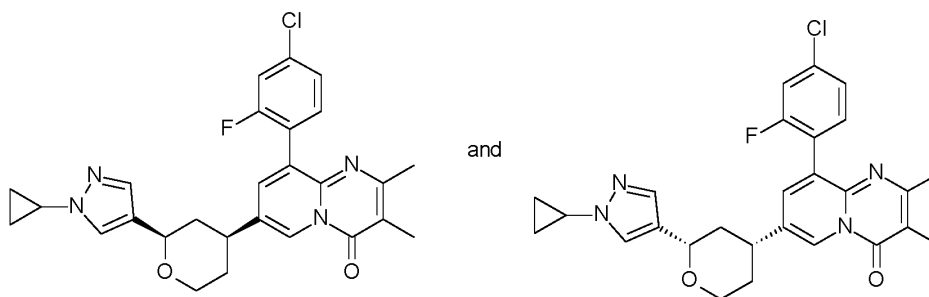
10 second eluting enantiomer with retention time 4.04 min, white powder, MS m/z: 495.4 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

The following **Examples 23 to 26** were prepared in analogy to Examples 4 and 5 by starting from the indicated intermediates. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
23		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B1 and C7	508.3 [M+H] ⁺

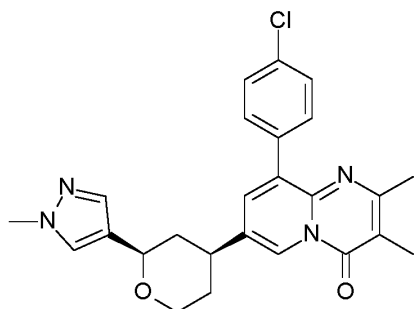
24		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C10	471.3 [M+H] ⁺
25		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one	B3 and C2	480.2 [M+H] ⁺
26		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one	B3 and C2	480.2 [M+H] ⁺

Example 27 and Example 28: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one



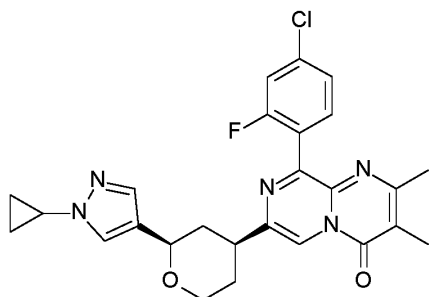
The title compounds was prepared in analogy to Example 15 from Intermediate C11 instead of Intermediate C8. The racemate was separated by chiral SFC (column Chiral IJ, 250 mm × 20 mm, 5 μm, 20% methanol) to give 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 1.921 min, white powder, MS m/z: 493.4 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one as second eluting enantiomer with retention time 2.398 min, white powder, MS m/z: 493.4 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 29: 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Example 15 using Intermediate B4 instead of Intermediate B1 and using Intermediate C9 instead of Intermediate C8. The racemate was separated by chiral SFC (Chiralpak Cel-SZ, 250 mm × 20 mm, 5 μm, 53% methanol) to give 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 2.809 min, white powder, MS m/z: 449.4 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 30: 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



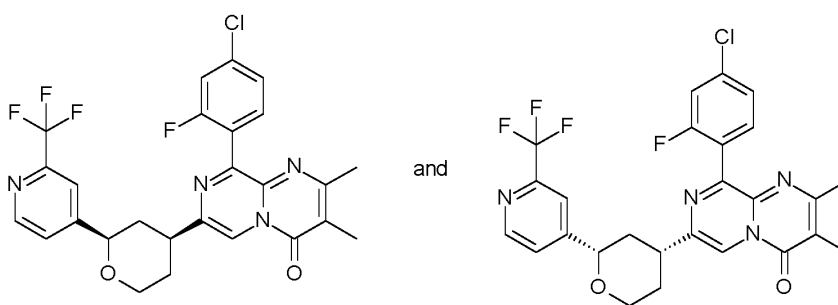
The title compound was prepared in analogy to Example 15 using Intermediate B2 instead of Intermediate B1 and using Intermediate C11 instead of Intermediate C8. Light yellow powder, MS m/z: 494.4 [M+H]⁺, ESI pos. The compound is a racemic mixture.

The following **Examples 31 to 33** were prepared in analogy to Examples 4 and 5 by starting from the indicated intermediates. Example 32 is a racemate, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
31		9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B5 and (+)-C1	504.2 [M+H] ⁺

32		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one	B1 and C7	508.1 [M+H] ⁺
33		9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B6 and (+)C1	487.3 [M+H] ⁺

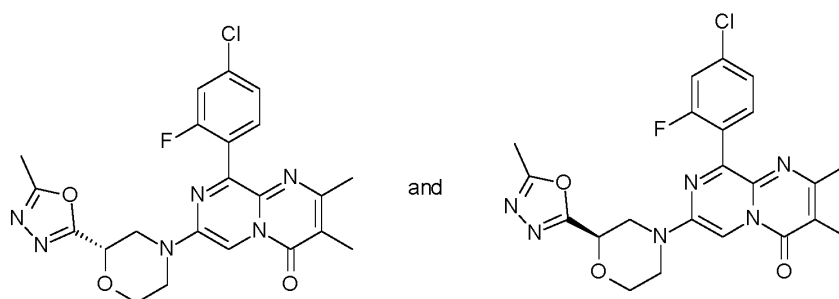
Example 34 and Example 35: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



The title compounds was prepared in analogy to Example 15 using Intermediate B2 instead of Intermediate B1 and Intermediate C13 instead of intermediate C8. The formed racemate was separated by chiral SFC (column Chiral IB, 250 mm × 20 mm, 5 μm, 25% methanol) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer with

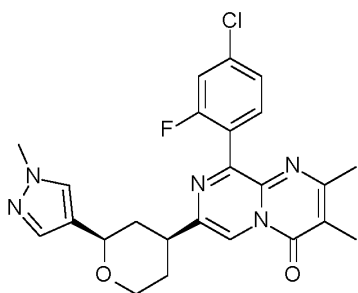
retention time 1.875 min, light yellow oil, MS m/z : 533.4 $[M+H]^+$, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one as second eluting enantiomer with retention time 2.094 min, light yellow oil, MS m/z : 533.4 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 36 and Example 37: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one



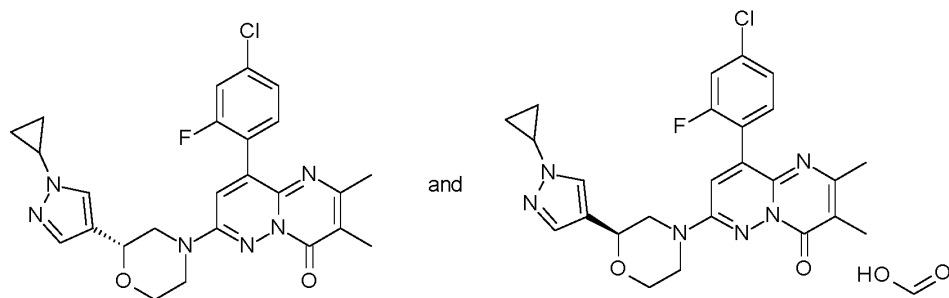
Racemic 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one was separated by chiral SFC (column Chiral AD-H, 250 mm $\times$ 20 mm, 5 μ m, 40% methanol) to give 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 3.25 min, light brown solid, MS m/z : 471.4 $[M+H]^+$, ESI pos. and 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one as second eluting enantiomer with retention time 3.82 min, light brown solid, MS m/z : 471.3 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 38: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Example 15 using Intermediate B2 instead of Intermediate B1 and Intermediate C9 instead of Intermediate C8. Light yellow solid, MS m/z : 468.3 $[M+H]^+$, ESI pos.

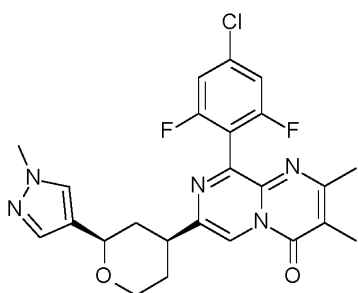
- 5 **Example 39 and Example 40:** 9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one formate



- 10 To a solution of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B3, 97 mg, 0.29 mmol) in dimethylsulfoxide (10 mL) was added diisopropyl ethylamine (0.15 ml, 0.86 mmol) and 2-(1-cyclopropylpyrazol-4-yl)morpholine (Intermediate C5, 166 mg, 0.86 mmol) and the mixture was stirred at 120 °C for 16 h. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (20 ml x 2). The combined
- 15 organic layers were washed with brine (20 ml x 2) and dried over Na_2SO_4 , then concentrated in vacuum. The residue was purified preparative HPLC (column: Phenomenex Luna C18, 150 x 25 mm x 10 μ m, water + 0.225% formic acid / acetonitrile, flow rate 25 ml/min) and extracted with ethyl acetate to give 9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (100 mg) as yellow oil. This racemate was
- 20 separated by chiral SFC (column Chiralpak AD, 250 mm x 30 mm, 10 μ m, 30% ethanol) to give

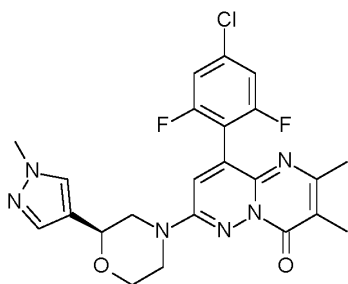
9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one as first eluting enantiomer (37 mg, 37% yield) as off-white solid, MS m/z: 495.1 $[M+H]^+$, ESI pos. and 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one formate as second eluting enantiomer (34 mg, 34% yield) as off-white solid, MS m/z: 495.1 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 41: 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one



10 The title compound was prepared in analogy to Example 15 using Intermediate B6 instead of Intermediate B1 and Intermediate C9 instead of Intermediate C8. Light yellow solid, MS m/z: 486.3 $[M+H]^+$, ESI pos.

Example 42: 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one

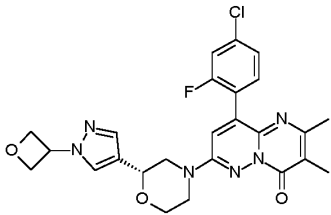
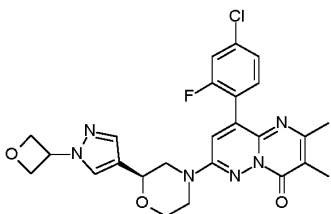


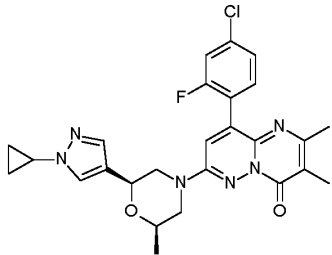
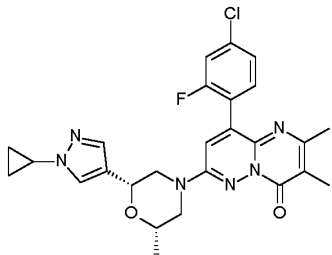
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To a solution of 7-chloro-9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B7, 50 mg, 0.14 mmol) in acetonitrile (1.4 ml) were added (2S)-2-(1-methylpyrazol-4-yl)morpholine (Intermediate (+)-C1, 23.5 mg, 0.140 mmol) and a 3 M aqueous solution of tripotassium phosphate (3.25M, 0.140 mL, 0.421 mmol). The mixture was

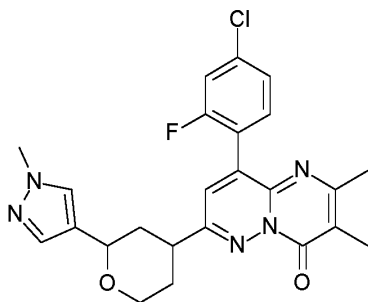
stirred for 6 h at 80 °C. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude material was purified by flash chromatography (silica gel, ethyl acetate in heptane 0-100% followed by methanol in dichloromethane 0-6%) to obtain the title compound (38 mg, 56%
 5 yield) as light brown solid, MS m/z: 487.3 [M+H]⁺, ESI pos.

The following **Examples 43 to 46** were prepared in analogy to Examples 39 and 40 by starting from the indicated intermediates. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
43		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one	B3 and C15	511.2 [M+H] ⁺
44		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one	B3 and C15	511.2 [M+H] ⁺

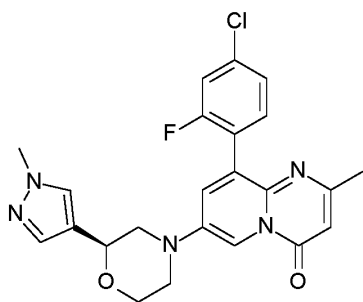
45		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C7	509.2 [M+H] ⁺
46		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C7	509.2 [M+H] ⁺

Example 47: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



- 5 The title compound was prepared in analogy to Example 15 using Intermediate B3 instead of Intermediate B1 and Intermediate C9 instead of Intermediate C8. Yellow solid, MS m/z: 468.3 [M+H]⁺, ESI pos.

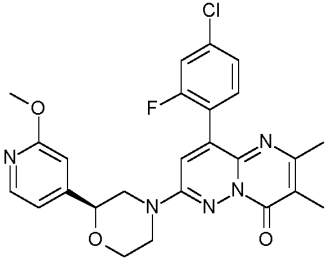
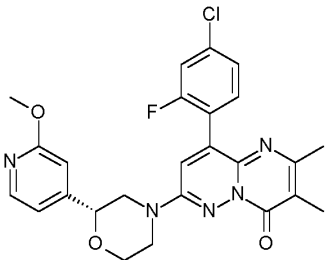
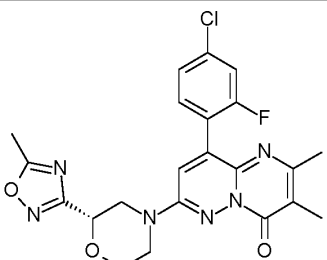
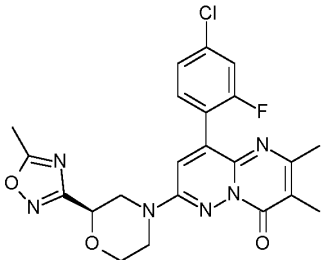
Example 48: 9-(4-chloro-2-fluoro-phenyl)-2-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one

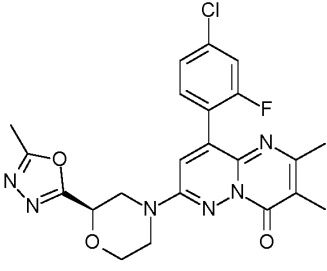
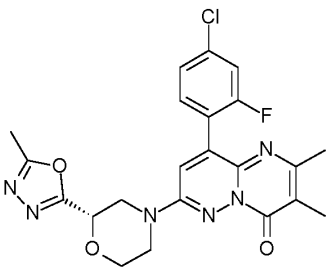


The title compound was prepared in analogy to Example 1 using Intermediate B8 instead of Intermediate B1. Yellow solid, MS m/z : 454.4 $[M+H]^+$, ESI pos.

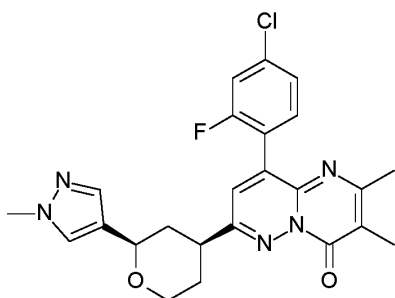
5 The following **Examples 49 to 56** were prepared in analogy to Examples 42 by starting from the indicated intermediates. Chiral separation was performed as described for Examples 4 and 5. The absolute stereochemistry was assigned arbitrarily.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
49		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one	B3 and C12	471.3 $[M+H]^+$
50		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one	B3 and C10	471.4 $[M+H]^+$

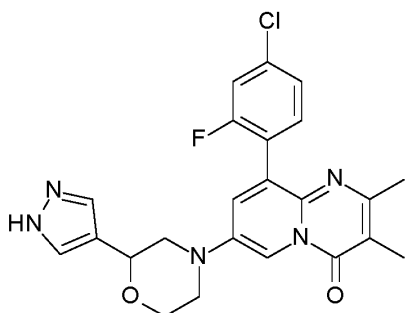
51		9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C4	496.1 [M+H] ⁺
52		9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C4	496.1 [M+H] ⁺
53		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one	B3 and C12	471.3 [M+H] ⁺
54		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one	B3 and C12	471.3 [M+H] ⁺

55		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one	B3 and C10	471.3 [M+H] ⁺
56		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one	B3 and C10	471.3 [M+H] ⁺

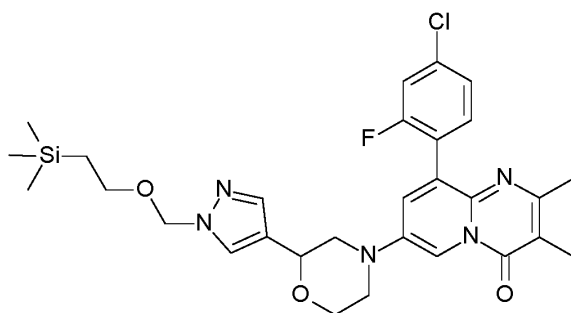
Example 57: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one



- 5 Racemic 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one (Example 47) was separated by chiral SFC (Chiral NR, 250 mm × 20 mm, 5 μm, 50% methanol) to give the title compound as second eluting enantiomer with retention time 5.406 min, light brown solid, MS m/z: 468.4 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.
- 10 **Example 58:** 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one

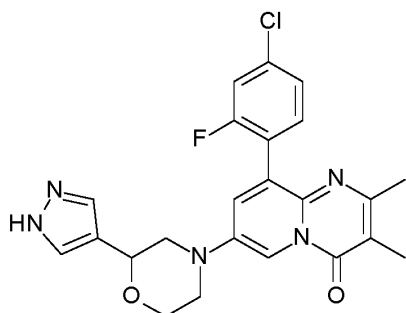


Step 1: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one



- 5 To a solution of 7-bromo-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one (Intermediate B1, 400 mg, 1.05 mmol) in t-amyl alcohol (4.0 ml) was added trimethyl-[2-
[(4-morpholin-2-ylpyrazol-1-yl)methoxy]ethyl]silane (Intermediate C22, 356 mg, 1.26 mmol), cesium carbonate (1.024 g, 3.14 mmol) and Xphos Pd G4 (90 mg, 0.1 mmol, 0.1 eq). Then the mixture was degassed by nitrogen with three times and stirred at 90 °C for 16 h under nitrogen
10 atmosphere. The reactiodimethylsin mixture was added into water (40 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (20 ml x 3) and dried over Na₂SO₄. The residue was purified by column chromatography (silica, ethyl acetate / petroleum ether = 1:1) to obtain 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (220 mg,
15 36% yield) as light yellow oil, MS m/z: 584.4 [M+H]⁺, ESI pos.

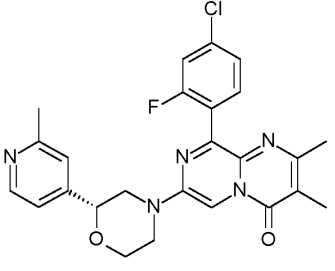
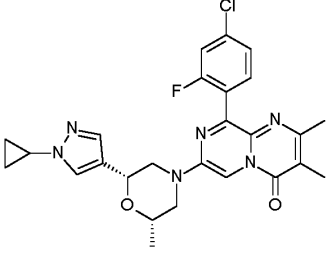
Step 2: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one



To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(2-trimethylsilylethoxy-methyl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (210 mg, 0.36 mmol) in dichloromethane (10 ml) trifluoroacetic acid (5.0 ml, 67 mmol) was added and the mixture was stirred at 20 °C for 1 h. The reaction mixture was added water (40 ml) and aqueous sodium carbonate solution was added to the reaction to adjust pH to 7-8. It was extracted three times with ethyl acetate, and the combined extracts were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by reversed phase chromatography (column: spherical C18, 20-45 mm 100 Å, mobile phase: water / 0.1% formic acid - acetonitrile, 0-100%, flow rate 80 ml/min) to afford the title compound (120 mg, 74% yield) as light yellow solid, MS m/z: 454.2 [M+H]⁺, ESI pos.

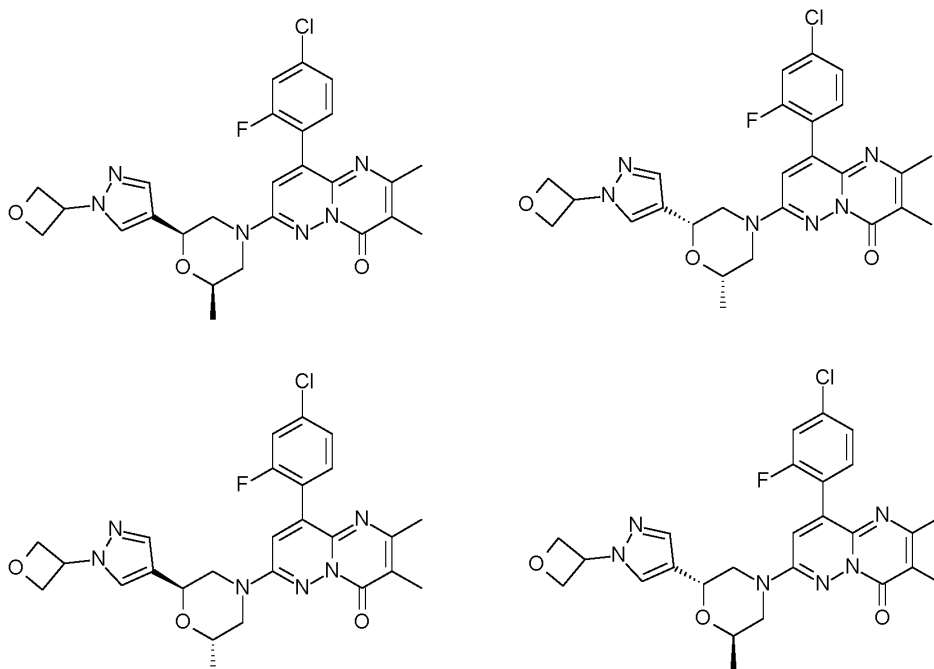
The following **Examples 59 to 61** were prepared in analogy to Examples 4 and 5 by starting from the indicated intermediates, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
59		9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B9 and (+)-C1	451.3 [M+H] ⁺

60		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C2	480.1 [M+H] ⁺
61		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C7	509.3 [M+H] ⁺

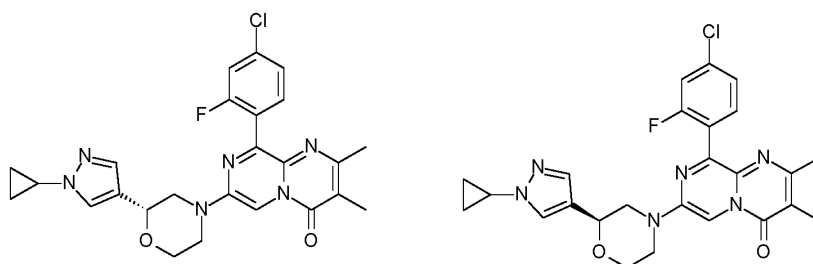
Example 62 and Example 63 and Example 64 and Example 65 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-

methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one



The title compounds were prepared in analogy to Example 39 and 40 using Intermediate C14 instead of Intermediate C5. All white solids with MS m/z : 525.2 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Example 66 and Example 67 9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one

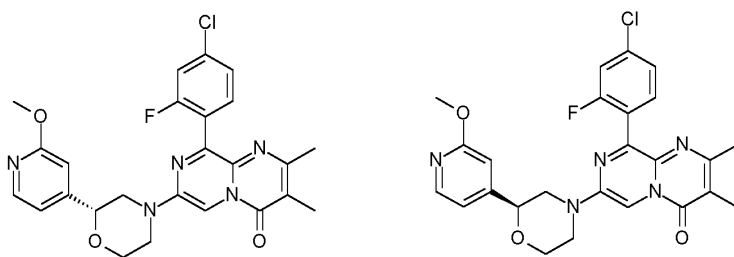


To a solution of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (Intermediate B2, 150 mg, 0.44 mmol) in 1,4-dioxane (5 ml) was added 2-(1-

cyclopropylpyrazol-4-yl)morpholine (Intermediate C5, 86 mg, 0.44 mmol), cesium carbonate (433 mg, 1.33 mmol) and Xantphos-Pd-G4 (43 mg, 0.04 mmol, 0.1 eq) in a glove-box and the mixture was stirred at 90 °C for 16 h. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (20 ml x 3). The combined layers were washed with brine (20 ml),
 5 dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (column: Phenomenex Luna C18 150 x 25 mm x 10 µm, mobile phase: water / 0.25% formic acid - acetonitrile, 0-100%, flow rate 25 ml/min) to give racemic 9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one. This material was separated into enantiomers by chiral SFC
 10 (Daicel Chiralpak AD, 250 mm x 30 mm, 10 µm, CO₂ / ethanol with 0.1% ammonium hydroxide) to obtain 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (20 mg, 30% yield) and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (22 mg, 32% yield) as yellow solids, MS m/z: 495.1 [M+H]⁺,
 15 ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 68 and Example 69 9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one

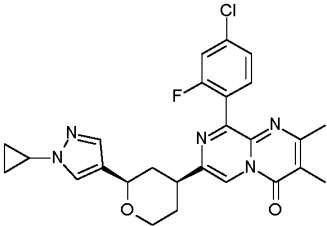
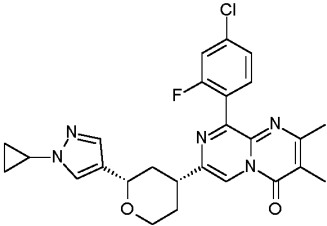
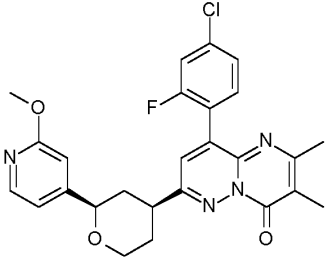
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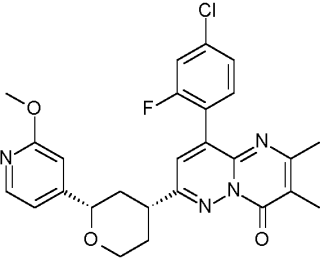


The title compounds were prepared in analogy to Example 66 and 67 using Intermediate C4 instead of Intermediate C5. Yellow solids with MS m/z: 496.1 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

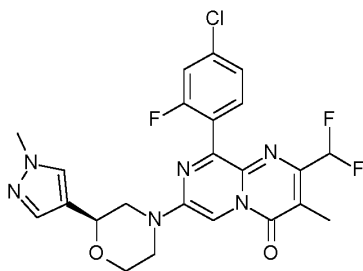
The following **Examples 70 to 73** were prepared in analogy to Examples 15 by starting from the
 25 indicated intermediates. Chiral separation was performed as described for Examples 34 and 35.

The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
70		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C11	494.2 [M+H] ⁺
71		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C11	494.2 [M+H] ⁺
72		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C8	495.3 [M+H] ⁺

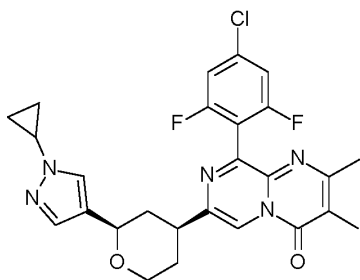
73		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C8	495.3 [M+H] ⁺
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Example 74: 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrazino[1,2-a]pyrimidin-4-one



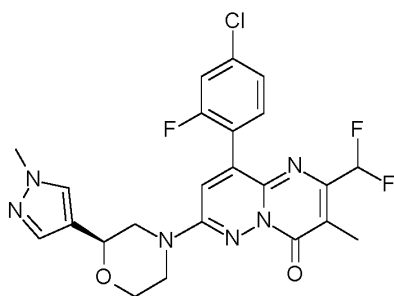
- 5 To a solution of (2S)-2-(1-methylpyrazol-4-yl)morpholine (Intermediate (+)-C1, 76 mg, 0.45 mmol) in ethanol (4.5 ml) 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one (Intermediate B10, 75 mg, 0.16 mmol) was added and the mixture was placed in a microwave for 5 h at 150 °C. The volatiles were evaporated and the residue was purified by chromatography (silica gel, 0 to 100% ethyl acetate in heptane) to yield
- 10 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrazino[1,2-a]pyrimidin-4-one (9 mg, 9% yield) as yellow powder, MS m/z: 505.4 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 75: 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one



The title compound was prepared in analogy to Example 15 using Intermediate B6 instead of Intermediate B1 and Intermediate C11 instead of Intermediate C8. Yellow solid, MS m/z : 512.3 $[M+H]^+$, ESI pos.

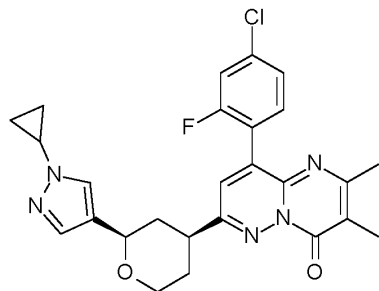
- 5 **Example 76:** 9-(4-chloro-2-fluorophenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one



The title compound was prepared in analogy to Example 42 using Intermediate B11 instead of Intermediate B7. White solid, MS m/z : 505.4 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

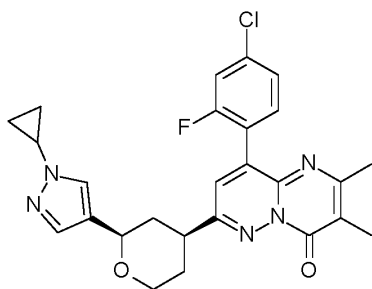
10

- Example 77:** 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one



The title compounds was prepared in analogy to Example 15 using Intermediate B3 instead of Intermediate B1 and Intermediate C11 instead of intermediate C8. Yellow solid, MS m/z: 494.3 $[M+H]^+$, ESI pos.

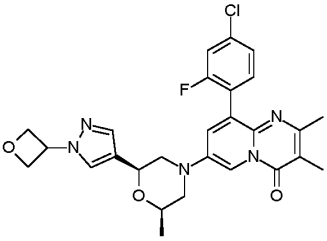
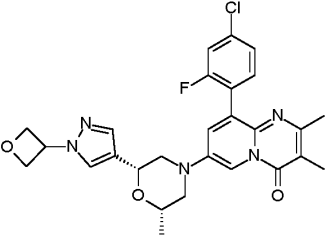
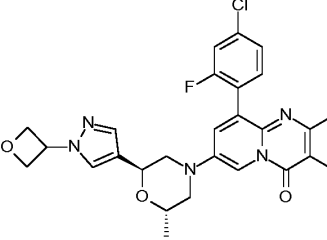
Example 78: 9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-
5 2,3-dimethylpyrimido[1,2-b]pyridazin-4-one



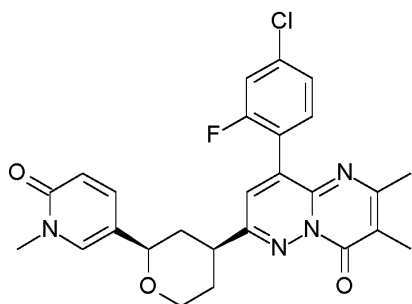
Racemic 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one (Example 77) was separated by chiral SFC
(Column chiral OD-H, 5 μ m, 250 x 20 mm, 33% methanol) to give the title compound as first
10 eluting enantiomer with retention time 3.184 min, yellow solid, MS m/z: 494.1 $[M+H]^+$, ESI pos.
The absolute stereochemistry was assigned arbitrarily.

The following **Examples 79 to 82** were prepared in analogy to Examples 39 and 40 by starting from the indicated intermediates. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
79		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-	B1 and C15	511.2 $[M+H]^+$

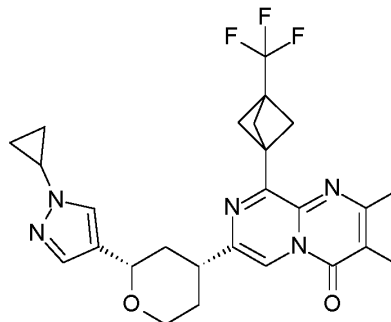
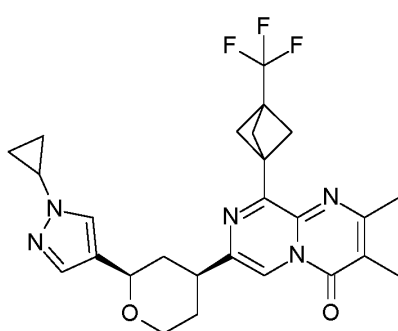
		yl]pyrido[1,2-a]pyrimidin-4-one		
80		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B1 and C14	524.2 [M+H] ⁺
81		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B1 and C14	524.2 [M+H] ⁺
82		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one	B1 and C14	524.2 [M+H] ⁺

Example 83: 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methyl-6-oxopyridin-3-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one



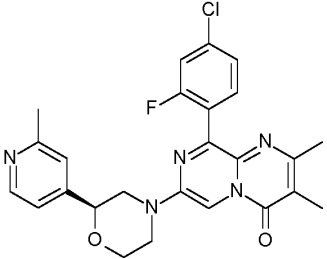
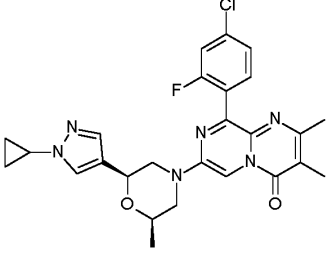
The title compound was prepared in analogy to Example 15 from Intermediate B3 instead of Intermediate B1 and intermediate C16 instead of C8. Light yellow solid, MS m/z : 495.3 $[M+H]^+$, ESI pos.

- 5 **Example 84 and Example 85:** 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one and 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one

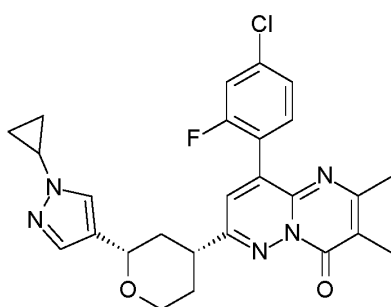


- 10 The title compounds were prepared in analogy to Example 15 from Intermediate B12 instead of Intermediate B1 and intermediate C11 instead of C8. Chiral separation was performed as described for Examples 34 and 35. The absolute stereochemistry was assigned arbitrarily. Light yellow solids, MS m/z : 500.2 $[M+H]^+$, ESI pos.

- 15 The following **Examples 86 to 87** were prepared in analogy to Examples 4 and 5 by starting from the indicated intermediates. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
86		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C2	480.1 [M+H] ⁺
87		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C7	509.3 [M+H] ⁺

Example 88: 9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one

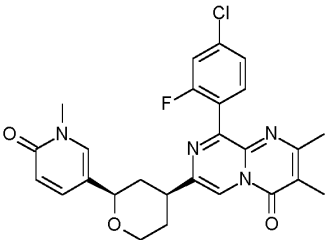
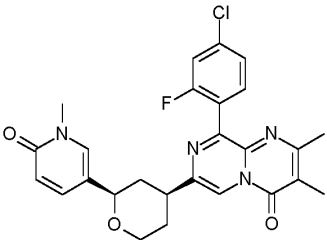
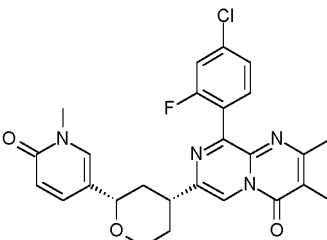


- 5 Racemic 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one (Example 77) was separated by chiral SFC (Column chiral OD-H, 5 μ m, 250 x 20 mm, 33% methanol) to give the title compound as second

eluting enantiomer with retention time 4.030 min, yellow solid, MS m/z : 494.1 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

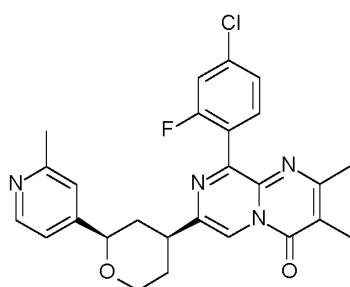
The following **Examples 89 to 91** were prepared in analogy to Example 15 by starting from the indicated intermediates. Chiral separation was performed as described for Examples 34 and 35.

- 5 The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

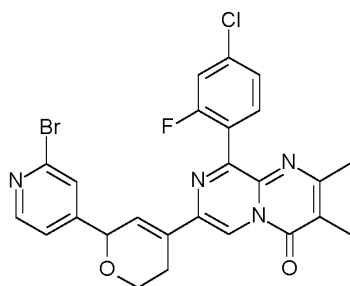
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
89		9-(4-chloro-2-fluorophenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	B2 and C16	495.3 $[M+H]^+$
90		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	B2 and C16	495.3 $[M+H]^+$
91		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	B2 and C16	495.3 $[M+H]^+$

		pyrazino[1,2-a]pyrimidin-4-one		
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Example 92: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



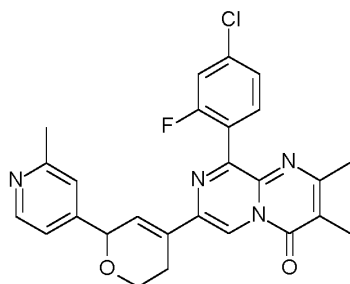
- 5 Step 1: 7-[6-(2-bromo-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



- To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one (Intermediate B13, 1.8 g, 4.2 mmol) in 1,4-dioxane (60 ml) and water (10 ml) were added under argon [6-(2-bromo-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (Intermediate C17, 1.63 g, 4.2 mmol), potassium carbonate (1.74 g, 12.6 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (347 mg, 0.420 mmol, 0.10 eq) and the mixture was heated to 60 °C and stirred for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0 to 50% ethyl acetate in heptane) to afford 7-[6-(2-bromo-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-9-(4-

chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (710 mg, 30% yield) as light yellow solid, MS m/z: 541.2 $[M-H]^+$, ESI neg.

Step 2: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(2-methyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one

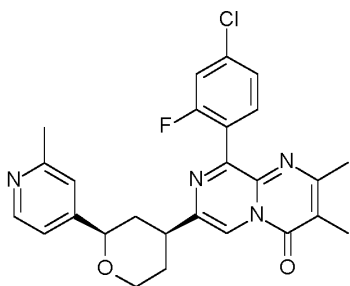


5

To a solution of 7-[6-(2-bromo-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (710 mg, 1.31 mmol) in 1,4-dioxane (12 ml) were added under argon 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M solution in tetrahydrofuran, 0.450 ml, 1.58 mmol), potassium carbonate (543 mg, 3.93 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (108 mg, 0.131 mmol, 0.10 eq) and the mixture was heated to 90 °C and stirred for 2 h. After cooling to room temperature, the reaction mixture was filtered over Celite and washed with ethyl acetate. The filtrate was poured into water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate + ethanol 3/1 - heptane 0 to 50%) to afford 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(2-methyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (482 mg, 73% yield) as orange foam, MS m/z: 477.2 $[M+H]^+$, ESI pos.

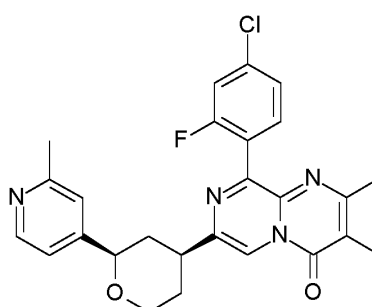
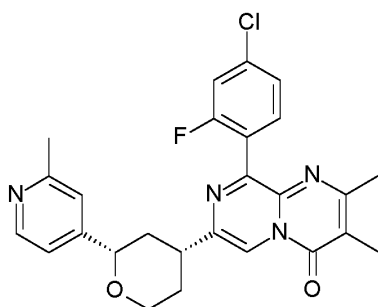
Step 3: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one

20



In a 100 ml round-bottomed flask 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(2-methyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (482 mg, 1.01 mmol) was dissolved in methanol (25 ml). The mixture was degassed with argon, then palladium on charcoal (10%, 108 mg) was added and the reaction mixture was stirred under hydrogen gas atmosphere (balloon) at room temperature for 2 h. The reaction mixture was filtered over Dicalite, washed with ethyl acetate and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, ethyl acetate + ethanol 3/1 - Heptane 0 to 50%), followed by a second chromatography (HP C18 RediSep Gold, 0% to 70% acetonitrile in water) to afford the title compound (210 mg, 43%) as yellow foam, MS m/z : 479.2 $[M+H]^+$, ESI pos.

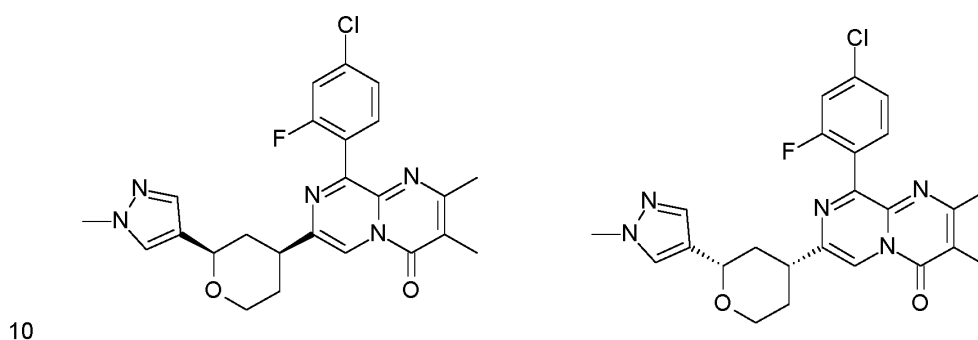
Example 93 and Example 94: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



Racemic 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (Example 92) was separated by chiral SFC (Column chiral IH, 5 μ m, 250 x 20 mm, 22% methanol + 0.2% diethylamine) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-

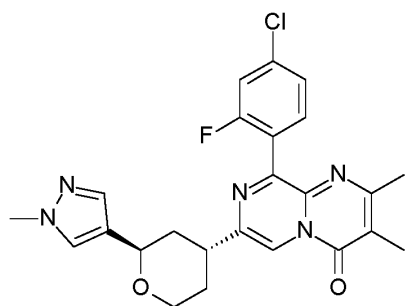
yl]pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer with retention time 1.571 min and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one as second eluting enantiomer with retention time 2.185 min, light yellow solids with MS m/z: 479.3 [M+H]⁺, ESI pos. The absolute stereochemistry was
5 assigned arbitrarily.

Example 95 and Example 96: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



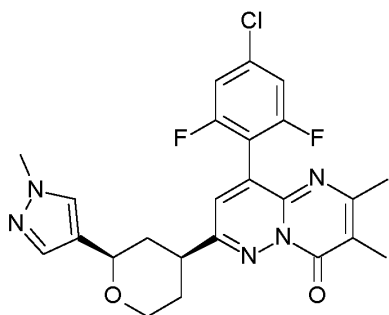
Racemic 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one (Example 38) was separated by chiral SFC (Column Daicel Chiralpak, 250 x 30 mm, 10 μm, ethanol + 0.1% ammonium hydroxide) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one as second eluting enantiomer, white solids with MS m/z: 468.2 [M+H]⁺, ESI
15 pos. The absolute stereochemistry was assigned arbitrarily.

Example 97: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one
20



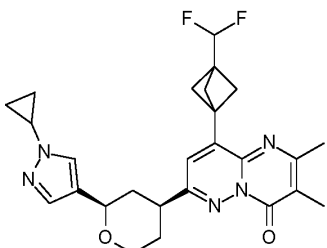
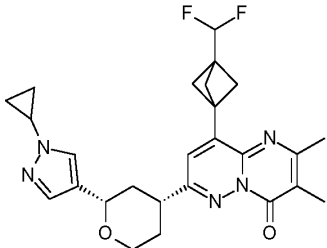
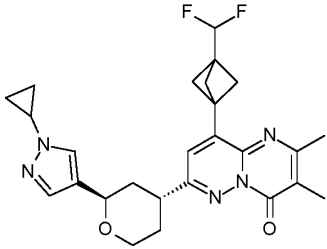
The title compound was isolated as minor diastereomer during the last step of the synthesis of Example 38, white solid, MS m/z : 468.2 $[M+H]^+$, ESI pos.

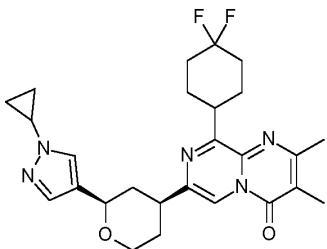
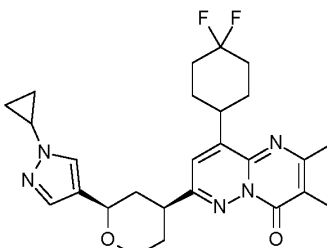
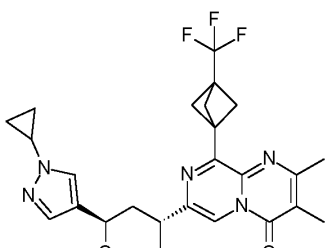
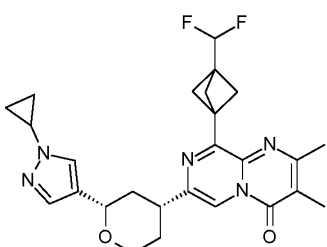
Example 98: 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one

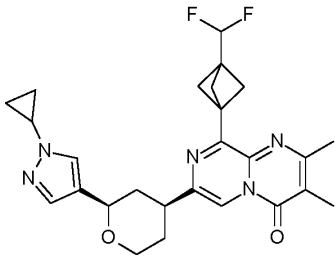
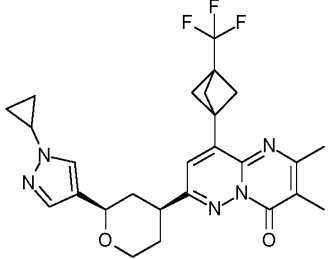
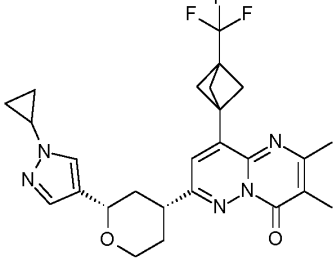
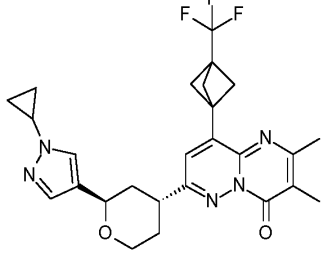


The title compound was prepared in analogy to Example 15 using Intermediate B7 instead of Intermediate B1 and Intermediate C9 instead of Intermediate C8. Chiral separation was performed by chiral SFC (column Chiral IK, 250 mm $\times$ 20 mm, 5 μ m, 37% methanol), second eluting enantiomer. Yellow solid, MS m/z : 486.2 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

The following **Examples 99 to 109** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Chiral separation was performed as described for Examples 95 and 96. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

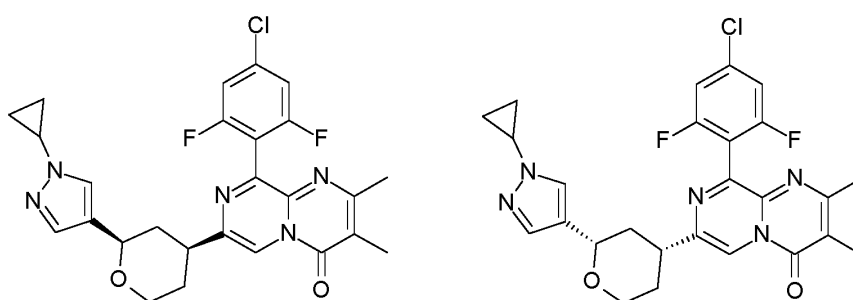
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
99		7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B14 and C11	482.3 [M+H] ⁺
100		7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B14 and C11	482.2 [M+H] ⁺
101		7-[(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B14 and C11	482.3 [M+H] ⁺

102		7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B15 and C11	484.3 [M+H] ⁺
103		7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C11	484.2 [M+H] ⁺
104		7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one	B12 and C11	500.2 [M+H] ⁺
105		7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B17 and C11	482.2 [M+H] ⁺

106		7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	B17 and C11	482.3 [M+H] ⁺
107		7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one	B18 and C11	500.2 [M+H] ⁺
108		7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one	B18 and C11	500.2 [M+H] ⁺
109		7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyr	B18 and C11	500.3 [M+H] ⁺

		imido[1,2-b]pyridazin-4-one		
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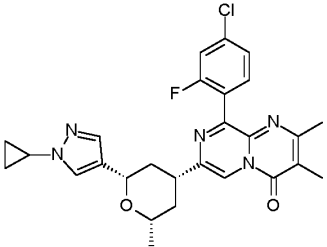
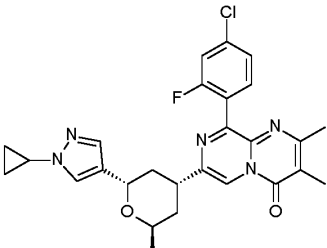
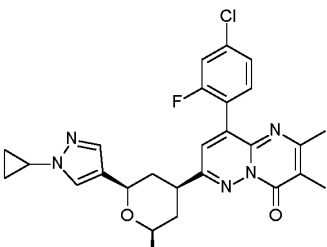
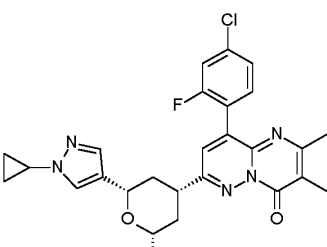
Example 110 and Example 111: 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

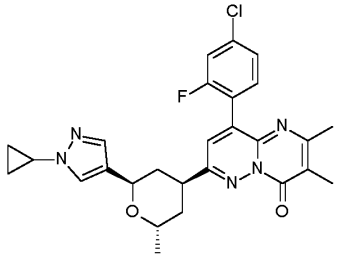
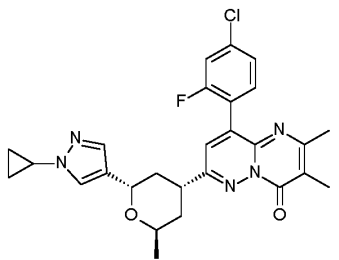
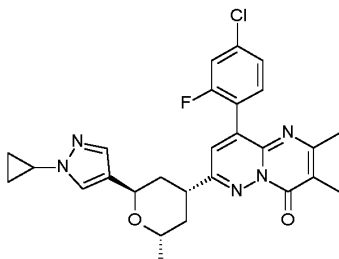
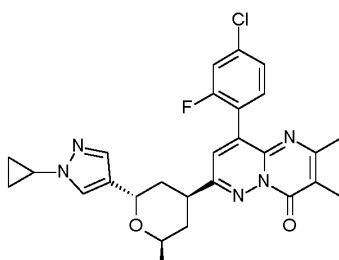


Racemic 9-(4-chloro-2,6-difluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (Example 75) was separated by chiral SFC (Column Chiral Cellulose-SZ, 250 x 20 mm, 5 μ m, 45% methanol) to 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer and 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one as second eluting enantiomer, light yellow solids with MS m/z : 512.3 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

The following **Examples 112 to 123** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Separation of diastereomers was performed by preparative HPLC (column Waters Xbridge C18, 150 x 25 mm x 10 μ m, 50-80% water-acetonitrile, 60 ml/min acetonitrile), chiral separation was performed by chiral SFC (Daicel Chiralpak IC 250 mm x 30 mm, 10 μ m, acetonitrile / methanol / 0.1% ammonium hydroxide, flow rate 80 ml/min). Relative stereochemistry was assigned by evaluation of 1H -NMR measurements, the absolute stereochemistry was assigned arbitrarily.

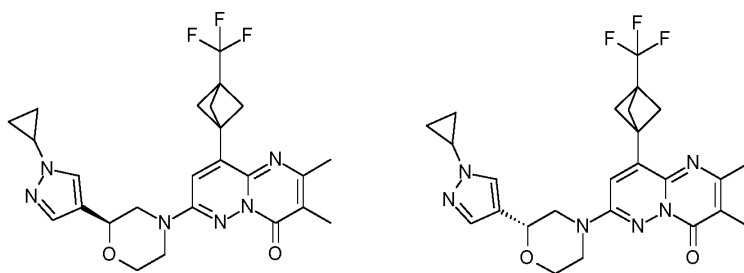
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
112		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C18	508.3 [M+H] ⁺
113		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C18	508.3 [M+H] ⁺
114		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C18	508.2 [M+H] ⁺
115		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C18	508.2 [M+H] ⁺

		dimethyl-pyrazino[1,2-a]pyrimidin-4-one		
116		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C18	508.2 [M+H] ⁺
117		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C18	508.1 [M+H] ⁺
118		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C18	508.2 [M+H] ⁺
119		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C18	508.2 [M+H] ⁺

120		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C18	508.1 [M+H] ⁺
121		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C18	508.1 [M+H] ⁺
122		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C18	508.1 [M+H] ⁺
123		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C18	508.1 [M+H] ⁺

Example 124 and Example 125 7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one and 7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one

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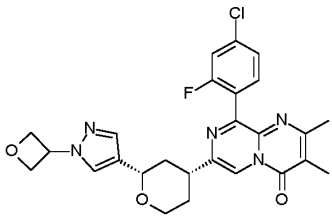
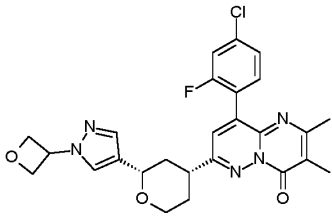
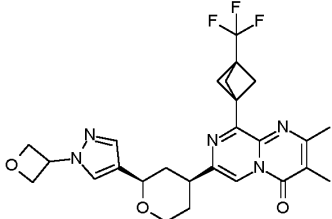
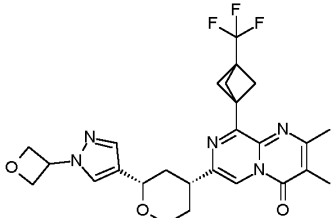


The title compounds were prepared in analogy to Example 39 and 40 using B18 instead of Intermediate B3. Light yellow solids with MS m/z : 501.3 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

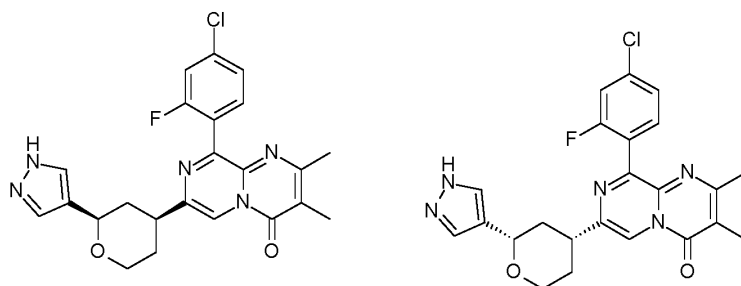
The following **Examples 126 to 130** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Chiral separation was performed as described for Examples 95 and 96. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

10

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
126		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C19	510.2 $[M+H]^+$

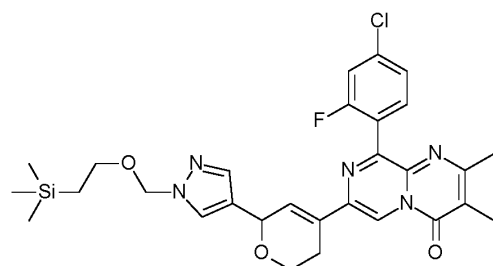
127		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C19	510.2 [M+H] ⁺
128		9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B3 and C19	510.2 [M+H] ⁺
129		2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one	B12 and C19	516.3 [M+H] ⁺
130		2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one	B12 and C19	516.3 [M+H] ⁺

Example 131 and Example 132 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



5

Step 1: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one

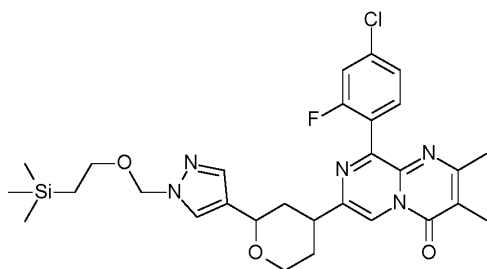


- 10 To a solution of trimethyl-[2-[[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyrazol-1-yl]methoxy]ethyl]silane (Intermediate C20, 600 mg, 1.48 mmol) in 1,4-dioxane (10 ml) and water (2 ml) was added 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (Intermediate B2, 1.25 g, 2.21 mmol), sodium carbonate (469 mg, 4.43 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-
- 15 palladium(II)dichloride dichloromethane complex (120 mg, 0.15 mmol, 0.1 eq). The reaction was degassed with nitrogen three times and the reaction mixture was stirred at 90 °C for 2 h under nitrogen atmosphere. After cooling to room temperature, the mixture was poured into water (100 ml). The aqueous layer was separated and extracted with ethyl acetate (50 ml x 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure.
- 20 The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate =

3 : 1 to 1 : 1) to afford 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (400 mg, 46% yield) as yellow oil, MS m/z: 582.2 [M+H]⁺, ESI pos.

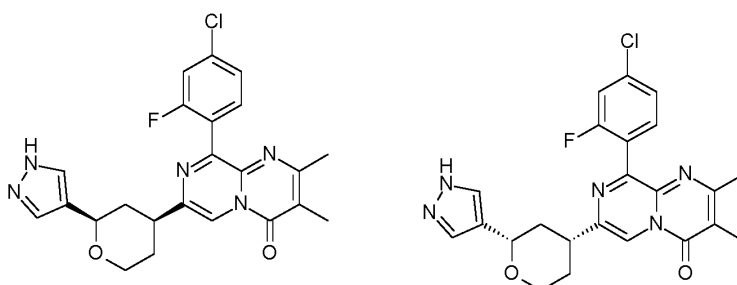
Step 2: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(2-

5 trimethylsilylethoxymethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



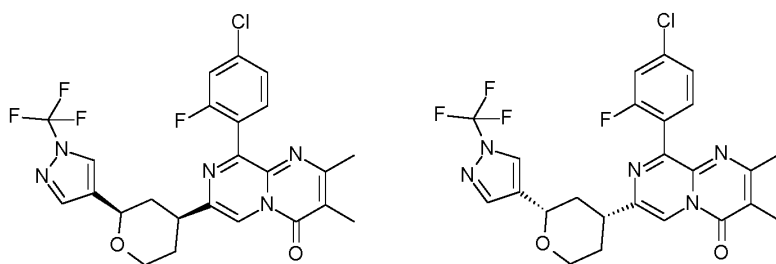
To a suspension of palladium on charcoal (10%, 73 mg) in ethyl acetate (1 ml) under nitrogen was added a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (400 mg, 0.69 mmol) in ethyl acetate (40 ml), magnesium oxide (277 mg, 6.87 mmol) and triethylamine (0.11 ml, 0.82 mmol). The mixture was degassed with hydrogen three times, then stirred at 30 °C for 1.5 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of diatomaceous earth to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (330 mg, 28% yield) as yellow oil, MS m/z: 584.2 [M+H]⁺, ESI pos.

Step 3: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(2-trimethylsilylethoxymethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (700 mg, 0.72 mmol) in dichloromethane (8 ml) was added trifluoroacetic acid (4.0 ml, 0.72 mmol) at room temperature, then the mixture was stirred at 25 °C for 2 h. The reaction mixture was carefully poured into aqueous sodium bicarbonate solution (20 ml) and extracted with dichloromethane (50 ml x 3). The combined layers were washed by brine (100 ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (column: Phenomenex Luna C18, 150 x 25 mm x 10 μm, mobile phase: water / 0.25% formic acid - acetonitrile, 0-100%, flow rate 25 ml/min) to afford the racemic compound (220 mg, 67% yield), from which 60 mg were separated by chiral SFC (Daicel Chiralpak OD 250 mm x 30 mm, 10 μm, acetonitrile / isopropanol / 0.1% ammonium hydroxide, flow rate 75 ml/min) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (first eluting enantiomer, 13 mg, 22% yield) as yellow solid, MS m/z: 454.1 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (second eluting enantiomer, 18 mg, 30% yield) as yellow solid. MS m/z: 454.1 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 133 and Example 134 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



Firstly, Rieke zinc is prepared by reduction of zinc chloride with lithium using a stoichiometric amount of naphthalene: in a pear-shaped flask naphthalene (179 mg, 1.4 mmol) and lithium (102 mg, 14.7 mmol) were placed. The flask was degassed three times with argon. To this mixture zinc chloride (1.9M in 2-methyltetrahydrofuran, 3.7 ml, 7 mmol) was added and the mixture was

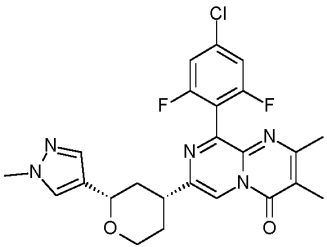
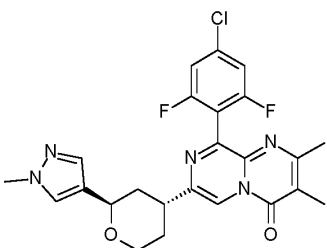
sonicated for 20 min and further stirred at room temperature overnight to afford a black suspension of highly reactive Rieke zinc.

4-(4-Bromotetrahydropyran-2-yl)-1-(trifluoromethyl)pyrazole (Intermediate C21, 600 mg, 2.01 mmol) was dissolved in tetrahydrofuran (extra dry, 2 ml) and argon was bubbled through the solution for 2-5 min. This solution was added dropwise at room temperature to the Rieke zinc suspension and the reaction mixture was stirred at room temperature for 3 h to afford a 0.23 M bromo-[2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]zinc solution (6.8 ml).

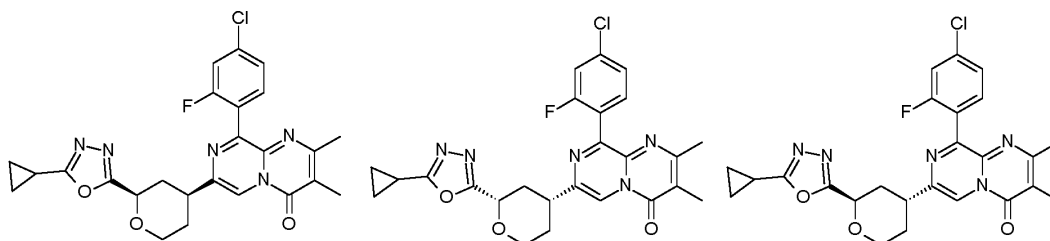
To a solution of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (Intermediate B2, 250 mg, 0.74 mmol) in tetrahydrofuran (extra dry, 2 ml) was added Xantphos palladacycle G3 (80 mg, 74 μ mol, 0.10 eq). The flask was degassed three times with argon, then bromo-[2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]zinc solution (0.23M, 5.1 ml, 1.18 mmol) was added. The mixture was stirred at room temperature for 30 min, then at 45 °C for 1.5 h. The reaction mixture was filtered through decalite and concentrated under reduced pressure. To the residue, saturated ammonium chloride solution was added and the resulting solution was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by reversed phase chromatography (column: YMC Triart C18, 100 mm x 30 mm, 5 μ m, mobile phase: water / 0.1% formic acid - acetonitrile, 0-100%) to afford 50 mg of racemic 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one. Separation by chiral SFC (column Chiral OD, 5 μ m, 250 x 20 mm, 20% methanol) obtained 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (first eluting enantiomer, 12 mg, 24%) as light yellow powder, MS m/z: 522.1 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (second eluting enantiomer, 12 mg, 24%) as light yellow powder, MS m/z: 522.1 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

The following **Examples 135 to 140** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Chiral separation was performed as described for Examples 95 and 96. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

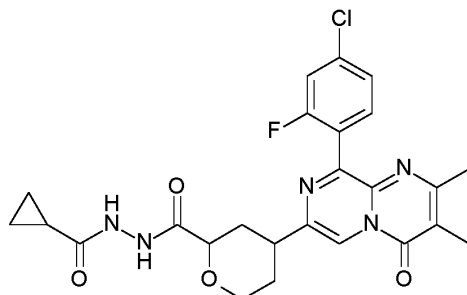
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
135		9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one	B11 and C11	530.1 [M+H] ⁺
136		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one	B11 and C11	530.1 [M+H] ⁺
137		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one	B11 and C11	530.1 [M+H] ⁺
138		9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]-pyrimido[1,2-b]pyridazin-4-one	B6 and C9	486.1 [M+H] ⁺

		yl]pyrazino[1,2-a]pyrimidin-4-one		
139		9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B6 and C9	486.1 [M+H] ⁺
140		9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B6 and C9	486.1 [M+H] ⁺

Example 141, Example 142 and Example 143 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

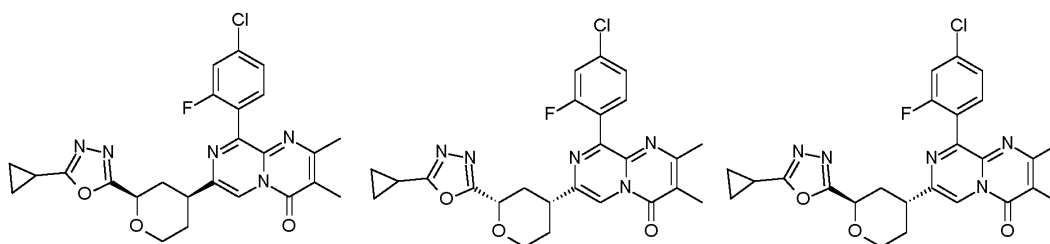


Step 1: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-N'-(cyclopropanecarbonyl)tetrahydropyran-2-carbohydrazide



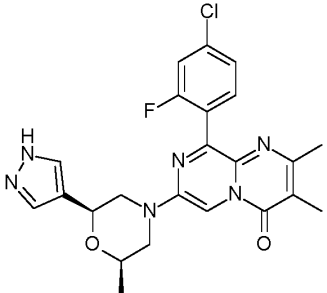
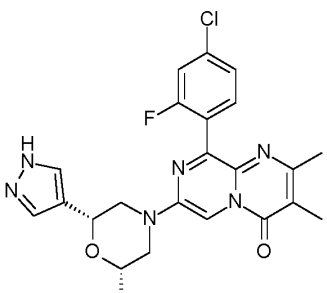
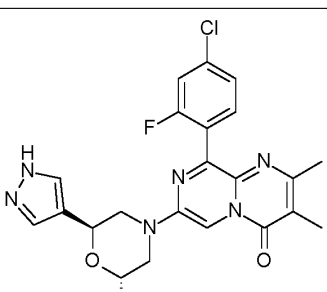
To a solution of 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylic acid (Intermediate D1, 100 mg, 0.23 mmol) in dimethylformamide (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (89 mg, 0.46 mmol), N,N-diisopropyl ethylamine (120 mg, 0.93 mmol), 1-hydroxybenzotriazole (31 mg, 0.23 mmol) and cyclopropane carbohydrazide (46 mg, 0.46 mmol) and the mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (30 ml x 3). The combined organic layers were washed with brine (30 ml x 3), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by preparative MPLC (column: Spherical C18, 20 - 45 µm, 100 Å; mobile phase: water + 0.1% formic acid / acetonitrile, flow rate 50 ml/min) to give 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-N'-(cyclopropanecarbonyl)tetrahydropyran-2-carbohydrazide (110 mg, 92% yield) as light yellow solid. MS m/z: 514.2 [M+H]⁺, ESI pos.

Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



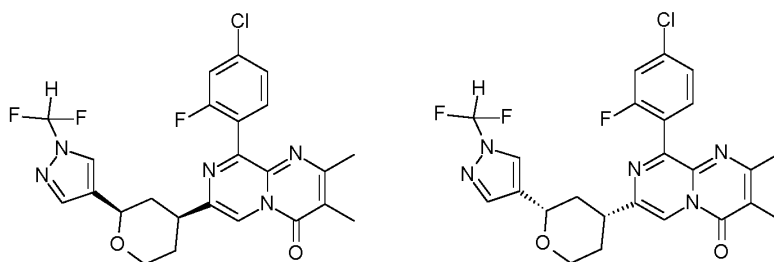
To a solution of 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-N'-(cyclopropanecarbonyl)tetrahydropyran-2-carbohydrazide (90 mg, 0.18 mmol) in tetrahydrofuran (3 ml) was added Burgess reagent (CAS 29684-56-8, 417 mg, 1.75 mmol) and the mixture was stirred at 130 °C for 0.5 h under microwave irradiation. The reaction mixture was poured into water (30 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were dried over Na₂SO₄, then concentrated in vacuum. The residue was purified by preparative HPLC (Phenomenex Luna, C18, 150 x 25 mm x 10 µm, mobile phase: water / 0.25% formic acid - acetonitrile, 0-82%, flow rate 25 ml/min) to afford the racemic compound which was separated by chiral SFC (Daicel Chiralpak AS 250 mm x 30 mm, 10 µm, acetonitrile / isopropanol / 0.1% ammonium hydroxide, flow rate 75 ml/min) to give 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (18 mg, 28% yield) as first eluting enantiomer, light yellow solid, MS m/z: 496.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (17 mg, 26% yield) as second eluting enantiomer, light yellow solid, MS m/z: 496.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (10 mg, 15% yield) as racemate, light yellow solid, MS m/z: 496.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

The following **Examples 144 to 149** were prepared in analogy to Examples 58 by starting from the indicated intermediates. Separation of diastereomers was performed by preparative HPLC (column Phenomenex Luna, C18, 150 x 25 mm x 10 µm, mobile phase: water / 0.25% formic acid - acetonitrile, 0-73%, flow rate 25 ml/min), chiral separation was performed by chiral SFC (Daicel Chiralpak IC 250 mm x 30 mm, 10 µm, acetonitrile / methanol / 0.1% ammonium hydroxide, flow rate 80 ml/min). Relative stereochemistry was assigned by evaluation of ¹H-NMR measurements, the absolute stereochemistry was assigned arbitrarily.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
144		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C23	469.1 [M+H] ⁺
145		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C23	469.1 [M+H] ⁺
146		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C23	469.2 [M+H] ⁺

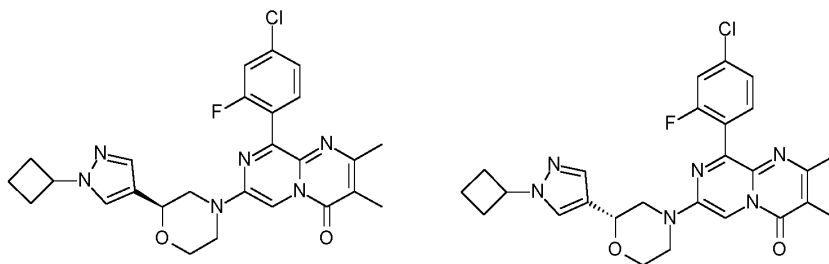
147		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C23	469.2 [M+H] ⁺
148		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C22	455.2 [M+H] ⁺
149		9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B2 and C22	455.2 [M+H] ⁺

Example 150 and Example 151 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



The title compounds were prepared in analogy to Example 133 and 134 using Intermediate C24 instead of Intermediate C21. Yellow solids with MS m/z: 504.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

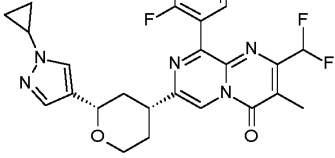
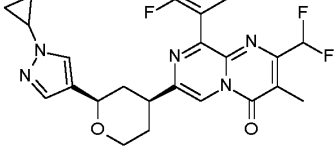
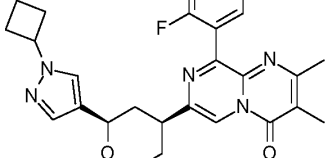
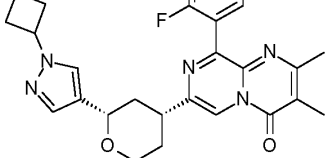
- Example 152 and Example 153** 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

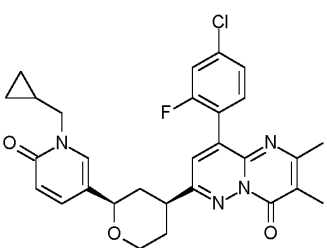
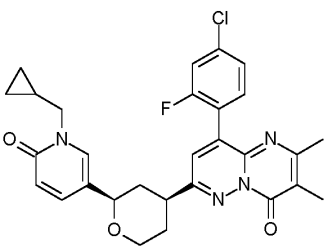
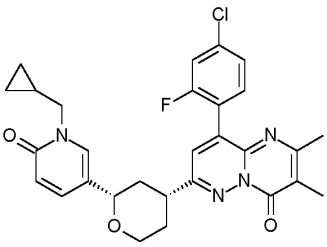
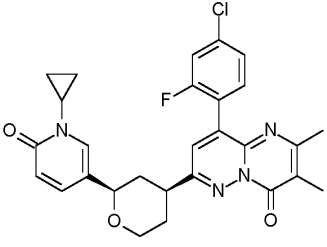


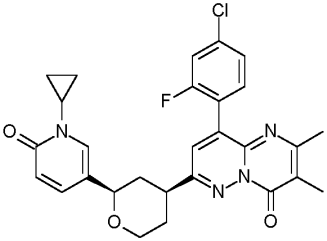
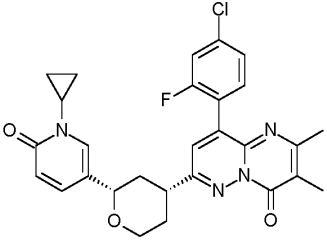
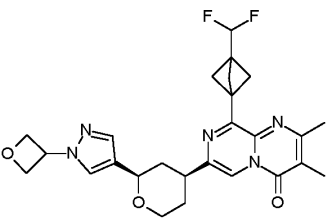
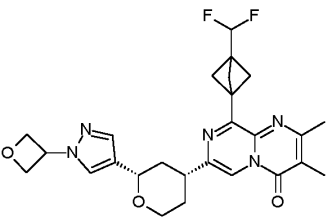
- The title compounds were prepared in analogy to Example 66 and 67 using Intermediate C25 instead of Intermediate C5. Yellow solids with MS m/z: 509.1 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

- The following **Examples 154 to 165** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Reduction in step 2 was performed with addition of magnesium oxide and triethylamine as described for Examples 131 and 132. Chiral separation was performed as described for Examples 95 and 96. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

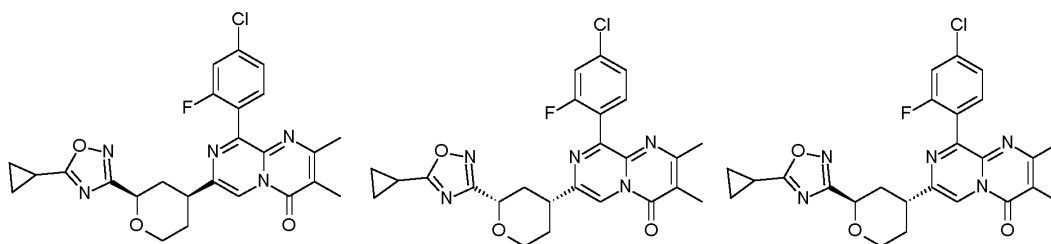
Ex.	Structure	Name	Intermediates	MS (ESI): m/z

154		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one	B10 and C11	530.1 [M+H] ⁺
155		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one	B10 and C11	530.1 [M+H] ⁺
156		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C26	508.2 [M+H] ⁺
157		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B2 and C26	508.2 [M+H] ⁺

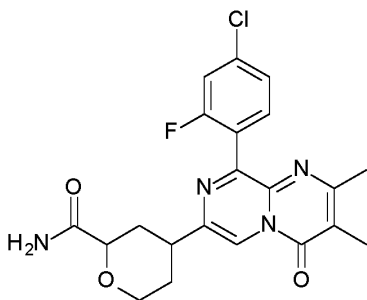
158		9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C28	535.2 [M+H] ⁺
159		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C28	535.2 [M+H] ⁺
160		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C28	535.2 [M+H] ⁺
161		9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-	B3 and C30	521.2 [M+H] ⁺

		pyrimido[1,2-b]pyridazin-4-one		
162		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C30	521.2 [M+H] ⁺
163		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C30	521.2 [M+H] ⁺
164		9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B17 and C19	498.3 [M+H] ⁺
165		9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B17 and C19	498.3 [M+H] ⁺

Example 166, Example 167 and Example 168 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



Step 1: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxamide

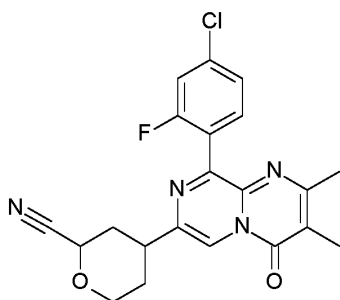


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A solution of ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylate (see Intermediate D1 step 3, 150 mg, 0.33 mmol) in ammonia in methanol (7 M, 5.0 ml, 35.0 mmol) was reacted in sealed tube at 60 °C for 16 h. Then the reaction mixture was concentrated in vacuo to give 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxamide (140 mg, 99% yield) as light yellow solid. MS m/z: 431.1 [M+H]⁺, ESI pos.

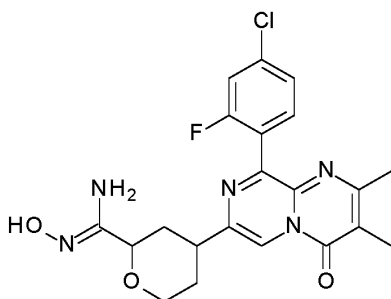
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Step 2: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carbonitrile



To a solution of 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxamide (140 mg, 0.32 mmol) in tetrahydrofuran (4 ml) was added pyridine (0.08 ml, 0.97 mmol) at 25 °C, then trifluoroacetic anhydride (0.14 ml, 0.97 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at 20 °C for 16 h. The reaction mixture was poured saturated aqueous NaHCO₃ solution (30 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with saturated brine (50 ml), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by preparative TLC (silica gel, ethyl acetate) to afford 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carbonitrile (100 mg, 74% yield) as light yellow solid. MS m/z: 413.1 [M+H]⁺, ESI pos.

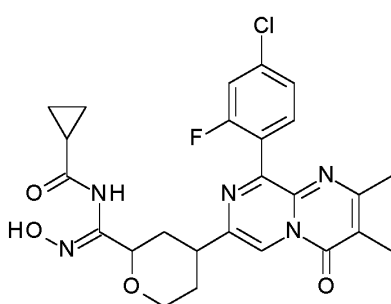
Step 3: 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-N-hydroxy-tetrahydropyran-2-carboxamidine



To a well-stirred solution of hydroxylamine hydrochloride (50 mg, 0.73 mmol) and triethylamine (98 mg, 0.97 mmol) in 1,4-dioxane (1 ml) was added a solution of 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carbonitrile (100 mg, 0.24 mmol) in 1,4-dioxane (2 ml) and then the reaction mixture was heated to 100 °C for 3 h. The reaction mixture was poured into water (30 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (50 ml), dried over Na₂SO₄ and

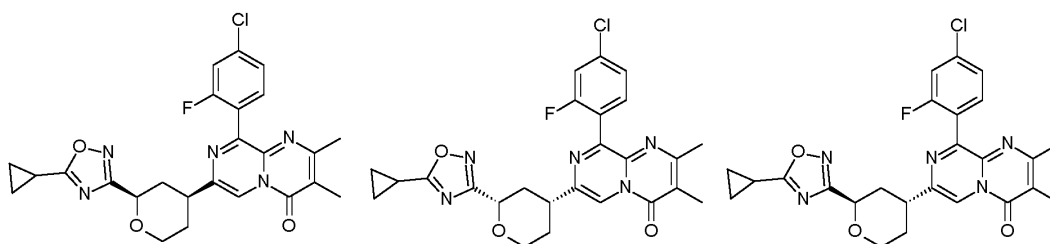
concentrated in vacuum. The residue was purified by preparative MPLC (column: Spherical C18, 20-45 μm , 100 $\text{\AA}$; mobile phase: water + 0.1% formic acid / acetonitrile 54-62%, flow rate 50 ml/min), the eluent was adjusted to 8 with saturated aqueous NaHCO_3 solution and then extracted to give 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-N-hydroxy-tetrahydropyran-2-carboxamide (80 mg, 74% yield) as light yellow solid. MS m/z: 446.1 $[\text{M}+\text{H}]^+$, ESI pos.

Step 4: N-[C-[4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-yl]-N-hydroxy-carbonimidoyl]cyclopropanecarboxamide



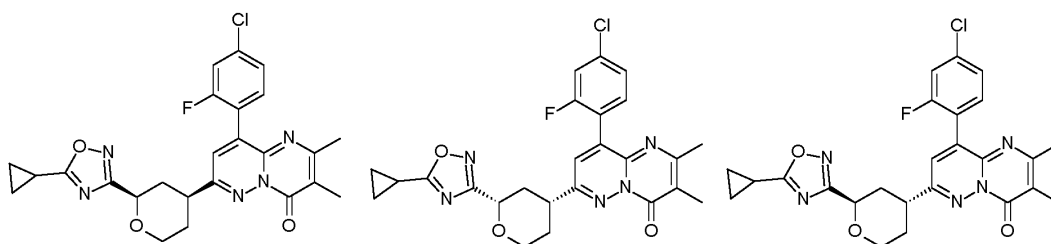
To a solution of 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]-N-hydroxy-tetrahydropyran-2-carboxamide (80 mg, 0.18 mmol) in dimethylformamide (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg, 0.36 mmol), N,N-diisopropyl ethylamine (93 mg, 0.72 mmol), 1-hydroxybenzotriazole (24 mg, 0.18 mmol) and cyclopropanecarboxylic acid (15.5 mg, 0.18 mmol). The reaction mixture was stirred at 20 $^{\circ}\text{C}$ for 16 h, then it was poured into water (30 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by preparative TLC (silica gel, ethyl acetate) to give N-[C-[4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-yl]-N-hydroxy-carbonimidoyl]cyclopropanecarboxamide (80 mg, 87% yield) as light yellow solid. MS m/z: 514.1 $[\text{M}+\text{H}]^+$, ESI pos.

Step 5: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



To a solution of N-[C-[4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-yl]-N-hydroxy-carbonimidoyl]cyclopropanecarboxamide (70 mg, 0.14 mmol) in ethanol (1 ml) and water (0.8 ml) was added sodium acetate (22 mg, 0.27 mmol) and the reaction was stirred at 80 °C for 48 h. The mixture was poured into water (20 ml) and extracted with ethyl acetate (20 ml x 3). The combined organic layers were dried over Na₂SO₄, then concentrated in vacuum. The residue was purified by preparative TLC (petroleum ether / ether = 1 : 1) to give 9-(4-chloro-2-fluoro-phenyl)-7-[2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one which was separated by chiral SFC (Daicel Chiralpak AS 250 mm × 30 mm, 10 μm, ethanol / 0.1% ammonium hydroxide, flow rate 80 ml/min) to give 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (13 mg, 18% yield) as first eluting enantiomer, light yellow solid, MS m/z: 496.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (10 mg, 14% yield) as second eluting enantiomer, light yellow solid, MS m/z: 496.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (6 mg, 8% yield) as racemate, light yellow solid, MS m/z: 496.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

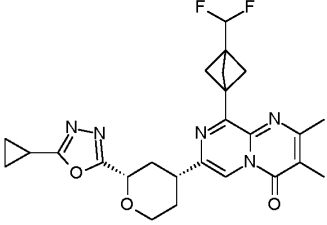
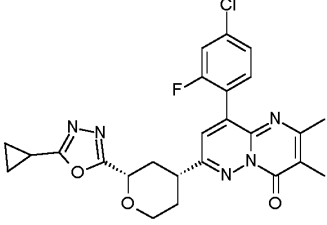
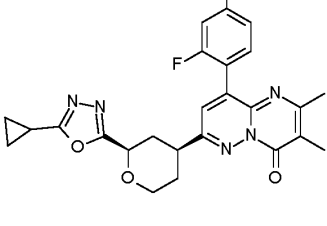
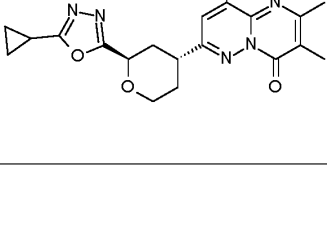
Example 169, Example 170 and Example 171 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



The title compounds were prepared in analogy to Example 166-168 using ethyl 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrimido[1,2-b]pyridazin-7-yl]-3,6-dihydro-2H-pyran-2-carboxylate (see Intermediate D2) instead of 4-[9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-4-oxo-pyrazino[1,2-a]pyrimidin-7-yl]tetrahydropyran-2-carboxylate in step 1. Light yellow solids, MS m/z: 496.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

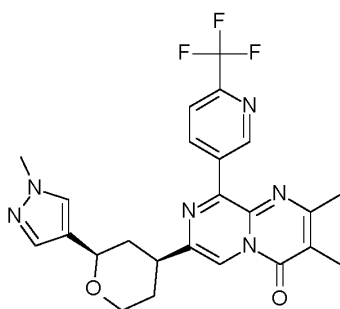
The following **Examples 172 to 176** were prepared in analogy to Examples 141-143 by starting from the indicated intermediate instead of Intermediate D1. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediate	MS (ESI): m/z
172		7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	D3	484.3 [M+H] ⁺

173		7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	D3	484.3 [M+H] ⁺
174		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	D2	496.2 [M+H] ⁺
175		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	D2	496.2 [M+H] ⁺
176		9-(4-chloro-2-fluorophenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-	D2	496.2 [M+H] ⁺

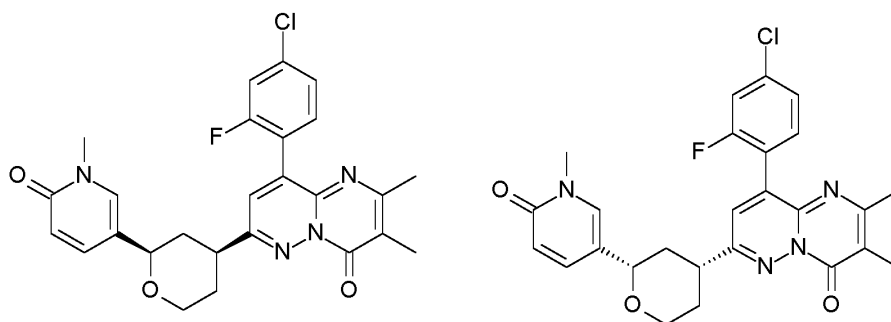
		pyrimido[1,2-b]pyridazin-4-one		
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Example 177 2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]-9-[6-(trifluoromethyl)pyridin-3-yl]pyrazino[1,2-a]pyrimidin-4-one



- 5 The title compounds were prepared in analogy to Example 133 using Intermediate C31 instead of Intermediate C21 and Intermediate B19 instead of Intermediate B2. Yellow solid, MS m/z : 485.4 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

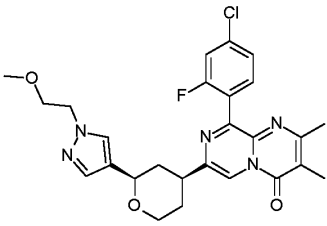
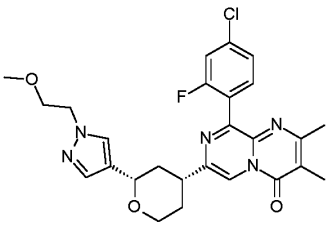
Example 178 and Example 179: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



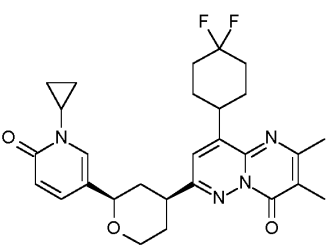
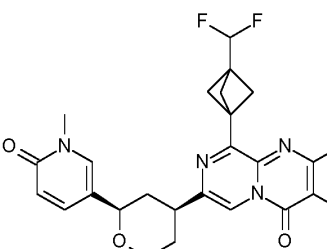
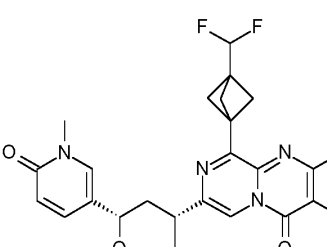
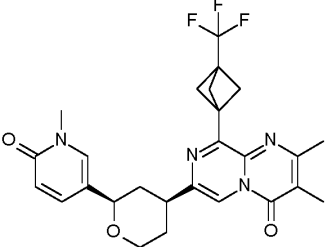
The title compounds were prepared by chiral separation of 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methyl-6-oxopyridin-3-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one (Example 83) using chiral SFC (column Chiral AD-H, 250 mm $\times$ 30 mm, 5 μ m, 55%

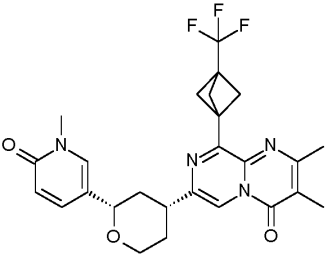
methanol + 0.2% diethylamine). The absolute stereochemistry was assigned arbitrarily. Yellow solids, MS m/z : 495.2 $[M+H]^+$, ESI pos.

The following **Examples 180 to 190** were prepared in analogy to Example 15 by starting from the indicated intermediates. Reduction in step 2 was performed with addition of magnesium oxide and triethylamine as described for Examples 131 and 132. Chiral separation was performed as described for Examples 178 and 179. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

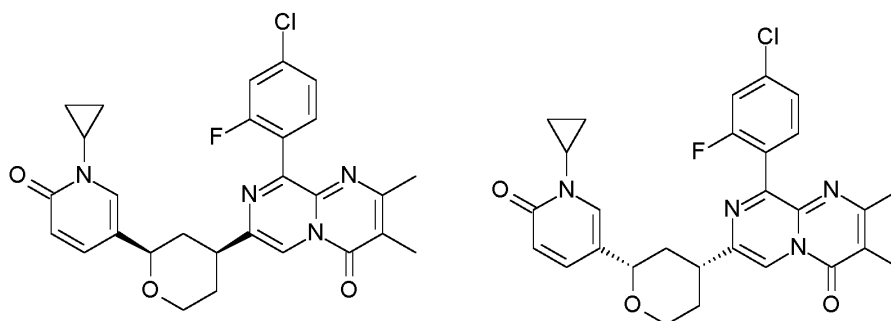
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
180		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	B2 and C32	512.3 $[M+H]^+$
181		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	B2 and C32	512.3 $[M+H]^+$

182		7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one	B18 and C16	501.3 [M+H] ⁺
183		7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one	B18 and C16	501.3 [M+H] ⁺
184		7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C30	511.2 [M+H] ⁺
185		7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C30	511.2 [M+H] ⁺

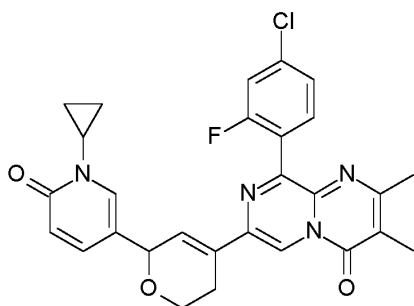
186		7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C30	511.2 [M+H] ⁺
187		9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B17 and C16	483.3 [M+H] ⁺
188		9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B17 and C16	483.3 [M+H] ⁺
189		7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyr	B12 and C16	501.2 [M+H] ⁺

		azino[1,2-a]pyrimidin-4-one		
190		7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one	B12 and C16	501.2 [M+H] ⁺

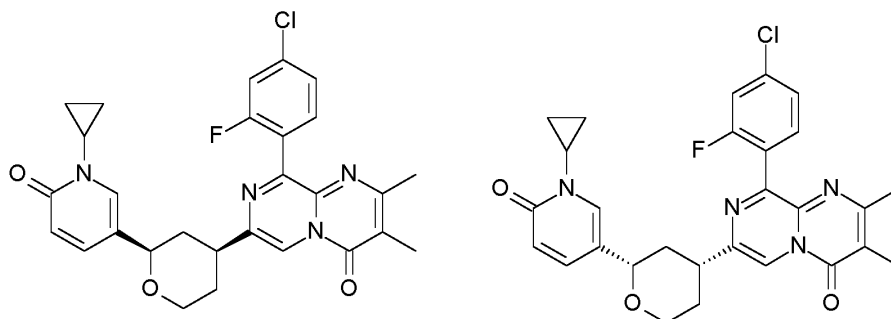
Example 191 and Example 192: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



Step 1: 9-(4-chloro-2-fluoro-phenyl)-7-[6-(1-cyclopropyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

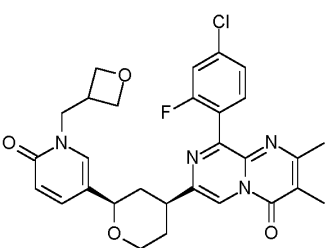


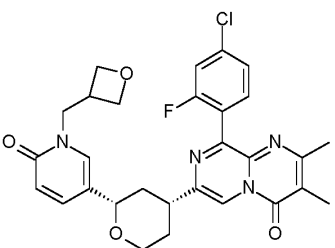
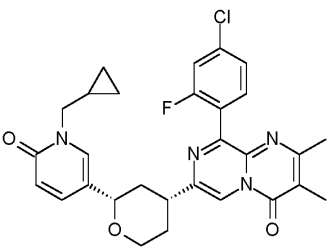
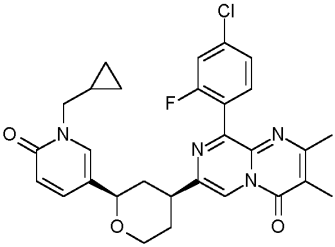
- To a solution of [6-(1-cyclopropyl-6-oxo-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (Intermediate C29, 400 mg, 1.09 mmol) in 1,4-dioxane (12 ml) and water (2.5 ml) were added under argon stream 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-
- 5 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one (Intermediate B13, 470 mg, 1.09 mmol), potassium carbonate (454 mg, 3.28 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (81 mg, 0.11 mmol, 0.10 eq). The reaction mixture was heated to 60 °C and stirred for 2.5 h, then it was filtered through dicalite and washed with ethyl acetate. The filtrate was poured into water and extracted with ethyl
- 10 acetate twice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, methanol in dichloromethane 0-10%) to afford 9-(4-chloro-2-fluoro-phenyl)-7-[6-(1-cyclopropyl-6-keto-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (566 mg, 90% yield) as light brown foam, MS m/z: 519.2 [M+H]⁺, ESI pos.
- 15 Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



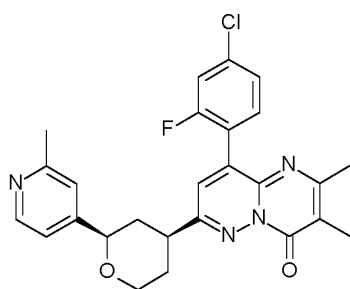
To a solution of 9-(4-chloro-2-fluoro-phenyl)-7-[6-(1-cyclopropyl-6-keto-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (250 mg, 0.482 mmol) in ethyl acetate (11 ml) were added under argon triethylamine (58 mg, 80 μ l, 0.578 mmol), magnesium oxide (194 mg, 4.82 mmol) and palladium on charcoal (10%, 102 mg). The mixture was degassed with argon several times, then it was stirred under hydrogen gas atmosphere (balloon pressure) at room temperature for 4 h. The reaction mixture was filtered through dicalite and the mother liquors were concentrated vacuo. The residue was purified by reversed phase chromatography (column C18, acetonitrile in water 10-70%) to afford 9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one. The enantiomers were separated by chiral SFC (column Chiralpak SZ, 250 mm $\times$ 20 mm, 5 μ m, 55% methanol) to give 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one as first eluting enantiomer (19 mg, 8% yield), yellow solid, MS m/z: 521.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one as second eluting enantiomer (15 mg, 6% yield), yellow solid. MS m/z: 521.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

The following **Examples 193 to 196** were prepared in analogy to Examples 191 and 192 by starting from the indicated intermediate instead of Intermediate C29. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

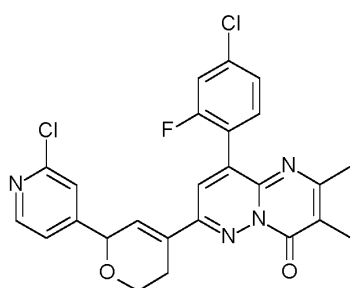
Ex.	Structure	Name	Intermediate	MS (ESI): m/z
193		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C33	551.2 [M+H] ⁺

194		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C33	551.2 [M+H] ⁺
195		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C27	535.2 [M+H] ⁺
196		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C27	535.2 [M+H] ⁺

Example 197: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one

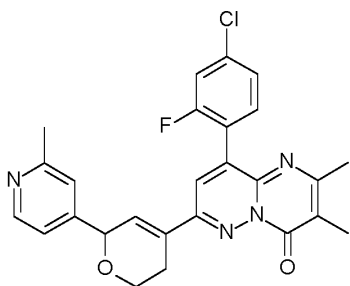


Step 1: 9-(4-chloro-2-fluoro-phenyl)-7-[6-(2-chloro-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



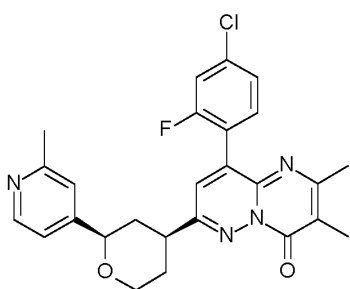
- 5 To a solution of 2-chloro-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine (Intermediate C34, 1.05 g, 3.25 mmol) and 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B3, 1 g, 2.96 mmol) in 1,4-dioxane (48 ml) and water (8 ml) were added potassium carbonate (1.23 g, 8.87 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (219 mg, 0.296 mmol, 0.10 eq). The
- 10 mixture was purged and backfilled with argon three times, then it was heated to 60 °C and stirred for 1.5 h. The reaction mixture was filtered through dicalite and washed with ethyl acetate twice. The filtrate was poured into water and extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄) and evaporated. The residue was purified by flash chromatography (silica gel, 0% to 70% ethyl acetate in heptane) to afford 9-(4-chloro-2-fluoro-phenyl)-7-[6-(2-chloro-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (930 mg,
- 15 51% yield) as off-white solid, MS m/z: 495.2 [M-H]⁺, ESI neg.

Step 2: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(2-methyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



To a solution of 9-(4-chloro-2-fluoro-phenyl)-7-[6-(2-chloro-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (720 mg, 1.45 mmol) in 1,4-dioxane (12 ml) were added under argon stream a solution of 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M in tetrahydrofuran, 538 μ l, 1.88 mmol), potassium carbonate (600 mg, 4.34 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (107.39 mg, 0.145 mmol, 0.10 eq). The reaction mixture was heated to 90 °C and stirred for 2 h. After cooling to room temperature, it was filtered over celite and washed with ethyl acetate. The filtrate was poured into water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (Si-Amine, 0% to 70% ethyl acetate in heptane) to afford 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(2-methyl-4-pyridyl)-3,4-dihydro-2H-pyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (380 mg, 52% yield) as yellow foam, MS m/z: 477.2 [M+H]⁺, ESI pos.

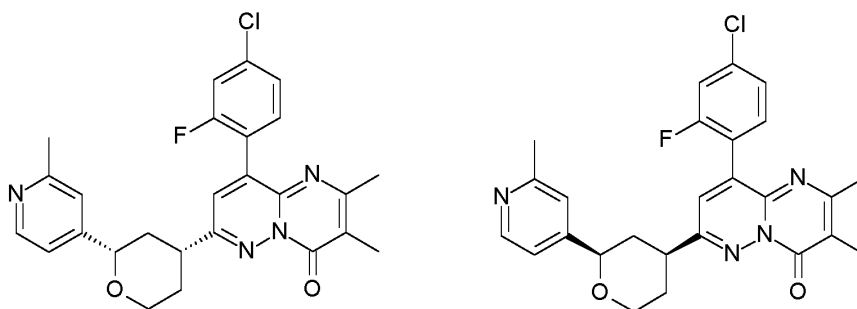
Step 3: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(2-methyl-4-pyridyl)-3,6-dihydro-2H-pyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (380 mg, 0.757 mmol) in ethanol (15 ml) was added palladium on charcoal (10%, 84 mg) under argon and the mixture was stirred under hydrogen gas atmosphere (balloon pressure) at room temperature for 10 h. The reaction

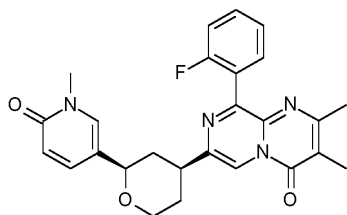
mixture was filtered and washed with ethyl acetate. The filtrate was concentrated in vacuo and purified by flash chromatography (column C18, acetonitrile in water 0-50%). The fractions containing the product were combined and the acetonitrile was removed by evaporation. The residue was poured into ethyl acetate and extracted. The combined organic layers were dried
 5 over Na₂SO₄ and concentrated in vacuo to afford the title compound (205 mg, 54% yield) as yellow foam, MS m/z: 479.2 [M+H]⁺, ESI pos.

Example 198 and Example 199: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one
 10



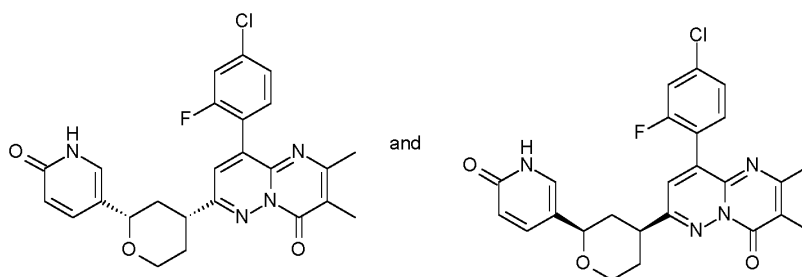
Racemic 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (Example 197) was separated by chiral SFC (Column chiral SZ, 5 μm, 250 x 20 mm, 43% methanol) to give 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one as first eluting enantiomer with retention time 3.595 min and 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one as second eluting enantiomer with retention time 4.843 min, yellow foams with MS m/z: 479.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned
 15
 20 arbitrarily.

Example 200: 9-(2-fluorophenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

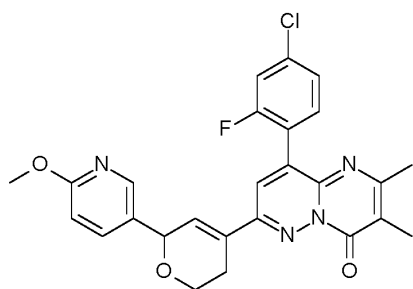


This compound was formed as by-product at the hydrogenation step during the synthesis of Example 89 and 90 and was isolated by column chromatography (silica gel, 10% methanol in dichloromethane) after this reaction (18% yield), yellow solid, MS m/z : 461.4 $[M+H]^+$, ESI pos.

- 5 **Example 201 and Example 202:** 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



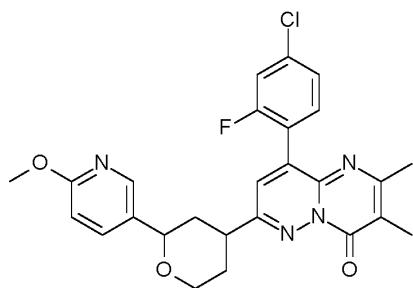
- 10 Step 1: 9-(4-chloro-2-fluoro-phenyl)-7-[6-(6-methoxy-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



- To 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B3, 1.8 g, 5.32 mmol) was added a solution of 2-methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran-6-yl]pyridine (Intermediate C35,
- 15

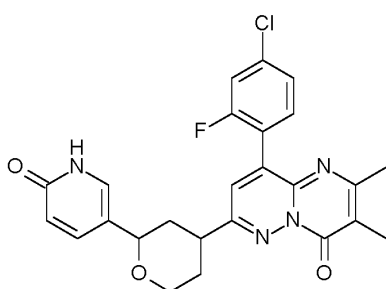
2.19 g, 6.92 mmol) in 1,4-dioxane (62 ml) and water (10 ml). The mixture was degassed and refilled with nitrogen three times. Then potassium carbonate (2.21 g, 16.0 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (395 mg, 0.532 mmol, 0.10 eq) were added and the mixture was stirred at 60 °C for 1 h. The reaction mixture was filtered through
 5 dicalite and washed with ethyl acetate. The filtrate was poured into water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0-80% ethyl acetate in heptane) to give 9-(4-chloro-2-fluoro-phenyl)-7-[6-(6-methoxy-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (1.95 g, 74% yield) as
 10 light yellow solid, MS m/z: 493.3 [M+H]⁺, ESI pos.

Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[2-(6-methoxy-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



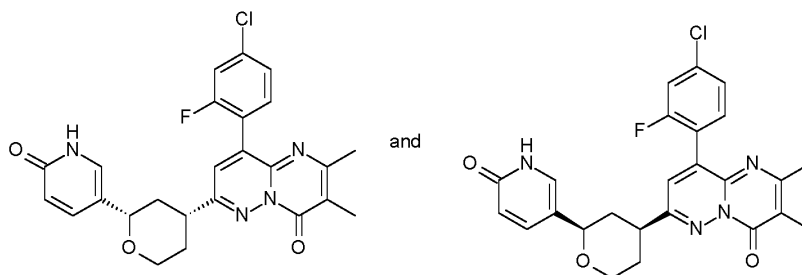
To a solution of 9-(4-chloro-2-fluoro-phenyl)-7-[6-(6-methoxy-3-pyridyl)-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (350 mg, 0.639 mmol), triethylamine
 15 (78 mg, 107 µl, 0.767 mmol) and magnesium oxide (257 mg, 6.39 mmol) in ethyl acetate (7 ml) was added platinum(IV) oxide (29 mg, 0.128 mmol, 0.20 eq) under argon and the reaction mixture was stirred under hydrogen atmosphere at room temperature overnight. The reaction mixture filtered through dicalite and evaporated. The crude material was purified by flash
 20 chromatography (silica gel, ethyl acetate / ethanol = 3:1 in heptane, 0 - 20%) to yield 9-(4-chloro-2-fluoro-phenyl)-7-[2-(6-methoxy-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one as yellow solid (184 mg, 58% yield), MS m/z: 493.3 [M+H]⁺, ESI pos.

Step 3: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(6-oxo-1H-pyridin-3-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



- To a solution of 9-(4-chloro-2-fluoro-phenyl)-7-[2-(6-methoxy-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (134 mg, 0.27 mmol) and sodium iodide (40.5 mg, 0.27 mmol) in acetonitrile (5.5 ml) was added trimethylsilyl chloride (29 mg, 34 μ l, 0.27 mmol) and the mixture was stirred at 65 °C for 3 h. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, ethyl acetate / ethanol = 3:1 in heptane, 0 - 90%) to yield 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(6-oxo-1H-pyridin-3-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one as yellow powder (107 mg, 78% yield), MS m/z: 481.3 [M+H]⁺, ESI pos.

- Step 4: 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



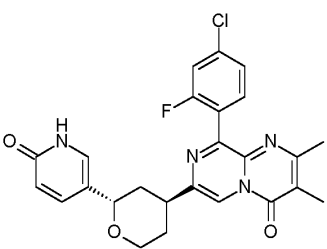
- Racemic 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(6-oxo-1H-pyridin-3-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one was separated by chiral SFC (column Chiral NR, 250 mm $\times$ 20 mm, 5 μ m, 60% methanol) to yield 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one, first eluting enantiomer, orange powder, MS m/z: 481.3 [M+H]⁺, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-

2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one, second eluting enantiomer, orange powder, MS m/z : 481.3 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

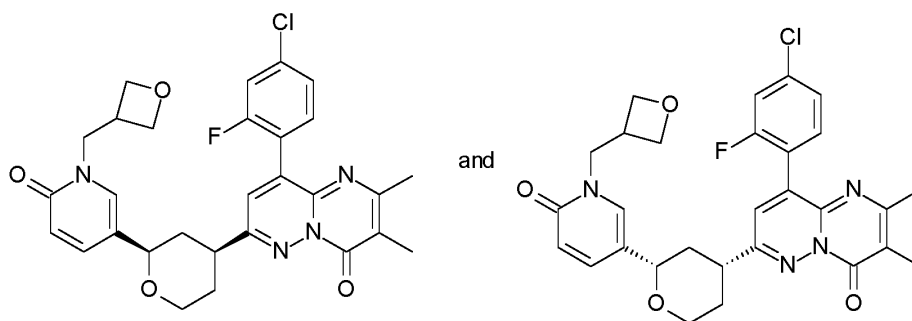
The following **Examples 203 to 206** were prepared in analogy to Examples 191 and 192 by starting from the indicated intermediate instead of Intermediate C29. The absolute

5 stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

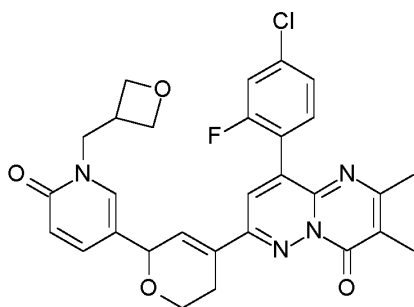
Ex.	Structure	Name	Intermediate	MS (ESI): m/z
203		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C36	481.2 $[M+H]^+$
204		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C36	481.2 $[M+H]^+$
205		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C36	481.2 $[M+H]^+$

206		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C36	481.2 [M+H] ⁺
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Example 207 and Example 208: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

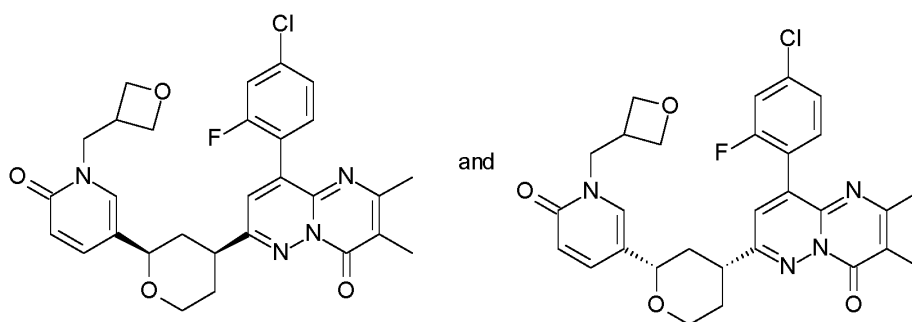


Step 1: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-[1-(oxetan-3-ylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



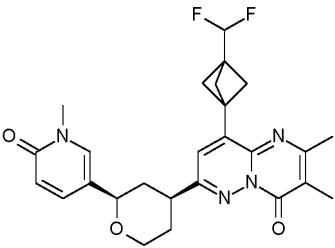
To a suspension of 7-chloro-9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Intermediate B3, 300 mg, 0.887 mmol) in 1,4-dioxane (6 ml) was added bis(pinacolato)diboron (338 mg, 1.33 mmol) and potassium acetate (261 mg, 2.66 mmol) at room temperature. The mixture was degassed with argon before 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (73 mg, 89 μ mol, 0.10 eq) was added and the mixture was stirred at 90 °C for 90 min. Then [6-[1-(oxetan-3-ylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (Intermediate C33, 421 mg, 1.06 mmol), cesium carbonate solution (3 M, 0.88 μ l, 2.66 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (73 mg, 89 μ mol, 0.10 eq) were added and the reaction mixture was stirred another 2 h at 90 °C. The reaction mixture was diluted with water and extracted two times with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated to dryness. The residue was purified by flash chromatography (silica C18, acetonitrile in water 10-100%) followed by a second flash chromatography (silica gel, methanol in dichloromethane 0-4%) to obtain 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-[1-(oxetan-3-ylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (47 mg, 9% yield) as light brown solid, MS m/z: 549.2 $[\text{M}+\text{H}]^+$, ESI pos.

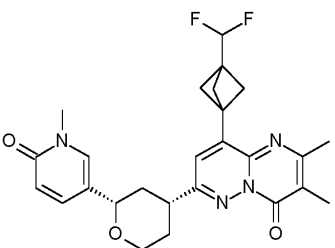
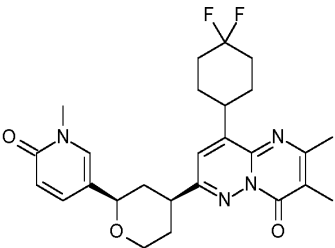
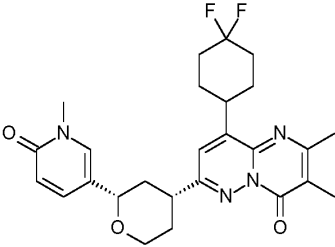
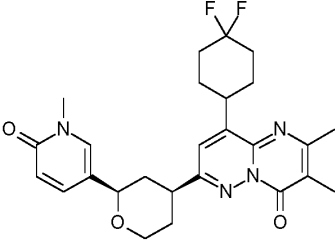
Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

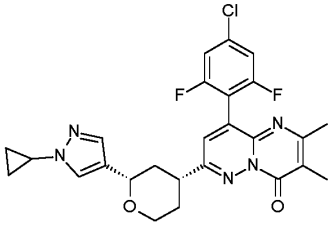
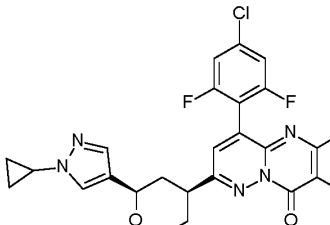
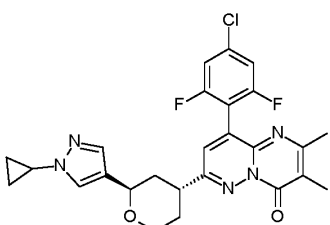
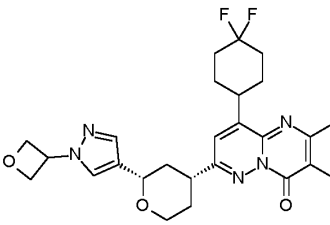


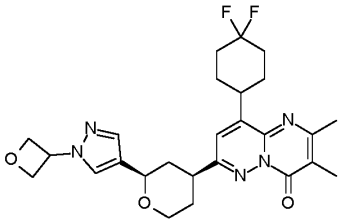
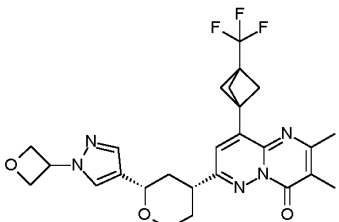
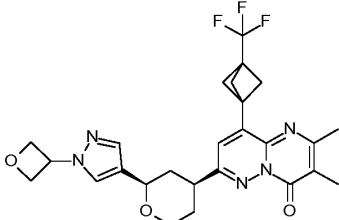
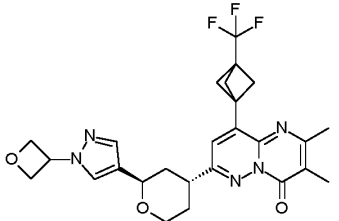
To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-[1-(oxetan-3-ylmethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (30 mg, 55 μ mol) in ethyl acetate (1.5 ml) and triethylamine (6.6 mg, 9 μ l, 66 μ mol) were added magnesium oxide (22 mg,

- 546 μmol) and platinum(IV) oxide (2.5 mg, 11 μmol , 0.20 eq) and the mixture was stirred under hydrogen atmosphere at room temp for 4 h. The reaction mixture was filtered and washed with dichloromethane / methanol = 9:1 and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica C18, acetonitrile in water 10-100 %) to obtain racemic
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one which was further separated by chiral SFC (column Chiral SZ, 5 μm , 250 x 20 mm, 55% methanol) to obtain 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (5 mg, 15% yield) as first eluting
- 10 enantiomer, light yellow solid, MS m/z : 551.2 $[\text{M}+\text{H}]^+$, ESI pos. and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (5 mg, 15% yield) as second eluting enantiomer, light yellow solid, MS m/z : 551.2 $[\text{M}+\text{H}]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.
- 15 The following **Examples 209 to 221** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Reduction in step 2 was performed with addition of magnesium oxide and triethylamine as described for Examples 131 and 132. Chiral separation was performed as described for Examples 178 and 179. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
209		9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B14 and C16	483.3 $[\text{M}+\text{H}]^+$

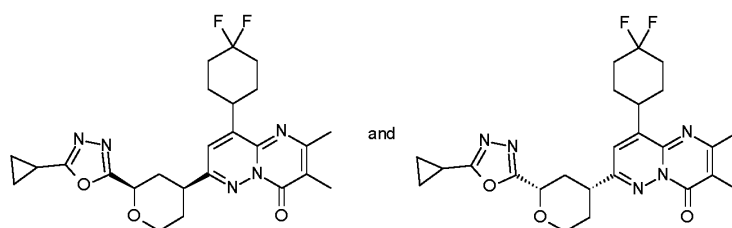
210		9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B14 and C16	483.3 [M+H] ⁺
211		9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B16 and C16	485.3 [M+H] ⁺
212		9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B16 and C16	485.3 [M+H] ⁺
213		9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B16 and C16	485.3 [M+H] ⁺

		pyrimido[1,2-b]pyridazin-4-one		
214		9-(4-chloro-2,6-difluorophenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B7 and C11	512.2 [M+H] ⁺
215		9-(4-chloro-2,6-difluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B7 and C11	512.2 [M+H] ⁺
216		9-(4-chloro-2,6-difluorophenyl)-7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B7 and C11	512.2 [M+H] ⁺
217		9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B16 and C19	500.3 [M+H] ⁺

218		9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B16 and C19	500.3 [M+H] ⁺
219		2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one	B18 and C19	516.2 [M+H] ⁺
220		2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one	B18 and C19	516.2 [M+H] ⁺
221		2,3-dimethyl-7-[rac-(2R,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyr	B18 and C19	516.2 [M+H] ⁺

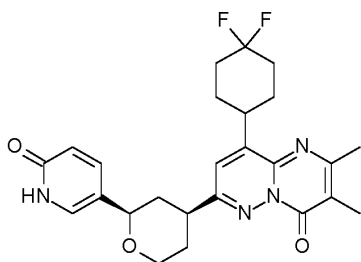
		imido[1,2-b]pyridazin-4-one		
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Example 222 and Example 223: 7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



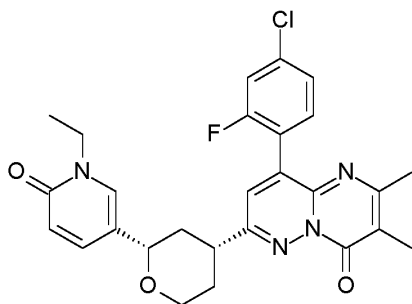
The title compounds were prepared in analogy to Example 141 and 142 using Intermediate D4 instead of Intermediate D1. Yellow solids with MS m/z : 486.2 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 224: 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



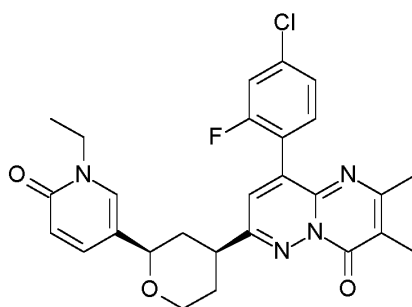
The title compound was prepared in analogy to Example 201 using Intermediate B16 instead of Intermediate B3 in step 1. Off-white solid, MS m/z : 471.3 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 225: 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



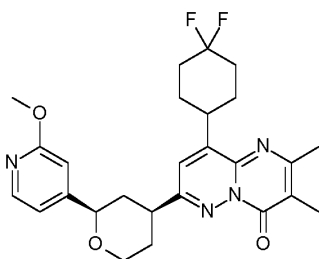
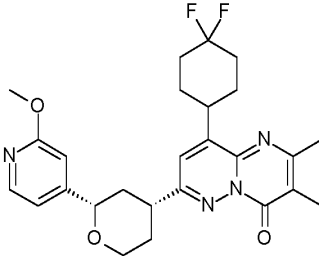
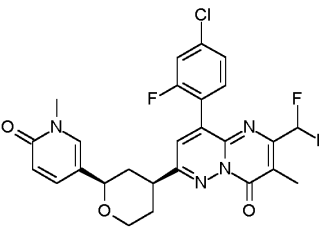
To a suspension of 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Example 201, 15 mg, 31 μ mol) in acetonitrile (2 ml) was added cesium carbonate (30.5 mg, 94 μ mol) and ethyl iodide (10 mg, 5 μ l, 62 μ mol) at room temperature and the mixture was stirred at 60 °C for 1 h. The solvent was evaporated and the crude material was purified by flash chromatography (silica gel, ethyl acetate / ethanol = 3:1 in heptane, 0 - 90%) to give the title compound as light yellow powder (9 mg, 57% yield), MS m/z: 509.3 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

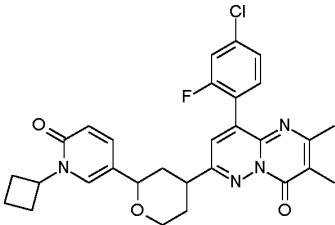
Example 226: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



The title compound was prepared in analogy to Example 225 using 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Example 202) instead of 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Example 201). Off-white solid, MS m/z: 509.3 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

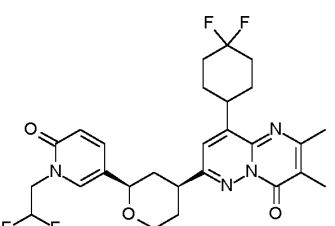
The following **Examples 227 to 230** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Reduction in step 2 was performed with addition of magnesium oxide and triethylamine as described for Examples 131 and 132. Chiral separation was performed as described for Examples 178 and 179. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

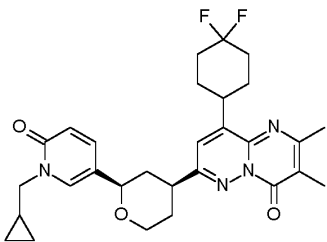
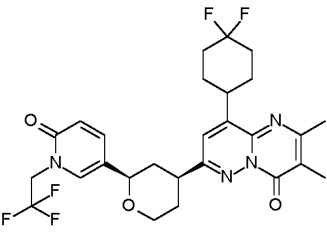
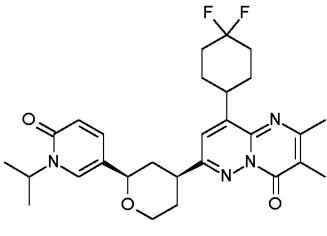
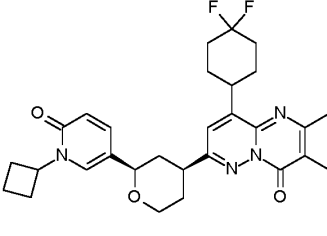
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
227		9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B16 and C8	485.3 [M+H] ⁺
228		9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B16 and C8	485.3 [M+H] ⁺
229		9-(4-chloro-2-fluorophenyl)-2-(difluoromethyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-3-methylpyrimido[1,2-b]pyridazin-4-one	B11 and C16	531.1 [M+H] ⁺

		pyrimido[1,2-b]pyridazin-4-one		
230		9-(4-chloro-2-fluorophenyl)-7-[2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B3 and C41	535.3 [M+H] ⁺

The following **Examples 231 to 235** were prepared in analogy to Examples 225 by alkylation of 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (Example 224) using the indicated alkylating agent.

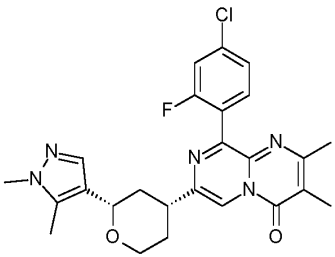
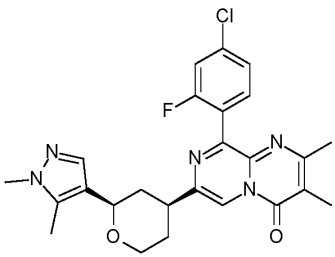
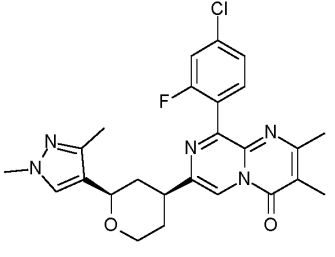
- 5 The absolute stereochemistry was assigned arbitrarily.

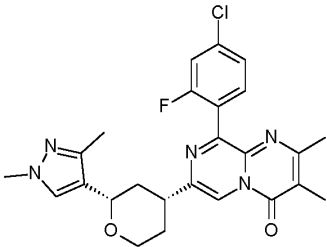
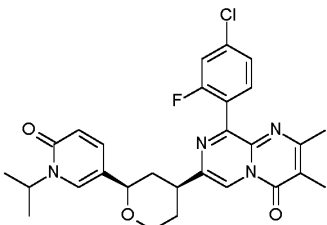
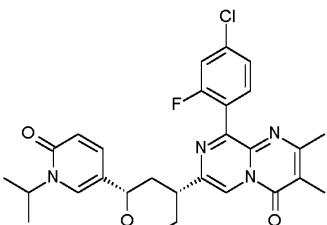
Ex.	Structure	Name	Alkylating agent	MS (ESI): m/z
231		9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	2,2-difluoroethyl trifluoromethanesulfonate	535.3 [M+H] ⁺

232		7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	bromomethylcyclopropane	525.3 [M+H] ⁺
233		9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	trifluoroethyltrifluoromethanesulfonate	553.3 [M+H] ⁺
234		9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	2-iodopropane	513.3 [M+H] ⁺
235		7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	iodocyclobutane	525.3 [M+H] ⁺

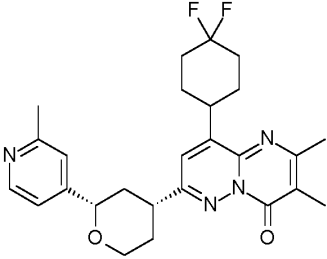
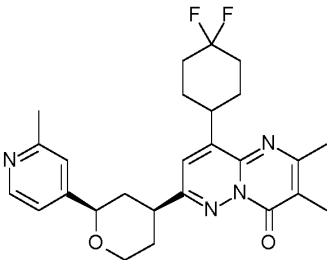
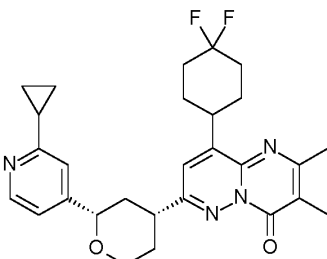
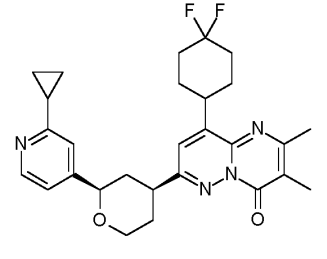
		dimethyl-pyrimido[1,2-b]pyridazin-4-one		
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The following **Examples 236 to 239** were prepared in analogy to Examples 191 by starting from the indicated intermediate. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediate	MS (ESI): m/z
236		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C37	482.2 [M+H] ⁺
237		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C37	482.2 [M+H] ⁺
238		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-	C38	481.9 [M+H] ⁺

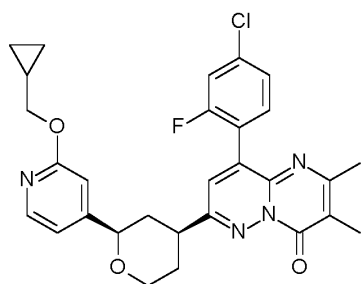
		pyrazino[1,2-a]pyrimidin-4-one		
239		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1,3-dimethylpyrazol-4-yl)]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	C38	482.2 [M+H] ⁺
240		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	C42	523.2 [M+H] ⁺
241		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	C42	523.2 [M+H] ⁺

The following **Examples 242 to 245** were prepared in analogy to Examples 207 / 208 by starting from the indicated intermediates in step 1. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

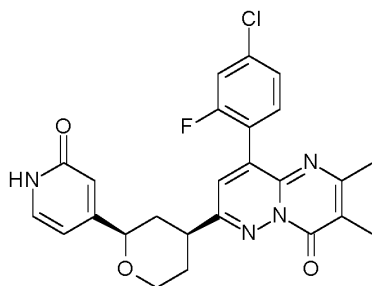
Ex.	Structure	Name	Intermediate	MS (ESI): m/z
242		9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B16 and C43	469.2 [M+H] ⁺
243		9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B16 and C43	469.2 [M+H] ⁺
244		7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C44	495.2 [M+H] ⁺
245		7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-	B16 and C44	495.2 [M+H] ⁺

		dimethyl-pyrimido[1,2-b]pyridazin-4-one		
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Example 246: 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

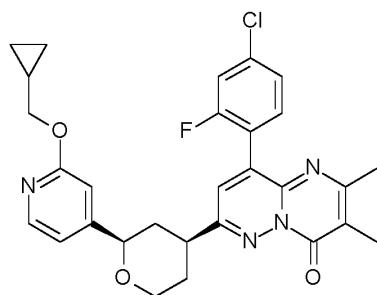


- 5 Step 1: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-oxo-1H-pyridin-4-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



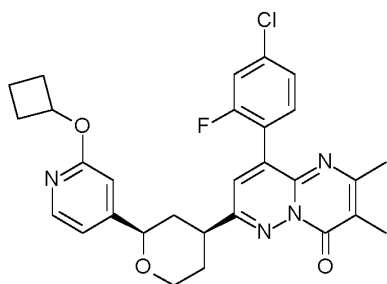
The title compound was prepared in analogy to Example 202 using Intermediate C8 instead of Intermediate C35 in step 1, yellow solid, MS m/z: 481.2 [M+H]⁺, ESI pos.

- 10 Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



The title compound was prepared in analogy to Example 225 using 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-oxo-1H-pyridin-4-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one instead of 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and iodomethylcyclopropane instead of ethyl iodide. Yellow foam, MS m/z: 579.3 [M+HCOO]⁻, ESI neg.

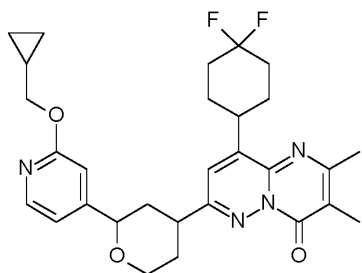
Example 247: 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclobutoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



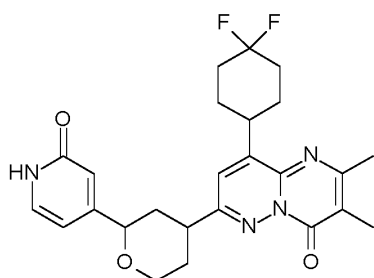
10

The title compound was prepared in analogy to Example 246 using iodocyclobutane instead of iodomethylcyclopropane in step 2, yellow foam, MS m/z: 535.2 [M+H]⁺, ESI pos.

Example 248: 7-[2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

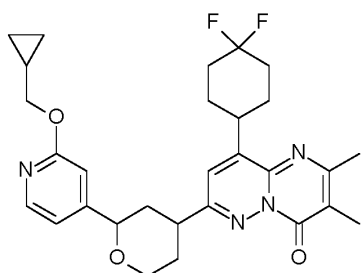


Step 1: 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[2-(2-oxo-1H-pyridin-4-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



- 5 The title compound was prepared in analogy to Example 202 using Intermediate B16 instead of Intermediate B3 and Intermediate C8 instead of Intermediate C35 in step 1, yellow solid, MS m/z : 471.3 $[M+H]^+$, ESI pos.

Step 2: 7-[2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

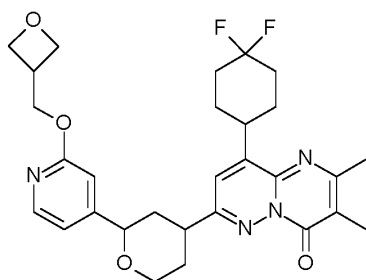


10

The title compound was prepared in analogy to Example 225 using 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[2-(2-oxo-1H-pyridin-4-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one instead of 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-

4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and iodomethylcyclopropane instead of ethyl iodide. White solid, MS m/z: 525.3 [M+H]⁺, ESI pos.

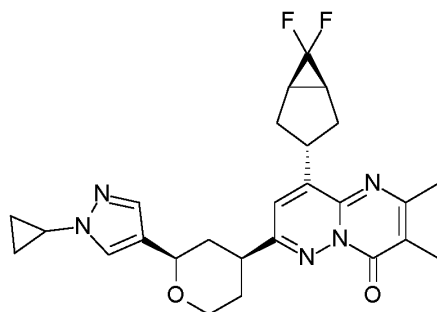
Example 249: 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[2-[2-(oxetan-3-ylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one



5

The title compound was prepared in analogy to Example 248 using 3-(bromomethyl)oxetane instead of iodomethylcyclopropane in step 2, white solid, MS m/z: 541.3 [M+H]⁺, ESI pos.

Example 250: 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one

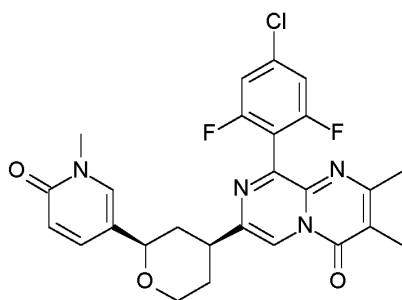


10

The title compound was prepared in analogy to Example 15 using Intermediate B21 instead of Intermediate B1 and Intermediate C11 instead of intermediate C8, white solid, MS m/z: 482.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 251: 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

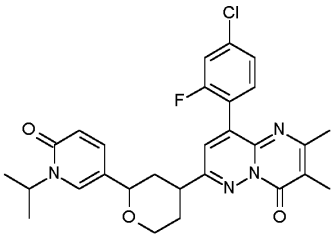
15



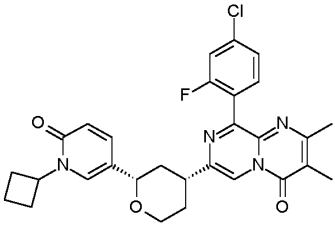
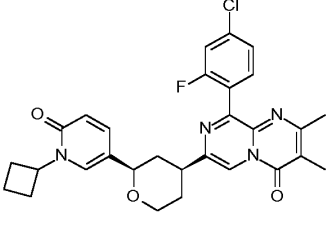
The title compound was prepared in analogy to Example 191 using Intermediate B20 instead of Intermediate B13 and Intermediate C39 instead of Intermediate C29 in step 1, yellow solid, MS m/z : 513.2 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

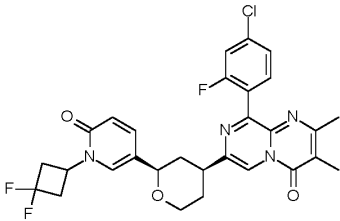
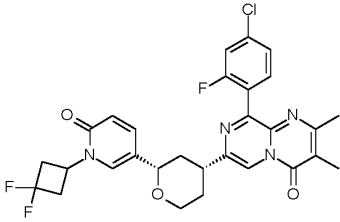
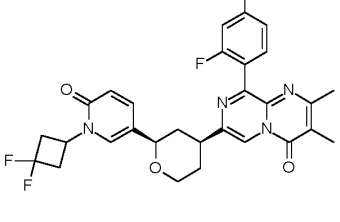
- 5 The following **Examples 252 to 254** were prepared in analogy to Examples 225 by alkylation of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(6-oxo-1H-pyridin-3-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (Example 201, step 3) using the indicated alkylating reagent. The absolute stereochemistry was assigned arbitrarily.

Ex.	Structure	Name	Alkylating agent	MS (ESI): m/z
252		9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	2,2-difluoroethyl trifluoromethanesulfonate	545.3 $[M+H]^+$
253		9-(4-chloro-2-fluoro-phenyl)-7-[2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	2,2,2-trifluoroethyl trifluoromethanesulfonate	563.2 $[M+H]^+$

		pyrimido[1,2-b]pyridazin-4-one		
254		9-(4-chloro-2-fluorophenyl)-7-[2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	2-iodopropane	523.3 [M+H] ⁺

The following **Examples 255 to 259** were prepared in analogy to Examples 191 by starting from the indicated intermediate. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediate	MS (ESI): m/z
255		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	C40	535.2 [M+H] ⁺
256		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-	C40	535.2 [M+H] ⁺

		pyrazino[1,2-a]pyrimidin-4-one		
257		9-(4-chloro-2-fluorophenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	C45	571.2 [M+H] ⁺
258		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	C45	571.2 [M+H] ⁺
259		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	C45	571.2 [M+H] ⁺

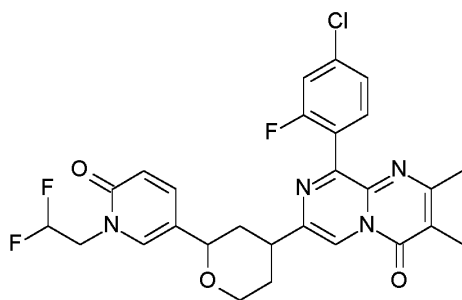
The following **Examples 260 to 265** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Reduction in step 2 was performed with addition of magnesium

oxide and triethylamine as described for Examples 131 and 132. Chiral separation was performed as described for Examples 178 and 179. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

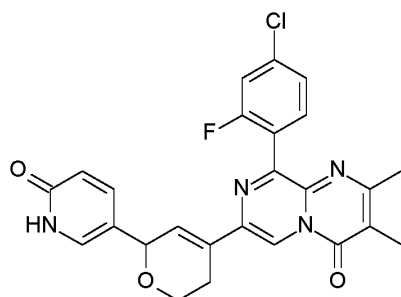
Ex.	Structure	Name	Intermediates	MS (ESI): m/z
260		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C41	535.3 [M+H] ⁺
261		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C41	535.3 [M+H] ⁺
262		7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C46	561.3 [M+H] ⁺

263		7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B16 and C46	561.3 [M+H] ⁺
264		9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one	B15 and C16	485.3 [M+H] ⁺
265		9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	B3 and C46	571.3 [M+H] ⁺

Example 266: 9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

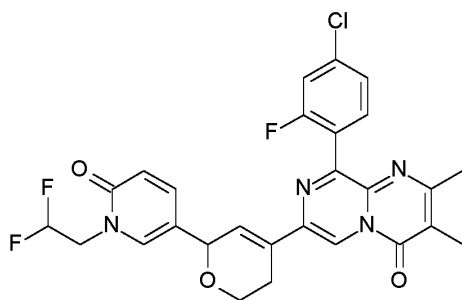


Step 1: 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one



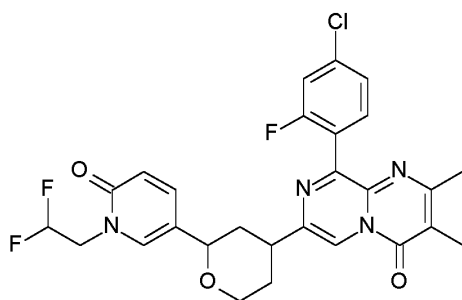
- 5 To a solution of 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazino[1,2-a]pyrimidin-4-one (Intermediate B13, 100 mg, 0.233 mmol) and [6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl] trifluoromethanesulfonate (Intermediate C36, 175 mg, 0.349 mmol) in 1,4-dioxane (2.3 ml) was added cesium carbonate solution (3 M in water, 0.233 ml, 0.698 mmol). The mixture was degassed with argon, then 1,1'-
- 10 bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (304 mg, 0.372 mmol) was added and mixture was stirred at 95°C for 2.5 h. The reaction mixture was diluted with dichloromethane, absorbed on silica gel and purified by column chromatography (silica gel, 0-100% ethyl acetate / ethanol 3:1 with 2% ammoniumhydroxide in heptane) to afford 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-
- 15 pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (44 mg, 40% yield) as brown solid, MS m/z: 479.3 [M+H]⁺, ESI pos.

Step 2: 9-(4-chloro-2-fluoro-phenyl)-7-[6-[1-(2,2-difluoroethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



- 9-(4-Chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[6-(6-oxo-1H-pyridin-3-yl)-3,6-dihydro-2H-pyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one (65 mg, 81.5 μ mol), ethylene glycol dimethyl ether (1.5 ml) and N,N-dimethylformamide (0.4 ml) were placed in a 4 ml vial. Sodium hydride (60% in
- 5 mineral oil, 4 mg, 165 μ mol) was added at 0 °C, the vial was closed and the mixture was stirred for 45 min at 0 °C. The ice bath was removed and lithium bromide (21 mg, 244 μ mol) was added. The resulting mixture was stirred at room temperature for 30 min before 2,2-difluoroethyl trifluoromethanesulfonate (52 mg, 32 μ l, 244 μ mol) was added, then the reaction was stirred for 48 h at room temperature. The reaction mixture was diluted with water (50 ml) and extracted
- 10 with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0-50% ethyl acetate / ethanol 3:1 with 2% ammoniumhydroxide in heptane) to afford 9-(4-chloro-2-fluoro-phenyl)-7-[6-[1-(2,2-difluoroethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (22 mg, 47% yield) as orange solid,
- 15 MS m/z: 543.2 [M+H]⁺, ESI pos.

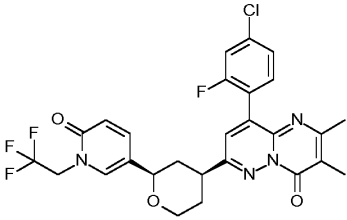
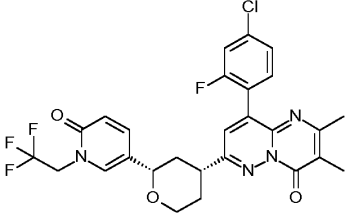
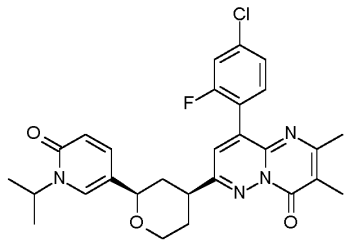
Step 3: 9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one

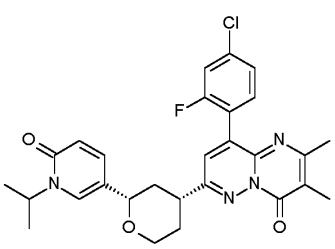
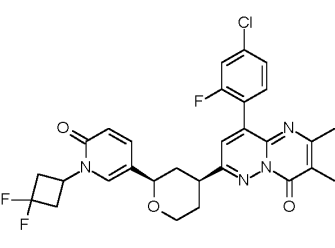
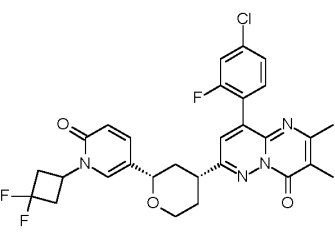
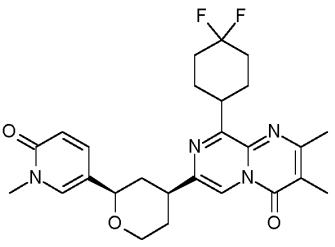


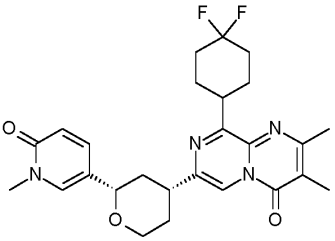
To a solution of 9-(4-chloro-2-fluoro-phenyl)-7-[6-[1-(2,2-difluoroethyl)-6-oxo-3-pyridyl]-3,6-dihydro-2H-pyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (29 mg, 53 μ mol) in ethyl acetate (1.6 ml) were added magnesium oxide (21 mg, 534 μ mol) and triethylamine (6.5 mg, 9 μ l, 65 μ mol). The flask was purged with argon, then palladium on charcoal (10%, 11 mg) was added and the flask was purged with argon again. After filling with hydrogen, the reaction was stirred under hydrogen atmosphere (balloon pressure) at room temperature for 8 h. The reaction mixture was filtered through Dicalite and concentrated under reduced pressure. The residue was purified by reversed phase column chromatography (C18 Gold, 10-100% water in acetonitrile) to afford 9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one (7 mg, 24%) as yellow solid, MS m/z: 545.1 [M+H]⁺, ESI pos.

The following **Examples 267 to 276** were prepared by chiral separation of the mentioned racemic compounds as described for Examples 95 and 96. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Racemic compound	MS (ESI): m/z
267		9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one	Example 252	545.2 [M+H] ⁺
268		9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-	Example 252	545.2 [M+H] ⁺

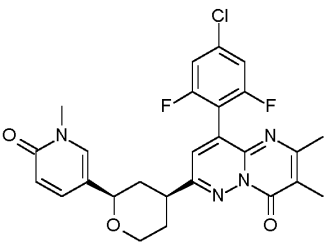
		4-yl]-2,3-dimethyl- pyrimido[1,2-b]pyridazin- 4-one		
269		9-(4-chloro-2-fluoro- phenyl)-7-[(2R,4S)-2-[6- keto-1-(2,2,2- trifluoroethyl)-3- pyridyl]tetrahydropyran- 4-yl]-2,3-dimethyl- pyrimido[1,2-b]pyridazin- 4-one	Example 253	563.2 [M+H] ⁺
270		9-(4-chloro-2-fluoro- phenyl)-7-[(2S,4R)-2-[6- keto-1-(2,2,2- trifluoroethyl)-3- pyridyl]tetrahydropyran- 4-yl]-2,3-dimethyl- pyrimido[1,2-b]pyridazin- 4-one	Example 253	563.2 [M+H] ⁺
271		9-(4-chloro-2-fluoro- phenyl)-7-[(2R,4S)-2-(1- isopropyl-6-keto-3- pyridyl)tetrahydropyran- 4-yl]-2,3-dimethyl- pyrimido[1,2-b]pyridazin- 4-one	Example 254	523.3 [M+H] ⁺

272		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	Example 254	523.3 [M+H] ⁺
273		9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	Example 265	571.3 [M+H] ⁺
274		9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	Example 265	571.3 [M+H] ⁺
275		9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	Example 264	485.4 [M+H] ⁺

		pyrazino[1,2-a]pyrimidin-4-one		
276		9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one	Example 264	485.4 [M+H] ⁺

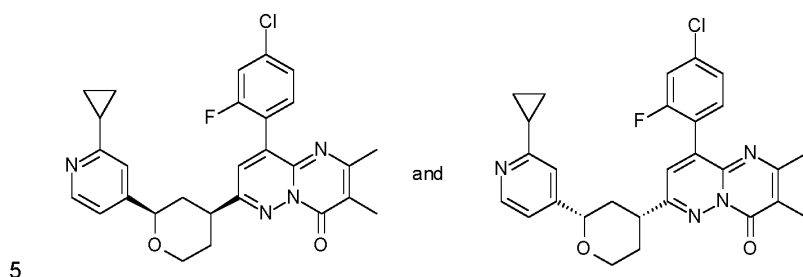
The following **Examples 277 to 221** were prepared in analogy to Examples 15 by starting from the indicated intermediates. Reduction in step 2 was performed with addition of magnesium oxide and triethylamine as described for Examples 131 and 132. Chiral separation was

5 performed as described for Examples 178 and 179. The absolute stereochemistry was assigned arbitrarily, the relative stereochemistry was determined by NMR.

Ex.	Structure	Name	Intermediates	MS (ESI): m/z
277		9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B7 and C16	513.2 [M+H] ⁺

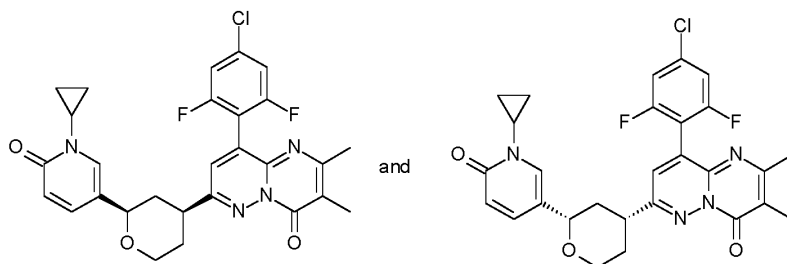
278		9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one	B7 and C16	513.2 [M+H] ⁺
279		9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B16 and C19	500.4 [M+H] ⁺
280		9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one	B16 and C19	500.2 [M+H] ⁺
281		9-(4-chloro-2-fluorophenyl)-7-[rac-(2R,4S)-2-[6-keto-1-(trifluoromethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one	B3 and C47	549.3 [M+H] ⁺

Example 282 and Example 283: 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



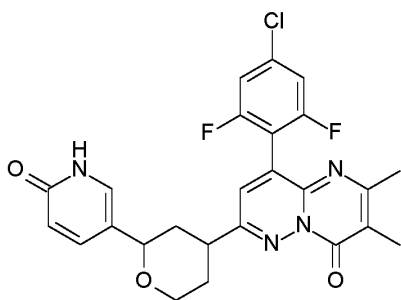
The title compounds were prepared in analogy to Example 207 and 208 using Intermediate C44 instead of Intermediate C33. Yellow solids with MS m/z: 505.2 $[M+H]^+$, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 284 and Example 285: 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



Step 1: 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[2-(6-oxo-1H-pyridin-3-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one

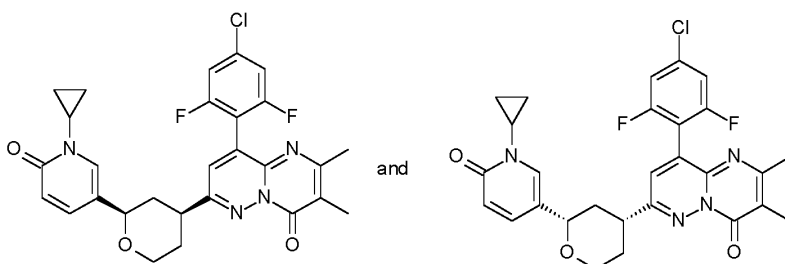
15



The title compound was prepared in analogy to Example 201 using Intermediate B7 instead of Intermediate B3 in step 1. Light yellow solid with MS m/z : 499.2 $[M+H]^+$, ESI pos.

Step 2: 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-

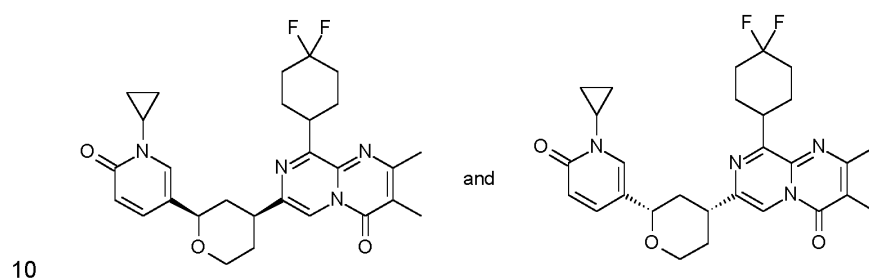
5 pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one and 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one



A mixture of 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[2-(6-oxo-1H-pyridin-3-yl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one (130 mg, 0.26 mmol),
 10 cyclopropylboronic acid (45 mg, 0.52 mmol), 2,2'-bipyridyl (45 mg, 0.29 mmol), copper diacetate (52 mg, 0.29 mmol) and sodium carbonate (55 mg, 0.52 mmol) in 1,2-dichloroethane (3 ml) was stirred at 70 °C for 2 h under oxygen atmosphere. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (15 ml x 3). The combined organic layers
 15 were washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by preparative HPLC (Phenomenex Luna, C18, 150 x 25 mm x 10 μm , mobile phase: water / 0.25% formic acid - acetonitrile, 0-65%, flow rate 25 ml/min) to afford the racemic compound which was separated by chiral SFC (Daicel Chiralpak AS 250 mm x 30 mm, 10 μm , acetonitrile / isopropanol / 0.1% ammonium hydroxide, flow rate 80 ml/min) to give 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-
 20

pyrimido[1,2-b]pyridazin-4-one (25 mg, 18% yield) as light yellow solid, MS m/z: 539.2 [M+H]⁺, ESI pos. and 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one (24 mg, 17% yield) as light yellow solid, MS m/z: 539.2 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 286 and Example 287: 7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one and 7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one



The title compounds were prepared in analogy to Example 284 and 285 using Intermediate B15 instead of Intermediate B7. White solids with MS m/z: 511.3 [M+H]⁺, ESI pos. The absolute stereochemistry was assigned arbitrarily.

Example 288

- 15 A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
20 Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

Example 289

- 25 A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

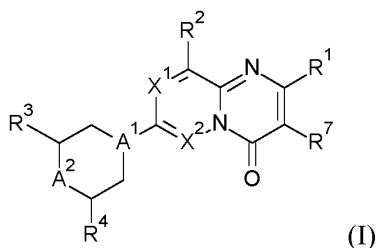
Per capsule

- 245 -

Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
5 Magnesium stearate	<u>0.5 mg</u>
	220.0 mg

Claims

1. A compound of formula (I)

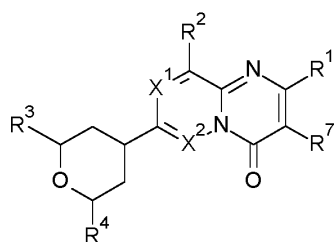


(I)

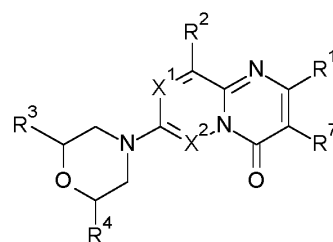
or a pharmaceutically acceptable salt thereof, wherein:

- 5 A¹, X¹ and X² are each independently selected from N and CH;
 A² is selected from O and CR⁵R⁶;
 R¹ is selected from C₁-C₆-alkyl and halo-C₁-C₆-alkyl;
 R² is selected from C₆-C₁₀-aryl, 5- to 6-membered heteroaryl and C₃-C₁₀-
 10 cycloalkyl, wherein said C₆-C₁₀-aryl, 5- to 6-membered heteroaryl and C₃-C₁₀-
 cycloalkyl are optionally substituted with 1-3 substituents independently
 selected from halogen, C₁-C₆-alkyl and halo-C₁-C₆-alkyl;
 R³ is selected from 5- to 6-membered heteroaryl and 3- to 6-membered
 heterocyclyl, wherein said 5- to 6-membered heteroaryl and 3- to 6-membered
 15 heterocyclyl are optionally substituted with 1-3 substituents independently
 selected from halogen, cyano, amino, hydroxy, oxo, C₁-C₆-alkyl, halo-C₁-C₆-
 alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₃-C₁₀-
 cycloalkyl, halo-C₃-C₁₀-cycloalkyl, C₃-C₁₀-cycloalkyl-C₁-C₆-alkyl, C₃-C₁₀-
 cycloalkyl-C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyloxy, 3- to 6-membered
 heterocyclyl, halo-3- to 6-membered heterocyclyl, 3- to 6-membered
 20 heterocyclyl-C₁-C₆-alkyl, 3- to 6-membered heterocyclyl-C₁-C₆-alkoxy and 3-
 to 6-membered heterocycliloxy;
 R⁴ is selected from hydrogen and C₁-C₆-alkyl;
 R⁵ and R⁶ are each independently selected from hydrogen and halogen; and
 R⁷ is selected from hydrogen and C₁-C₆-alkyl.
- 25 2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable
 salt thereof, wherein:
 (i) X¹ and X² are both CH; or
 (ii) X¹ is CH and X² is N; or

- (iii) X^1 is N and X^2 is CH.
3. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- (i) X^1 is CH and X^2 is N; or
- 5 (ii) X^1 is N and X^2 is CH.
4. The compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein A^1 is CH.
5. The compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein A^1 is N.
- 10 6. The compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein:
- A^2 is selected from O and CR^5R^6 ;
 R^5 and R^6 are both hydrogen or
 R^5 and R^6 are both halogen.
- 15 7. The compound of formula (I) according to claim 6, or a pharmaceutically acceptable salt thereof, wherein:
- A^2 is selected from O and CR^5R^6 ;
 R^5 and R^6 are both hydrogen or
 R^5 and R^6 are both fluoro.
- 20 8. The compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein A^2 is O.
9. The compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is a compound of formula (II) or (III):



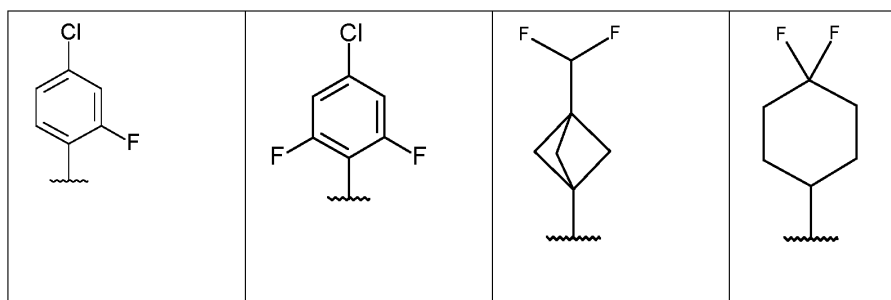
(II)



(III)

wherein the variables are as defined in any one of claims 1 to 3.

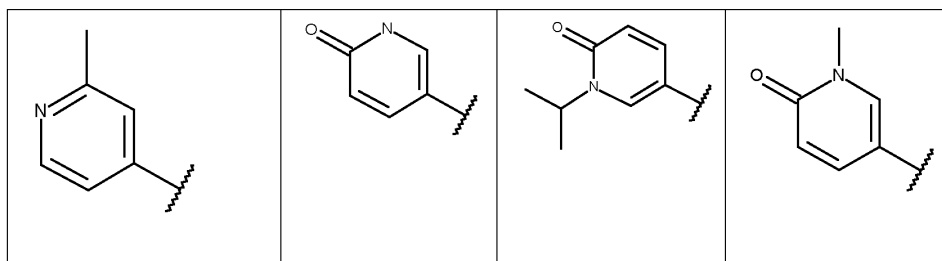
10. The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from methyl and CHF_2 .
- 5 11. The compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from C_6 - C_{10} -aryl, C_3 - C_{10} -cycloalkyl, and 5- to 6-membered heteroaryl comprising 1-2 heteroatoms independently selected from N, O and S, wherein said C_6 - C_{10} -aryl, C_3 - C_{10} -cycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with 1-3 substituents
10 independently selected from halogen and halo- C_1 - C_6 -alkyl.
12. The compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, pyridyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane are optionally
15 substituted with 1-3 substituents independently selected from fluoro, chloro, CHF_2 , and CF_3 .
13. The compound of formula (I) according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from C_6 - C_{10} -aryl and C_3 - C_{10} -cycloalkyl, wherein said C_6 - C_{10} -aryl and C_3 - C_{10} -cycloalkyl are substituted with 1-3
20 substituents independently selected from halogen and halo- C_1 - C_6 -alkyl.
14. The compound of formula (I) according to claim 13, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, cyclohexyl, and bicyclo[1.1.1]pentane substituted with 1-3 substituents independently selected from fluoro, chloro, and CHF_2 .
- 25 15. The compound of formula (I) according to claim 14, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

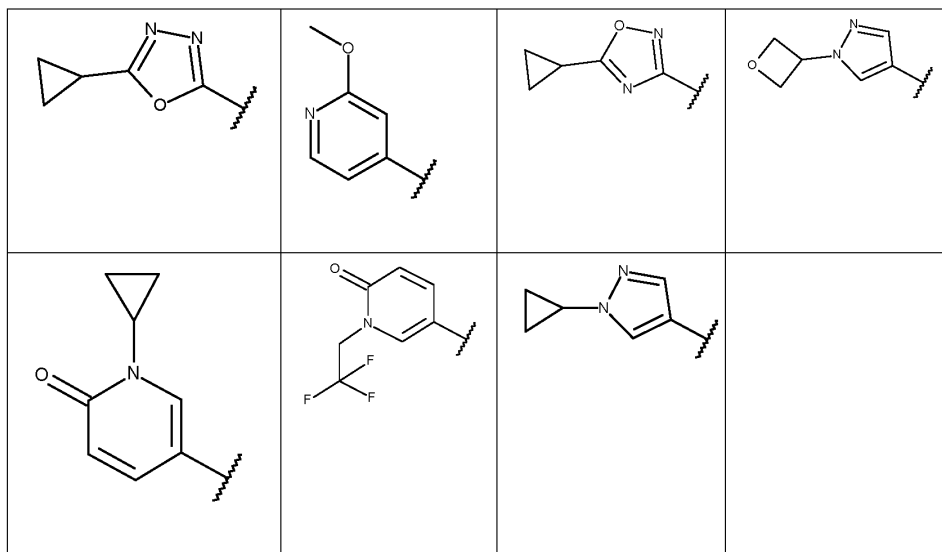


16. The compound of formula (I) according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is optionally substituted with 1-2 substituents independently selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkyl, and 3- to 6-membered heterocyclyl- C_1 - C_6 -alkoxy, and wherein said 3- to 6-membered heterocyclyl is optionally substituted with 1-2 substituents independently selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkoxy, and oxo.
17. The compound of formula (I) according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF_2 , CF_3 , 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutylloxy, oxetanyl, oxetanylmethyl, and oxetanylmethoxy, and wherein said

1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF_2 , CF_3 , 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, oxetanylmethoxy, and oxo.

18. The compound of formula (I) according to claim 16, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is substituted with 1 substituent selected from C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, and 3- to 6-membered heterocyclyl, and wherein said 3- to 6-membered heterocyclyl is substituted with oxo and optionally one further substituent selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, and C_3 - C_{10} -cycloalkyl.
19. The compound of formula (I) according to claim 18, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are substituted with 1 substituent selected from methyl, methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is substituted with oxo and optionally one further substituent selected from methyl, isopropyl, 2,2,2-trifluoroethyl, and cyclopropyl.
20. The compound of formula (I) according to claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:





21. The compound of formula (I) according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen and methyl.
- 5 22. The compound of formula (I) according to claim 21, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.
23. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen and methyl.
- 10 24. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1 - C_6 -alkyl.
25. The compound of formula (I) according to claim 24, or a pharmaceutically acceptable salt thereof, wherein R^7 is methyl.
- 15 26. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- (i) X^1 and X^2 are both CH; or
 - (ii) X^1 is CH and X^2 is N; or
 - (iii) X^1 is N and X^2 is CH;
- A^1 is selected from N and CH;

- A^2 is selected from O and CR^5R^6 ;
- R^1 is selected from C_1 - C_6 -alkyl and halo- C_1 - C_6 -alkyl;
- R^2 is selected from C_6 - C_{10} -aryl, C_3 - C_{10} -cycloalkyl, and 5- to 6-membered heteroaryl comprising 1-2 heteroatoms independently selected from N, O and S, wherein said C_6 - C_{10} -aryl, C_3 - C_{10} -cycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with 1-3 substituents independently selected from halogen and halo- C_1 - C_6 -alkyl;
- R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is optionally substituted with 1-2 substituents independently selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkyl, and 3- to 6-membered heterocyclyl- C_1 - C_6 -alkoxy, and wherein said 3- to 6-membered heterocyclyl is optionally substituted with 1-2 substituents independently selected from C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyl, halo- C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl- C_1 - C_6 -alkoxy, C_3 - C_{10} -cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkyl, 3- to 6-membered heterocyclyl- C_1 - C_6 -alkoxy, and oxo;
- R^4 is selected from hydrogen and C_1 - C_6 -alkyl;
- R^5 and R^6 are both hydrogen or
- R^5 and R^6 are both halogen; and
- R^7 is selected from hydrogen and C_1 - C_6 -alkyl.
27. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- (i) X^1 and X^2 are both CH; or
- (ii) X^1 is CH and X^2 is N; or
- (iii) X^1 is N and X^2 is CH;

- A^1 is selected from N and CH;
 A^2 is selected from O and CR^5R^6 ;
 R^1 is selected from methyl and CHF_2 ;
 R^2 is selected from phenyl, pyridyl, cyclohexyl, bicyclo[3.1.0]hexane and
 5 bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl, bicyclo[3.1.0]hexane
 and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents
 independently selected from fluoro, chloro, CHF_2 , and CF_3 ;
 R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and
 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and
 10 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents
 independently selected from methyl, ethyl, isopropyl, CHF_2 , CF_3 , 2,2-
 difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl,
 cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl,
 oxetanylmethyl, and oxetanylmethoxy, and wherein said 1,2-dihydropyridine
 15 is optionally substituted with 1-2 substituents independently selected from
 methyl, ethyl, isopropyl, CHF_2 , CF_3 , 2,2-difluoroethyl, 2,2,2-trifluoroethyl,
 methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl,
 cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl,
 oxetanylmethoxy, and oxo;
 20 R^4 is selected from hydrogen and methyl;
 R^5 and R^6 are both hydrogen or
 R^5 and R^6 are both fluoro; and
 R^7 is selected from hydrogen and methyl.
28. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable
 25 salt thereof, wherein:
 (i) X^1 is CH and X^2 is N; or
 (ii) X^1 is N and X^2 is CH;
 A^1 is CH;
 A^2 is O;
 30 R^1 is selected from C_1 - C_6 -alkyl and halo- C_1 - C_6 -alkyl;
 R^2 is selected from C_6 - C_{10} -aryl and C_3 - C_{10} -cycloalkyl, wherein said C_6 - C_{10} -aryl
 and C_3 - C_{10} -cycloalkyl are substituted with 1-3 substituents independently
 selected from halogen and halo- C_1 - C_6 -alkyl;

- R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is substituted with 1 substituent selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₁₀-cycloalkyl, and 3- to 6-membered heterocyclyl, and wherein said 3- to 6-membered heterocyclyl is substituted with oxo and optionally one further substituent selected from C₁-C₆-alkyl, halo-C₁-C₆-alkyl, and C₃-C₁₀-cycloalkyl;
- R^4 is hydrogen; and
 R^7 is C₁-C₆-alkyl.
29. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:
- (i) X^1 is CH and X^2 is N; or
 (ii) X^1 is N and X^2 is CH;
- A^1 is CH;
 A^2 is O;
 R^1 is selected from methyl and CHF₂;
 R^2 is selected from phenyl, cyclohexyl, and bicyclo[1.1.1]pentane substituted with 1-3 substituents independently selected from fluoro, chloro, and CHF₂;
 R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are substituted with 1 substituent selected from methyl, methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is substituted with oxo and optionally one further substituent selected from methyl, isopropyl, 2,2,2-trifluoroethyl, and cyclopropyl;
 R^4 is hydrogen; and
 R^7 is methyl.
30. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from:
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(3S)-3-(1-methylpyrazol-4-yl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(3S)-4,4-difluoro-3-(1-methylpyrazol-4-yl)-1-piperidyl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 20 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one formiate;
- 10 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methylmorpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methyl-6-oxopyridin-3-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 25 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 7-[(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 15 7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 15 7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 25 2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
5 9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one;
10 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
15 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
25 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
30 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
5 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
10 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
15 7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
25 2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]-9-[6-(trifluoromethyl)pyridin-3-yl]pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
30 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 5 7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 15 7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 25 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(2-fluorophenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2,6-difluoro-phenyl)-7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 10 2,3-dimethyl-7-[rac-(2R,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-3-methyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 20 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 25 7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclobutoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 7-[2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[2-[2-(oxetan-3-ylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

- 7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
5 9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
10 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
15 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
20 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
25 7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
30 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 5 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 10 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 15 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;
- 20 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;
- 25 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[6-keto-1-(trifluoromethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 30 9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
- 9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

- 9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
5 7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one; and
7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.
31. The compound of formula (I) according to any one of claims 1 to 30, or a
10 pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.
32. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.
- 15 33. A method of treating or preventing a condition associated with a loss of function of human TREM2 in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 32.
- 20 34. The method according to claim 33, wherein said condition associated with a loss of function of human TREM2 is selected from Parkinson's disease, rheumatoid arthritis, Alzheimer's disease, amyotrophic lateral sclerosis, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, and stroke.
35. A compound according to any one of claims 1 to 30, or a pharmaceutically
25 acceptable salt thereof, or a pharmaceutical composition according to claim 32, for use in a method according to claim 33 or 34.
36. Use of a compound according to any one of claims 1 to 30, or of a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 32, in a method according to claim 33 or 34.

37. Use of a compound according to any one of claims 1 to 30, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in a method according to claim 33 or 34.
38. The invention as described hereinbefore.