PYRIDAZINE COMPOUNDS, THEIR PREPARATION, AND THEIR THERAPEUTIC USES

FIELD OF THE DISCLOSURE

Disclosed herein are pyridazine compounds, their preparation, a medicament and a pharmaceutical composition comprising said pyridazine compounds, their use as a medicament and more particularly their use as inhibitor of NOD-like receptor protein 3 (NLRP3) inflammasome pathway, and more particularly their use in the prevention and/or in the treatment of Parkinson's disease, frontotemporal Dementia, Multiple System Atrophy, Alzheimer's disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or brain injury.

BACKGROUND OF THE DISCLOSURE

The NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) or NACHT, LRR and PYD domains-containing protein 3 (NALP3), is a cytosolic sensor of diverse pathogen- and host-derived molecules. Upon activation, NLRP3 oligomerizes and recruits an adaptor protein called apoptosis-associated speck like protein (ASC). ASC then polymerizes to form a large aggregate known as ASC speck. In turn, polymerized ASC interacts with the cysteine protease caspase-1 to form a complex termed the inflammasome. This multicomplex protein forms a platform for the binding, dimerization, and activation of the caspase-1 protease. Caspase-1 then cleaves the precursor forms of the pro-inflammatory cytokines IL1β and IL18 (termed pro- IL1β and pro-IL18) and thereby activates adapted inflammatory responses. However, this pathway was shown to be associated with various inflammation associated processes and diseases, including:

- Neurodegenerative diseases such as Parkinson's Disease (PD), Multiple System Atrophy (MSA), Alzheimer's Disease (AD), Frontotemporal Dementia (FTD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Brain injury (Guan Y & Han F. Front. Integr., Neurosci. 14 :37, 2020);
- Inflammatory diseases including Muckle-Wells Autoinflammatory Disorder (Agostini et al., 2004), cryopyrin-associated periodic syndrome (CAPS) (Mortimer et al., Nature Immunol. 2016, 17(10), 1176-1188); sickle cell disease; systemic lupus erythematosus (SLE); liver related diseases, viral hepatitis, non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis, and alcoholic liver disease (Petrasek et al., J. Clin. Invest. 2012, 122, 3476-

89), and inflammatory arthritis related disorders, such as gout, pseudogout (chondrocalcinosis), osteoarthritis (Ridker et al., N. Engl. J. Med. 2017, 377, 1119-31), and rheumatoid arthritis (Mathews et al., Ann. Rheum. Dis. 2014, 73, 1202-10), acute or chronic arthropathy, and kidney related diseases such as hyperoxaluria (Knaufet et al., Kidney Int. 2013, 84, 895-901), lupus nephritis, hypertensive nephropathy (Krishnan et al., Br. J. Pharmacol. 2016, 173, 752-10 65), hemodialysis related inflammation and diabetic nephropathy (Shahzad et al., Kidney Int. 2015, 87, 74-84);

- Obesity & insulin resistance (Rheinheimer J. et al., Metabolism Clin & Experimental 74: 1-9, 2017); Pancreatitis (Fu Q. et al., BioMed Research International Volume 2018, Article ID 12949512018); Myocarditis (Toldo S et al, Int J Cardiol 2014);

- Eye diseases, where the NLRP3 inflammasome has been shown to contribute to diabetic retinopathy (Perrone L. et al., J. Cell. Physiol. 221: 262–272, 2009), acute glaucoma (Chi W. et al. National Academy Science 111: 11181-11186, 2014), age-related macular degeneration (Tseng W.A. et al., Investigative Ophthal & Visual Science 54: 11-120, 2013), Behcet's syndrome and dry eye disease (Zheng Q. et al., Experimental Eye Research 134: 133-140, 2015);

- Metabolic, cardiac, skin disorder & cancer, *e.g.,* diabetic cardiomyopathy (Luo B. et al., PLoS ONE 9(8): e104771, 2014); Kawasaki disease (Jia et al. Cell Death and Disease 10:778; 2019; Anzai F. et al., J. Molecular & Cell Cardiology 138: 185-196, 2020); cardiovascular metabolic disorders, atherosclerosis, type I and type II diabetes and related complications, peripheral artery disease (PAD), acute heart failure and hypertension (Ridker et al., N. Engl. J. Med. 2017, 377, 1119-31; wound healing and scar formation; inflammatory skin diseases (Sweeney et al., Br. J. Dermatol. 2015, 173, 1361), asthma, sarcoidosis, age-related macular degeneration; cancer related diseases, *e.g.,* myeloproliferative neoplasms, leukemias, myelodysplastic syndromes (MDS), myelofibrosis, lung cancer, colon cancer (Ridker et al., Lancet 2017, 390, 1833-42); and

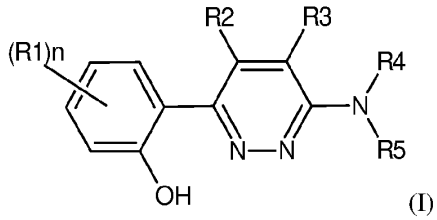
- SARS-Cov-2: NLRP3 inflammasome is key player in antiviral responses (Zhao C. and Zhao W. 11, 211: 2020; Freeman & Swartz, Frontiers in Immunol. 11, 1518, 2020).

Inhibitors of NLRP3 are potential treatments for these conditions with unmet clinical needs.

Therefore, there is a need for inhibitors of the NLRP3 inflammasome pathway to provide new or alternative treatments.

SUMMARY OF THE DISCLOSURE

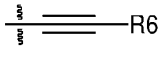
Provided herein is a compound of formula (I) or a pharmaceutically acceptable salt thereof:



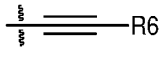
(I)

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R4 and **R5** form together with the nitrogen atom to which they are attached:

- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

- a 8 to 11 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one to three additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 4 to 10 carbon atoms, or

- a 7 to 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 11 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Herein provided are also:

- a medicament comprising said compound of formula (I) as defined in the present disclosure or a pharmaceutically acceptable salt thereof,

- a pharmaceutical composition comprising said compound of formula (I) as defined in the present disclosure or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient,

- said compound of formula (I) according to the present disclosure or a pharmaceutically acceptable salt thereof, for use as a medicine,

- said compound of formula (I) according to the present disclosure or a pharmaceutically acceptable salt thereof, for use as inhibitor of NOD-like receptor protein 3 (NLRP3) inflammasome,

- said compound of formula (I) according to the present disclosure or a pharmaceutically acceptable salt thereof, for use in the prevention and/or in the treatment of Parkinson's disease, frontotemporal Dementia, Multiple System Atrophy, Alzheimer's disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or brain injury.

Definitions

In the context of the present disclosure, the terms below have the following definitions unless otherwise mentioned throughout the instant specification:

- a **halogen atom**: a fluorine (F), a chlorine (Cl), a bromine (Br) or an iodine (I) atom, and for example a fluorine or a chlorine or an iodine atom;
- a **hydroxyl** group: a "-OH" group;
- an **oxo** group: a "=O" group;
- a **cyano** group: a "-C≡N" group or a CN group;
- a -**(C_x-C_y)alkyl** group: a linear or branched saturated hydrocarbon-based aliphatic group comprising from x to y carbon atoms, for example from 1 to 4 carbon atoms, By way of examples, mention may be made of, but not limited to: methyl, ethyl, propyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl groups, and the like;
- a -**(C_x-C_y)alkoxy** group: an -O-alkyl group where the alkyl group is as previously defined. For example, a -(C_1-C_4)alkoxy group. By way of examples, mention may be made of, but not limited to: methoxy, ethoxy, propoxy, isopropoxy, linear, secondary or tertiary butoxy, isobutoxy groups, and the like;
- a **halo(C_x-C_y)alkyl-** group: an alkyl group as previously defined in which one or more hydrogen atoms have been replaced by one or more different or identical halogen atom as previously defined. By way of examples, mention may be made of, but not limited to:

trifluoromethyl, fluoromethyl, difluoromethyl, chloromethyl, dichloromethyl, iodomethyl, diiodomethyl, triiodomethyl, diiodofluoromethyl, bromomethyl, tribromomethyl, trichloromethyl, chlorofluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, tetrafluoroethyl, chloroethyl, dichloroethyl, trichloroethyl, tetrachloroethyl, iodopropyl, diiodopropyl, bromopropyl, dibromopropyl, tetraiodopropyl, pentaiodopropyl, fluoropropyl, difluoropropyl, trifluoropropyl, tetrafluoropropyl, chloropropyl, dichloropropyl, trichloropropyl, tetrachloropropyl, pentachloropropyl, bromobutyl, dibromobutyl, tetraiodobutyl, pentaiodobutyl, fluorobutyl, difluorobutyl, trifluorobutyl, tetrafluorobutyl, chlorobutyl, dichlorobutyl, trichlorobutyl, tetrachlorobutyl, pentachlorobutyl, hexachlorobutyl, perfluoroethyl, perfluoropropyl, perfluorobutyl, perbromoethyl, perbromoethyl, perbromopropyl, perbromobutyl, periodoethyl, periodoethyl, periodopropyl, periodobutyl, perchloroethyl, perchloroethyl, perchloropropyl, perchlorobutyl groups, and the like;

- a **halo(C_x-C_y)alkoxy-** group: a radical -O-alkyl group in which the alkyl group is as previously defined, said alkyl group being substituted by one or more identical or different halogen atoms as previously defined. By way of examples, mention may be made of, but not limited to: trifluoromethoxy, fluoromethoxy, difluoromethoxy, chlorofluoromethoxy, chloromethoxy, dichloromethoxy, iodomethoxy, diiodomethoxy, triiodomethoxy, bromomethoxy, tribromomethoxy, trichloromethoxy, dichlorobromomethoxy, fluoroethoxy, difluoroethoxy, trifluoroethoxy, tetrafluoroethoxy, chloroethoxy, dichloroethoxy, trichloroethoxy, tetrachloroethoxy, iodopropoxy, diiodopropoxy, bromopropoxy, dibromopropoxy, tetraiodopropoxy, pentaiodopropoxy, fluoropropoxy, difluoropropoxy, trifluoropropoxy, tetrafluoropropoxy, chloropropoxy, dichloropropoxy, trichloropropoxy, tetrachloropropoxy, pentachloropropoxy, bromobutoxy, dibromobutoxy, tetraiodobutoxy, pentaiodobutoxy, fluorobutoxy, difluorobutoxy, trifluorobutoxy, tetrafluorobutoxy, chlorobutoxy, dichlorobutoxy, trichlorobutoxy, tetrachlorobutoxy, pentachlorobutyoxy, hexachlorobutoxy, perfluoroethoxy, perfluoropropoxy, perfluorobutoxy, perbromoethoxy, perbromoethoxy, perbromopropoxy, perbromobutoxy, periodoethoxy, periodoethoxy, periodopropoxy, periodobutoxy, perchloroethoxy, perchloroethoxy, perchloropropoxy, perchlorobutoxy groups, and the like;

- a **hydroxy(C_x-C_y)alkyl-** group: a alkyl group as previously defined in which one or more hydrogen atom have been replaced by one or more hydroxy group as previously defined. By

way of examples, mention may be made of, but not limited to: OH-CH_2-, OH-$C(CH_3)_2$-, CH_3-CH(OH)-, CH_2(OH)-CH(OH)-, CH_3-CH(OH)-CH_2-, CH_3-CH(OH)-CH(OH)-, $(CH_3)_2$-C(OH)-CH_2-, $(CH_3)_2$-C(OH)-CH(OH)-, $(CH_3)_3$-C-CHOH- groups, and the like;

- a **SH-(C_1-C_4)alkyl-** group: a alkyl group as previously defined in which one or more hydrogen atom have been replaced by one or more SH groups. By way of examples, mention may be made of, but not limited to: SH-CH_2-, SH-$C(CH_3)_2$-, CH_3-CH(SH)-, CH_2(SH)-CH(SH)-, CH_3-CH(SH)-CH_2-, $(CH_3)_2$-C(SH)-CH_2-, $(CH_3)_2$-C(SH)-CH(SH)-, $(CH_3)_3$-C-CH(SH)- groups, and the like;

- a **CN-(C_1-C_4)alkyl-** group: a alkyl group as previously defined in which one or more hydrogen atom have been replaced by one or more CN groups. By way of examples, mention may be made of, but not limited to: CN-CH_2-, CN-$C(CH_3)_2$-, CH_3-CH(CN)-, CH_2(CN)-CH(CN)-, CH_3-CH(CN)-CH_2-, $(CH_3)_2$-C(CN)-CH_2-, $(CH_3)_2$-C(CN)-CH(CN)-, $(CH_3)_3$-C-CH(CN)- groups, and the like

- a **NH_2-(C_1-C_4)alkyl-** group: a alkyl group as previously defined in which one or more hydrogen atom have been replaced by one or more NH_2 groups. By way of examples, mention may be made of, but not limited to: NH_2-CH_2-, NH_2-$C(CH_3)_2$-, CH_3-CH(NH_2)-, CH_2(NH_2)-CH(NH_2)-, CH_3-CH(NH_2)-CH_2-, $(CH_3)_2$-C(NH_2)-CH_2-, $(CH_3)_2$-C(NH_2)-CH(NH_2)-, $(CH_3)_3$-C-CH(NH_2)- groups, and the like;

- a **mono(C_1-C_4)alkylamino- group** : an amino group which is substituted by one alkyl group as previously defined. By way of examples, mention may be made of, but not limited to: CH_3-NH-, CH_3-CH_2-NH-, CH_3-CH_2-CH_2-NH-, CH_3-CH_2-CH_2-CH_2-NH-, $(CH_3)_2$-CH-CH_2-NH-, $(CH_3)_3$-C-NH-, CH_3-CH_2-CH(CH_3)-NH- groups, and the like;

- a **di(C_1-C_4)alkylamino- group** : an amino group which is substituted by two alkyl groups as previously defined. By way of examples, mention may be made of, but not limited to: $(CH_3)_2$N-, $(CH_3$-$CH_2)_2$N-, (CH_3)(CH_3-CH_2)N-, $(CH_3$-CH_2-$CH_2)_2$N-, $(CH_3$-CH_2-CH_2-$CH_2)_2$N-, $((CH_3)_2$-CH-CH_2)(CH_3)N-, $((CH_3)_3$-C)(CH_3CH_2)N-, (CH_3-CH_2-CH(CH_3))(CH_3-CH_2-CH_2)N- groups, and the like;

- a **(C_2-C_5)acyl-** group: a (C_1-C_4)alkyl group as previously defined linked to a -C(=O)- group. By way of examples, mention may be made of, but not limited to: CH_3-C(=O)-, CH_3-CH_2-C(=O)-, CH_3-CH_2-CH_2-C(=O)-, CH_3-CH_2-CH_2-CH_2-C(=O)-, $(CH_3)_2$-CH-CH_2-C(=O)-, $(CH_3)_3$-C-C(=O)-, CH_3-CH_2-CH(CH_3)-C(=O)-groups, and the like;

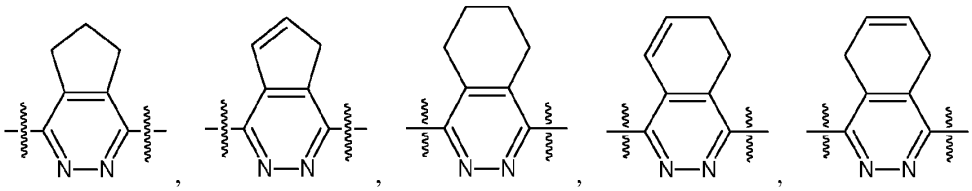
- a **(C_2-C_5)acylamino-** group: an amino group -NH- which is substituted by one acyl group comprising from 2 to 5 carbon atoms, the acyl group being a (C_1-C_4)alkyl group as previously defined linked to a -C(=O)- group which is itself linked to the amino group. By way of examples, mention may be made of, but not limited to: CH_3-C(=O)-NH-, CH_3-CH_2-C(=O)-NH-, CH_3-CH_2-CH_2-C(=O)-NH-, CH_3-CH_2-CH_2-CH_2-C(=O)-NH-, $(CH_3)_2$-CH-CH_2-C(=O)-NH-, $(CH_3)_3$-C-C(=O)-NH-, CH_3-CH_2-CH(CH_3)-C(=O)-NH-groups, and the like;

- a **(C_3-C_6)cycloalkyl-** group: a cyclic alkyl group comprising, unless otherwise mentioned, from 3 to 6 carbon atoms, saturated or partially unsaturated and unsubstituted or substituted. By way of examples, mention may be made of, but not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexyl, and the like;

- a **OH-(C_3-C_6)cycloalkyl**- group: a cyclic alkyl group as defined above in which one or more hydrogen atom have been replaced by one or more hydroxyl groups. By way of examples, mention may be made of, but not limited to: hydroxycyclopropyl, hydroxycyclobutyl, hydroxycyclopentyl, hydroxycyclobutenyl, hydroxycyclopentenyl, hydroxycyclohexenyl, hydroxycyclohexyl, dihydroxycyclopropyl, dihydroxycyclobutyl, trihydroxycyclopentyl, dihydroxycyclobutenyl, trihydroxycyclopentenyl, dihydroxycyclohexenyl, tetrahydroxycyclohexyl and the like;

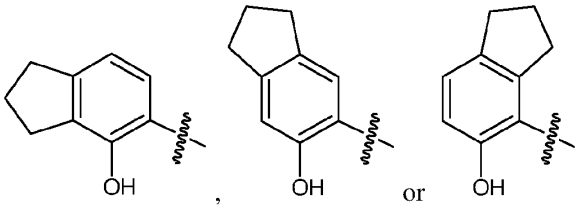
- a **NH_2-(C_3-C_6)cycloalkyl**- group: a cyclic alkyl group as defined above in which one or more hydrogen atom have been replaced by one or more NH_2 groups. By way of examples, mention may be made of, but not limited to: aminocyclopropyl, aminocyclobutyl, aminocyclopentyl, aminocyclobutenyl, aminocyclopentenyl, aminocyclohexenyl, aminocyclohexyl, diaminocyclopropyl, diaminocyclobutyl, triaminocyclopentyl, diaminocyclobutenyl, triaminocyclopentenyl, diaminocyclohexenyl, tetraaminocyclohexyl and the like;

- a **(C_5-C_6)carbocyclic ring which is fused to the pyridazine ring**: a saturated or partially saturated ring comprising 5 or 6 carbon atoms which is fused to the pyridazine ring. Such carbocyclic ring may be saturated or partially saturated and unsubstituted or substituted. In other terms, the (C_5-C_6)carbocyclic ring is not an aromatic ring and the bicyclic structure formed by the carbocyclic ring and the pyridazine ring comprises three or four double bonds. By way of examples, mention may be made of, but not limited to a cyclopentyl fused to the pyridazine ring, a cyclohexyl fused to the pyridazine ring, so as to form for example:



rings, and the like ;

- **a cyclopentane ring which is fused to the phenol group**: By way of examples, mention may be made of the following groups:



in which the symbol  represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring. In other words, **a cyclopentane ring which is fused to the phenol group** as defined in the present disclosure means an indane ring substituted by one hydroxy group, said indane being linked to the pyridazine ring *via* a single bond in ortho position of the hydroxy group;

- a **3 to 7 membered monocyclic heterocycloalkyl ring** (also named (C_2-C_6)heterocycloalkyl group): a monocyclic alkyl group comprising, unless otherwise mentioned, from 2 to 6 carbon atoms and comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom. Such heterocycloalkyl group may be saturated or partially saturated and unsubstituted or substituted. By way of examples of monocyclic heterocycloalkyl groups, mention may be made of, but not limited to: azepane, piperazine, morpholino, pyrrolidine, tetrahydropyrane, thietane dioxide, piperidine, thiolane, thiolane oxide, thiolane dioxide, dihydrofurane, tetrahydrofurane, azetidine, oxetane, thietane, 2H-pyrrole, 1H-, 2H- or 3H-pyrroline, tetrahydrothiophene, oxadiazole and for example 1,3,4-oxadiazole or 1,3,5-oxadioazole, thiadiazole and for example 1,3,4-thiadiazole, isoxazoline, 2- or 3-pyrazoline, pyrroline, pyrazolidine, imidazoline, imidazolidine, thiazolidine, isooxazoline, isoxazolidine, dioxalane, oxathiazole, oxathiadiazole, dioxazole, thiomorpholino, hexahydropyrimidine groups, and the like;

- a **8 to 11 membered bicyclic heterocycloalkyl ring** (also named (C_4-C_{10})heterocycloalkyl group): a bicyclic alkyl group comprising, unless otherwise mentioned, from 4 to 10 carbon atoms and comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom. Such heterocycloalkyl group may be saturated or partially saturated, and unsubstituted or substituted, and bridged or not bridged. By way of examples of bicyclic heterocycloalkyl groups, mention may be made of, but not limited to: a dihydropyrazolooxazinyl group such as a dihydro-2H-pyrazolo[4,3-b][1,4]oxazinyl group for instance a 5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazinyl group; a hexahydropyridooxazinyl group or a octahydropyridooxazinyl group such as a hexahydro-2H-pyrido[3,4-b][1,4]oxazinyl group, a hexahydro-2H-pyrido[4,3-b][1,4]oxazinyl group, or a octahydropyrido[4,3-b][1,4]oxazinyl group for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazinyl group, a 3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazinyl group or a 2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazinyl group; a dihydropyridooxazinyl group such as a dihydropyrido[3,4-b][1,4]oxazinyl group or dihydropyrido[4,3-b][1,4]oxazinyl ring, for instance a 2,3-dihydropyrido[3,4-b][1,4]oxazinyl group or a 2,3-dihydropyrido[4,3-b][1,4]oxazinyl group; a hexahydropyranooxazinyl group or a octahydropyranooxazinyl group such as hexahydro-2H-pyrano[3,4-b][1,4]oxazinyl group for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazinyl group, or a hexahydro-2H-pyrano[4,3-b][1,4]oxazinyl group for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazinyl group; an isoindoline group; an indoline group; a decahydroisoquinoline group; a decahydroquinoline group; a tetrahydroquinoline group; a dihydroquinoline group or a tetrahydroquinoline group such as a dihydro-2H-quinolinyl group for instance a 3,4-dihydro-2H-quinolinyl group; a dihydroisoquinoline group; an azabicyclooctanyl group such as an azabicyclo[3.2.1]octanyl group for instance a 6-azabicyclo[3.2.1]octanyl group; an oxaazabicyclooctanyl group such as an oxaazabicyclo[3.2.1]octanyl group for instance a 3-oxa-8-azabicyclo[3.2.1]octanyl group; a diazabicyclononanyl group for instance a diazabicyclo[3.2.2]nonanyl group such as a 3,6-diazabicyclo[3.2.2]nonanyl group; a hexahydropyrrolooxazinyl group or a octahydropyrrolooxazinyl group such as a hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl group for instance a 2,3,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl group, a 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl group, a 3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl group or

a 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl group; a dihydrobenzoxazine group such as a 2,3-dihydro-1,4-benzoxazine group; a octahydropyridooxazinyl group such as a octahydropyrido[4,3-b][1,4]oxazinyl group for instance a 2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazinyl group; a hexahydrofuropyrrolyl ring such as a hexahydrofuro[3,4-c]pyrrolyl ring for instance a 1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrolyl ring; a hexahydropyrrolopyrrolyl ring such as a hexahydropyrrolo[3,4-b]pyrrolyl ring or a hexahydro-2H-pyrrolo[3,4-b]pyrrolyl ring for instance a 2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrolyl ring or a 3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrolyl ring, a hexahydropyrrolo[3,2-b]pyrrolyl ring or a hexahydro-1H-pyrrolo[3,2-b]pyrrolyl ring for instance a 2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrolyl ring; a hexahydropyrrolopyridyl ring or a octahydropyrrolopyridyl ring such as a hexahydropyrrolo[3,4-c]pyridyl ring for instance a 2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridyl ring, a hexahydropyrrolo[2,3-c]pyridyl ring for instance a 3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridyl ring, or a 2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridinyl ring; a hexahydrocyclopentaoxazinyl group such as a hexahydrocyclopenta[b][1,4]oxazinyl group for instance a 3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazinyl group; a dihydronaphthyridinyl ring, a tetrahydronaphthyridinyl ring, a hexahydronaphthyridinyl ring or a octahydronaphthyridinyl ring such as a dihydro-2H-naphthyridinyl ring for instance a 3,4-dihydro-2H-1,6-naphthyridinyl ring, a hexahydro-2H-1,7-naphthyridinyl ring for instance a 3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridinyl ring, a octahydro-1,5-naphthyridinyl ring for instance a 2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridinyl ring, or a octahydro-1,7-naphthyridinyl ring for instance a 2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridinyl ring or a 2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridinyl ring; and the like;

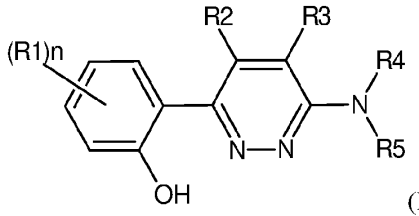
- a **7 to 12 membered bicyclic heterocyclic spiro ring:** a bicyclic heterocyclic ring system in which the two rings have only one common atom, in particular one common carbon atom, said bicyclic heterocyclic ring system comprises one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprises 3 to 11 carbon atoms. Such bicyclic heterocyclic spiro ring system may be saturated or partially saturated and unsubstituted or substituted. By way of examples of bicyclic heterocyclic spiro ring systems, mention may be made of, but not limited to: an azaspirononanyl ring such as an azaspiro[3.5]nonanyl ring, for instance a 7-

azaspiro[3.5]nonanyl ring; an azaspirooctanyl ring such as an azaspiro[3.4]octanyl ring, for instance a 6-azaspiro[3.4]octanyl ring or a 2-azaspiro[3.4]octanyl ring; an azaspiroheptanyl ring such as an azaspiro[3.3]heptanyl ring, for instance a 2- azaspiro[3.3]heptanyl ring; a diazaspirononanyl ring such as a diazaspiro[3.5]nonanyl ring, for instance a 2,7-diazaspiro[3.5]nonanyl ring; a diazaspiroheptanyl ring such as a diazaspiro[3.3]heptanyl ring, for instance a 1,6-diazaspiro[3.3]heptanyl ring; an oxaazaspirononanyl ring such as a oxaazaspiro[3.5]nonanyl ring, for instance a 2-oxa-7-azaspiro[3.5]nonanyl ring; an oxaazaspiroheptanyl ring such as an oxaazaspiro[3.3]heptanyl ring, for instance a 2-oxa-6-azaspiro[3.3]heptanyl ring; a dithiaazaspirononanyl ring such as a dithiaazaspiro[4.4]nonanyl ring for instance a 1,4-dithia-7-azaspiro[4.4]nonanyl ring; an oxadiazaspirononanyl ring such as an oxadiazaspiro[3.5]nonanyl ring for instance a 8-oxa-2,5-diazaspiro[3.5]nonanyl ring; an oxadiazaspirodecanyl ring such as an oxadiazaspiro[4.5]decanyl ring for instance a 2-oxa-6,9-diazaspiro[4.5]decanyl ring, a 6-oxa-2,9-diazaspiro[4.5]decanyl ring or a 9-oxa-2,6-diazaspiro[4.5]decanyl ring; an oxadiazaspiroundecanyl ring such as an oxadiazaspiro[5.5]undecanyl ring for instance a 4-oxa-1,8-diazaspiro[5.5]undecanyl ring ; a diazaspirodecanyl ring such as a diazaspiro[4.5]decanyl ring for instance a 1,9-diazaspiro[4.5]decanyl ring; a dioxadiazaspirododecanyl ring such as a dioxadiazaspiro[5.6]dodecanyl ring for instance a 1,11-dioxa-4,8-diazaspiro[5.6]dodecanyl ring; and the like;

- "**optionally substituted**" means "unsubstituted or "substituted with".
- R and S indicate the stereochemistry of the pseudo-asymmetric carbon atoms, according to the IUPAC rules.
- in each radical or group as defined in the present disclosure, each hydrogen atom can be replaced by a deuterium atom, which forms part of the present disclosure.

DETAILED DESCRIPTION OF THE DISCLOSURE

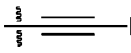
As mentioned above, herein is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



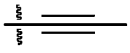
(I)

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R4 and **R5** form together with the nitrogen atom to which they are attached:

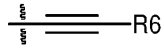
- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,
- a 8 to 11 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one to three additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 4 to 10 carbon atoms, or

- a 7 to 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 11 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

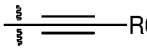
Also provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

R4 and **R5** form together with the nitrogen atom to which they are attached:

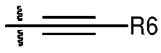
- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,
- a 8 to 11 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one to three additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 4 to 10 carbon atoms, or
- a 7 to 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 11 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-

C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Also provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R4 and **R5** form together with the nitrogen atom to which they are attached:

- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,
- a 8 to 11 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one to three additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 4 to 10 carbon atoms, or
- a 7 to 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 11 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-

C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

The compounds of formula (I) may comprise one or more asymmetric carbons. They may exist in the form of enantiomers or diastereoisomers. The compounds of formula (I) may also exist in the form of *cis* or *trans* stereoisomers. These stereoisomers, enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the disclosure.

The compounds of formula (I) may be present as well under tautomer forms.

The compounds of formula (I) may exist in the form of bases, acids, zwitterion or of addition salts with acids or bases. Hence, herein are provided compounds of formula (I) or pharmaceutically acceptable salts thereof.

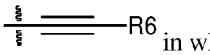
These salts may be prepared with pharmaceutically acceptable acids or bases, although the salts of other acids or bases useful, for example, for purifying or isolating the compounds of formula (I) are also provided.

Among suitable salts of the compounds of formula (I), trifluoroacetate, and formate may be cited.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **n** is 1.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **n** is 2.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R1** represent independently

of each other a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a (C_3-C_6)cycloalkyl group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a halo(C_1-C_4)alkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R1** represent independently of each other a fluorine atom (F), a chlorine atom (Cl), a methyl group, an ethyl group, an isopropyl group, a methoxy group, a trifluoromethoxy group, a cyclopropyl group, a -CHF_2 group, an ethynyl group or a trifluoromethyl group.

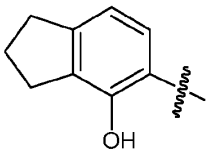
Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which when **n** is 1, **R1** is in ortho, meta or para position on the phenyl with respect to pyridazine ring.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which when **n** is 1, **R1** is in ortho or para position on the phenyl with respect to pyridazine ring.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which when **n** is 2, the two **R1** are in ortho and in para position on the phenyl with respect to pyridazine ring.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which when **n** is 2, the two **R1** are in ortho and in meta position on the phenyl with respect to pyridazine ring.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which when **n** is 2, the two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group, in particular these two R1 represent a group of formula



in which the symbol  represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R2** and **R3** represent independently of each other a hydrogen atom, a cyano group, a halo(C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a (C_1-C_4)alkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R2** and **R3** represent independently of each other a hydrogen atom, a cyano group, a -CHF_2 group, a trifluoromethyl group, a -CH_2OH group, an ethyl group, an isopropyl group or a methyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R2** represents a hydrogen atom, a halo(C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a (C_1-C_4)alkyl group.

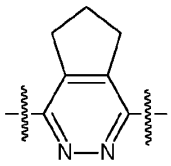
Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R2** represents a hydrogen atom, a -CHF_2 group, a trifluoromethyl group, a -CH_2OH group, an ethyl group, an isopropyl group or a methyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R3** represents a hydrogen atom, a cyano group, a halo(C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a (C_1-C_4)alkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R3** represents a hydrogen atom, a cyano group, a -CHF_2 group, a -CH_2OH group, or a methyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentyl ring fused to the pyridazine ring which has the following formula:



Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R4** and **R5** form together with the nitrogen atom to which they are attached:

- a 4 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 6 carbon atoms,

- a 8 to 10 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one or two additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 6, 7, 8 or 9 carbon atoms, or

- a 7 to 10 or 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 5 to 8 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group; a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, or a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R4** and **R5** form together with the nitrogen atom to which they are attached:

- a 4 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 6 carbon atoms selected from the group consisting of an azepanyl ring, a morpholino ring, a thiomorpholino ring, a piperidinyl ring, a pyrrolidinyl ring, an isoxazolidinyl ring, a piperazinyl ring, a hexahydropyrimidinyl ring, and an azetidinyl ring;

- a 8 to 10 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one or two additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 6, 7, 8 or 9 carbon atoms selected from the group consisting of an indolinyl ring; a hexahydropyridooxazinyl ring, a hexahydropyranooxazinyl ring, a octahydropyranooxazinyl ring, a dihydropyridooxazinyl ring, a dihydroquinolinyl group, a tetrahydroquinolinyl group, an azabicyclooctanyl group, an oxaazabicyclooctanyl group; a diazabicyclononanyl group, a hexahydropyrrolooxazinyl group; a octahydropyrrolooxazinyl group; a dihydrobenzoxazinyl group; a octahydropyridooxazinyl group; a hexahydrofuropyrrolyl ring; a hexahydropyrrolopyrrolyl ring; a hexahydropyrrolopyridinyl ring; a octahydropyrrolopyridinyl ring; a dihydropyrazolooxazolinyl ring, a hexahydrocyclopentaoxazinyl group, a hexahydronaphthyridinyl ring, a octahydronaphthyridinyl ring, a tetrahydronaphthyridinyl ring and a dihydronaphthyridinyl ring; or

- a 7 to 10 or 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 5 to 8 carbon atoms selected from the group consisting of an azaspirononanyl ring, an azaspirooctanyl ring, an azaspiroheptanyl ring, a diazaspirodecanyl ring, a diazaspirononanyl ring, a diazaspiroheptanyl ring, an oxadiazaspirodecanyl ring, an oxadiazaspiroundecanyl ring, an oxadiazaspirononanyl ring, an dioxadiazaspirododecanyl ring, an oxaazaspirononanyl ring, and an oxaazaspiroheptanyl ring,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents

independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, or a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which **R4** and **R5** form together with the nitrogen atom to which they are attached:

- an azepanyl ring unsubstituted or substituted by one OH-CH_2- group;

- a morpholino ring unsubstituted or substituted by one or two substituents independently selected from a methyl group, a CH_2F- group, NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a CH_3-NH-$(CH_2)_2$- group, a SH-CH_2- group, a CN-CH_2- group, a OH-CH_2- group, a OH-CD_2- group, a OH-$(CH_2)_2$- group, a OH-$C(CH_3)_2$- group, a CH_3-CH(OH)- group, a CH_3-C(=O)-NH-CH_2- group, a CH_3-C(=O)-NH-CH_2- CH_2- group a $CH(CH_3)_2$-C(=O)-NH-CH_2- group, a NH_2-C(=O)- group, a $NH(CH_3)$-C(=O)- group, a $N(CH_3)_2$-C(=O)- group, a NH_2-cyclopropyl- group, a NH_2-C(=O)-CH_2- group, a $NH(CH_3)$-C(=O)-CH_2- group, a $N(CH_3)_2$-C(=O)-CH_2- group, a CH_3-CH_2-C(=O)- group, an oxo group, and a CH_3-O-CH_2- group,

- a thiomorpholino ring unsubstituted or substituted by one to two oxo groups;

- a piperidinyl ring unsubstituted or substituted by one to two substituents independently selected from a NH_2 group, a NH_2-CH_2- group, a $NH(CH_2CH_3)$- group, a $N(CH_3)_2$- group, a NH_2-cyclopropyl- group, a $N(CH_3)_2$-CH_2- group, a OH-CH_2- group, a CH_3-C(=O)-NH-CH_2- group, a cyano group, a hydroxyl group, an oxo group and a fluorine atom,

- a pyrrolidinyl ring unsubstituted or substituted by one to two substituents independently selected from a NH_2- group, a NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a OH-CH_2- group, a CH_3-O-CH_2- group, a hydroxyl group, and an oxo group,

- an isoxazolidinyl ring unsubstituted or substituted by one hydroxyl group,

- a piperazinyl ring unsubstituted or substituted by one to two substituents independently selected from a methyl group, an oxo group and a OH-CH_2- group;

- a hexahydropyrimidinyl ring substituted by one oxo group;

- an azetidinyl ring unsubstituted or substituted by one OH-CH_2- group,

- a tetrahydroquinolinyl ring or a dihydroquinolinyl ring such as 3,4-dihydro-2H-quinolinyl ring, unsubstituted or substituted by one hydroxyl group

- a hexahydropyridooxazinyl ring such as a hexahydro-2H-pyrido[3,4-b][1,4]oxazinyl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazinyl group, or a hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazinyl ring, unsubstituted or substituted by one cyclobutyl group, one methyl group, one ethyl group, one 2,2,2-trifluoroethyl group, one 2-fluoroethyl group, one 3-fluoropropyl group, one isopropropyl group or one acetyl group;

- a hexahydropyranooxazinyl ring such as hexahydro-2H-pyrano[3,4-b][1,4]oxazinyl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazinyl group, or such as a hexahydro-2H-pyrano[4,3-b][1,4]oxazinyl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazinyl ring, unsubstituted;

- a dihydropyridooxazinyl ring such as dihydropyrido[3,4-b][1,4]oxazinyl ring or dihydropyrido[4,3-b][1,4]oxazinyl ring, for instance 2,3-dihydropyrido[3,4-b][1,4]oxazinyl ring or 2,3-dihydropyrido[4,3-b][1,4]oxazinyl ring, unsubstituted;

- a dihydropyrazolooxazinyl ring such as dihydro-2H-pyrazolo[4,3-b][1,4]oxazinyl ring, for instance 5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazinyl ring, unsubstituted;

- a dihydrobenzoxazinyl ring such as dihydro-1,4-benzoxazinyl ring, for instance 2,3-dihydro-1,4-benzoxazinyl ring substituted by one hydroxyl group;

- a tetrahydronaphthyridinyl ring or a dihydronaphthyridinyl ring such as 3,4-dihydro-2H-1,6-naphthyridinyl ring substituted by one hydroxyl group;

- a hexahydronaphthyridinyl ring such as hexahydro-2H-1,7-naphthyridinyl ring for instance a 3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridinyl ring substituted by one methyl group and one oxo group;

- a octahydronaphthyridinyl ring such as octahydro-1,7-naphthyridinyl ring or octahydro-1,5-naphthyridinyl ring for instance a 2,3,4,4a,5,6,7,8a-octahydro-1,7-

naphthyridinyl ring, a 2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridinyl ring, or a 2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridinyl ring, substituted by one oxo group, one methyl group, or one acetyl group;

- an octahydropyrrolopyridinyl ring or a hexahydropyrrolopyridinyl ring such as hexahydro-1H-pyrrolo[3,4-c]pyridinyl ring, octahydropyrrolo[2,3-c]pyridinyl ring, or hexahydro-2H-pyrrolo[2,3-c]pyridinyl ring, for instance 2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridinyl ring, 2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridinyl ring or 3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridinyl ring, unsubstituted or substituted by one methyl group, one ethyl group, one acetyl group, one isopropyl group or one oxo group ;

- an octahydropyrrolooxazinyl ring or a hexahydropyrrolooxazinyl ring such as hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring, for instance 2,3,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring, 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring or 3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring, unsubstituted or substituted by one methyl group, one ethyl group or one acetyl group;

- a hexahydrocyclopentaoxazinyl ring such as 3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazinyl ring substituted by one hydroxyl group;

- an octahydropyridooxazinyl ring such as octahydropyrido[4,3-b][1,4]oxazinyl ring, for instance 2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazinyl ring, unsubstituted;

- an indolinyl ring substituted by one hydroxyl group or one -CH_2OH group;

- a hexahydropyrrolopyrrolyl ring such as hexahydropyrrolo[3,4-b]pyrrolyl ring, hexahydro-1H-pyrrolo[3,2-b]pyrrolyl ring, or hexahydro-2H-pyrrolo[3,4-b]pyrrolyl ring, for instance 2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrolyl ring, 2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrolyl ring, or a 3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrolyl ring unsubstituted or substituted by one methyl group, one ethyl group or one acetyl group;

- a hexahydrofuropyrrolyl ring such as hexahydrofuro[3,4-c]pyrrolyl ring for instance 1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrolyl ring, unsubstituted;

- a azabicyclooctanyl ring such as 6-azabicyclo[3.2.1]octanyl ring substituted by one hydroxyl group ;

- a diazabicyclononanyl ring such as 3,6-diazabicyclo[3.2.2]nonanyl ring substituted by one methyl group

- a oxaazabicyclooctanyl ring such as 3-oxa-8-azabicyclo[3.2.1]octanyl ring unsubstituted ;

- an azaspirononanyl ring such as an azaspiro[3.5]nonanyl ring, unsubstituted or substituted by one substituent selected from a NH_2 group, a CH_3-C(=O)-NH- group, and a hydroxyl group;

- an azaspirooctanyl ring such as an azaspiro[3.4]octanyl ring, unsubstituted or substituted by one hydroxyl group;

- an azaspiroheptanyl ring such as an azaspiro[3.3]heptanyl ring, unsubstituted or substituted by one hydroxyl group;

- a diazaspirodecanyl ring such as 1,9-diazaspiro[4.5]decanyl ring substituted by one methyl group;

- a diazaspirononanyl ring such as a diazaspiro[3.5]nonanyl ring, unsubstituted or substituted by one methyl group;

- a diazaspiroheptanyl ring such as a diazaspiro[3.3]heptanyl ring, unsubstituted or substituted by one a methyl group;

- an oxadiazaspirononanyl ring such as 8-oxa-2,5-diazaspiro[3.5]nonanyl ring substituted by one methyl group;

- an oxadiazaspirodecanyl ring such as 2-oxa-6,9-diazaspiro[4.5]decanyl ring, 9-oxa-2,6-diazaspiro[4.5]decanyl ring, or 6-oxa-2,9-diazaspiro[4.5]decanyl ring unsubstituted or substituted by one ethyl group or one methyl group;

- an oxadiazaspiroundecanyl ring such as 4-oxa-1,8-diazaspiro[5.5]undecanyl ring substituted by one methyl group;

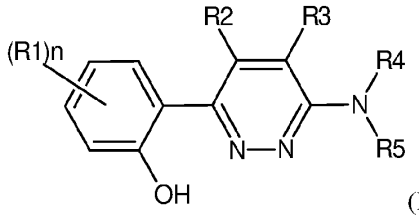
- an dioxadiazaspirododecanyl ring such as 1,11-dioxa-4,8-diazaspiro[5.6]dodecanyl ring substituted by one ethyl group;

- an oxaazaspirononanyl ring such as a oxaazaspiro[3.5]nonanyl ring; and

- an oxaazaspiroheptanyl ring such as an oxaazaspiro[3.3]heptanyl ring.

All these sub-groups taken alone or in combination are part of the present disclosure.

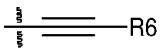
According to a particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof:



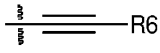
(I)

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R4 and **R5** form together with the nitrogen atom to which they are attached:

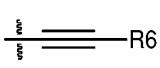
- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

said monocyclic heterocycloalkyl ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl-

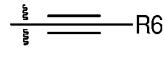
group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

According to another particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein

n is 1or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring; and

R4 and **R5** form together with the nitrogen atom to which they are attached:

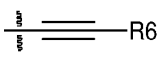
- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

said monocyclic heterocycloalkyl ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl-

group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl-group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

According to another particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

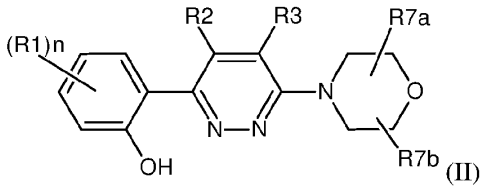
R4 and **R5** form together with the nitrogen atom to which they are attached:

- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

said monocyclic heterocycloalkyl ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl-group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-

C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

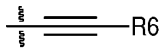
According to another particular embodiment, the disclosure relates to a compound of formula (II) or a pharmaceutically acceptable salt thereof:



(II)

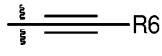
wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

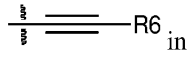
or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R7a and **R7b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

According to another particular embodiment, the disclosure relates to a compound of formula (II) or a pharmaceutically acceptable salt thereof:

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a halo(C_1-C_4)alkyl group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a halo(C_1-C_4)alkyl group ;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

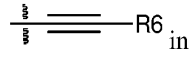
R7a and **R7b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a halo-(C_1-C_4)alkyl- group, a NH_2-C(=O)- group, NH_2-(C_1-C_4)alkyl- group, a

mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_2-C_5)acyl group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-(C_3-C_6)cycloalkyl- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, an oxo group, or a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group.

According to another particular embodiment, the disclosure relates to a compound of formula (II) or a pharmaceutically acceptable salt thereof:

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a halo(C_1-C_4)alkyl group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a halo(C_1-C_4)alkyl group ;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R7a represents a hydrogen atom, a (C_1-C_4)alkyl- group, a halo-(C_1-C_4)alkyl- group, a NH_2-C(=O)- group, NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_2-C_5)acyl group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-(C_3-C_6)cycloalkyl- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-

C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, an oxo group or a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group; and

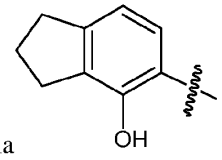
R7b represents a hydrogen atom, or a hydroxy-(C_1-C_4)alkyl- group.

According to another particular embodiment, the disclosure relates to a compound of formula (II) or a pharmaceutically acceptable salt thereof:

wherein

n is 1 or 2

R1 represent independently of each other a methyl group, an ethyl group, an isopropyl group, an ethynyl group, F, Cl, a methoxy group, a cyclopropyl group, a trifluoromethoxy group or a trifluoromethyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group so as to form the following formula  in which the symbol  represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a -CHF_2 group, a trifluoromethyl group, a OH-CH_2- group, a methyl group, an ethyl group, or an isopropyl group;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentyl ring which is fused to the pyridazine ring; and

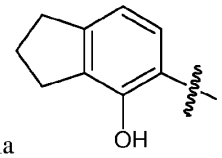
R7a and **R7b** represent independently of each other a hydrogen atom, a methyl group, a CH_2F- group, NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a SH-CH_2- group, a CN-CH_2- group, a CH_3-NH-(CH_2)$_2$- group, a OH-CH_2- group, a OH-CD_2- group, a OH-(CH_2)$_2$- group, a OH-$C(CH_3)_2$- group, a CH_3-CH(OH)- group, a CH_3-C(=O)-NH-CH_2- group, a CH_3-C(=O)-NH-CH_2-CH_2- group a $CH(CH_3)_2$-C(=O)-NH-CH_2- group, a NH_2-C(=O)- group, a $NH(CH_3)$-C(=O)- group, a $N(CH_3)_2$-C(=O)- group, a NH_2-cyclopropyl- group, a NH_2-C(=O)-CH_2- group, a $NH(CH_3)$-C(=O)-CH_2- group, a $N(CH_3)_2$-C(=O)-CH_2- group, a CH_3-CH_2-C(=O)- group, an oxo group, or a CH_3-O-CH_2- group.

According to another particular embodiment, the disclosure relates to a compound of formula (II) or a pharmaceutically acceptable salt thereof:

wherein

n is 1 or 2;

R1 represent independently of each other a methyl group, an ethyl group, an isopropyl group, an ethynyl group, F, Cl, a methoxy group, a cyclopropyl group, a trifluoromethoxy group or a trifluoromethyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group so as to form the following formula 

in which the symbol ≋ represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring;

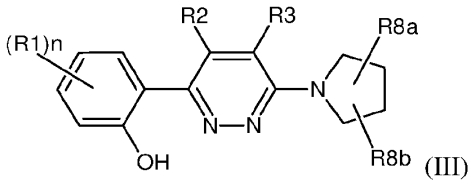
R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a -CHF_2 group, a trifluoromethyl group, a OH-CH_2- group, a methyl group, an ethyl group, or an isopropyl group;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentyl ring which is fused to the pyridazine ring;

R7a represents a hydrogen atom, a methyl group, a CH_2F- group, NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a SH-CH_2- group, a CN-CH_2- group, a CH_3-NH-$(CH_2)_2$- group, a OH-CH_2- group, a OH-CD_2- group, a OH-$(CH_2)_2$- group, a OH-$C(CH_3)_2$- group, a CH_3-CH(OH)- group, a CH_3-C(=O)-NH-CH_2- group, a CH_3-C(=O)-NH-CH_2-CH_2- group a $CH(CH_3)_2$-C(=O)-NH-CH_2- group, a NH_2-C(=O)- group, a $NH(CH_3)$-C(=O)- group, a $N(CH_3)_2$-C(=O)- group, a NH_2-cyclopropyl- group, a NH_2-C(=O)-CH_2- group, a $NH(CH_3)$-C(=O)-CH_2- group, a $N(CH_3)_2$-C(=O)-CH_2- group, a CH_3-CH_2-C(=O)- group, an oxo group, or a CH_3-O-CH_2- group; and

R7b represents a hydrogen atom or a OH-CH_2- group.

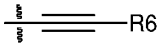
According to another particular embodiment, the disclosure relates to a compound of formula (III) or a pharmaceutically acceptable salt thereof:



(III)

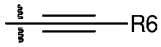
wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R8a and **R8b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl-group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a

mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

According to another particular embodiment, the disclosure relates to a compound of formula (III) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 and **R3** represent a hydrogen atom, or a halo(C_1-C_4)alkyl group; and

R8a and **R8b** represent independently of each other a hydrogen atom, a NH_2- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, or an oxo group.

According to another particular embodiment, the disclosure relates to a compound of formula (III) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 represents a halo(C_1-C_4)alkyl group or a hydrogen atom;

R3 represents a hydrogen atom;

R8a represents a hydrogen atom, a NH_2- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, or an oxo group.; and

R8b represents a hydrogen atom, or an oxo group.

According to another particular embodiment, the disclosure relates to a compound of formula (III) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

R2 represents a hydrogen atom or a -CHF_2 group;

R3 represents a hydrogen atom; and

R8a and **R8b** represent independently of each other a hydrogen atom, a NH_2- group, a NH_2-(CH_2)- group, a $N(CH_3)_2$-(CH_2)- group, a OH-CH_2- group, a CH_3-O-CH_2- group, a hydroxyl group, or an oxo group.

According to another particular embodiment, the disclosure relates to a compound of formula (III) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

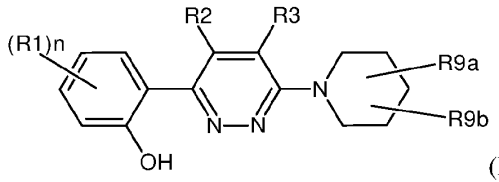
R2 represents a hydrogen atom or a -CHF_2 group;

R3 represents a hydrogen atom;

R8a represents a hydrogen atom, a NH_2- group, a NH_2-(CH_2)- group, a $N(CH_3)_2$-(CH_2)- group, a OH-CH_2- group, a CH_3-O-CH_2- group, a hydroxyl group, or an oxo group; and

R8b represents a hydrogen atom, or an oxo group.

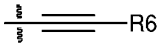
According to another particular embodiment, the disclosure relates to a compound of formula (IV) or a pharmaceutically acceptable salt thereof:



(IV)

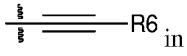
wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol

represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R9a and **R9b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

According to another particular embodiment, the disclosure relates to a compound of formula (IV) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 and **R3** represent a hydrogen atom; and

R9a and **R9b** represent independently of each other a hydrogen atom, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a hydroxyl group, a cyano group, an oxo group or a halogen atom.

According to another particular embodiment, the disclosure relates to a compound of formula (IV) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 and **R3** represent a hydrogen atom;

R9a represents a hydrogen atom, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a hydroxyl group, a cyano group, or a halogen atom; and

R9b represents a hydrogen atom, an oxo group, or a halogen atom.

According to another particular embodiment, the disclosure relates to a compound of formula (IV) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

R2 and **R3** represent a hydrogen atom; and

R9a and **R9b** represent independently of each other a hydrogen atom, a NH_2 group, a $N(CH_3)_2$- group, a CH_3-CH_2-NH- group, a NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a NH_2-cyclopropyl- group, a CH_3-(C=O)-NH-CH_2- group, a OH-CH_2- group, a hydroxyl group, a cyano group, an oxo group or a fluorine atom (F).

According to another particular embodiment, the disclosure relates to a compound of formula (IV) or a pharmaceutically acceptable salt thereof:

wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

R2 and **R3** represent a hydrogen atom;

R9a represents a hydrogen atom, a NH_2 group, a $N(CH_3)_2$- group, a CH_3-CH_2-NH- group, a NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a NH_2-cyclopropyl- group, a CH_3-(C=O)-NH-CH_2- group, a OH-CH_2- group, a hydroxyl group, a cyano group, or a fluorine atom (F); and

R9b represents a hydrogen atom, an oxo group, or a fluorine atom (F).

Among the compounds of formula (I) or a pharmaceutically acceptable salt thereof that are subject-matter of the present disclosure, mention may be made for instance to the following compounds:

(1) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-4-ol;

(2) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidine-4-carbonitrile;

(3) 7-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-7-azaspiro[3.5]nonan-2-ol;

(4) 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol;

(5) 2-[6-[(3R)-3-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(6) 2-[6-[(3S)-3-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(7) 2-[6-(2,7-diazaspiro[3.5]nonan-7-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid;

(8) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(9) 2-[6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(10) 2-[6-[(4aR,8aS)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol Enantiomer 1;

(11) 2-[6-[(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; formic acid Enantiomer 2;

(12) 2-[6-[(4aR,8aS)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 1;

(13) 2-[6-[(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 2;

(14) 2-[6-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(15) 2-[6-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(16) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(17) 2-[6-[3-(1-aminocyclopropyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;

(18) 2-[6-[(3S)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;

(19) 2-[6-[4-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;

(20) 2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(21) 3,5-dichloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(22) 2-[6-[(3R)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;

(23) 2-[6-[(3S)-3-(aminomethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dichloro-phenol;

(24) 2-[6-[2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(25) 2-[6-[(3R)-3-(aminomethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dichloro-phenol;

(26) 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(27) 2-[6-[(2R)-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(28) 2-[6-[(3S)-3-(hydroxymethyl)-1-piperidyl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(29) 3-methyl-2-[6-(4-methylpiperazin-1-yl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(30) 2-[6-[3-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(31) 2-[6-[(3R)-3-amino-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;formic acid;

(32) 2-[6-(2-amino-7-azaspiro[3.5]nonan-7-yl)pyridazin-3-yl]-3,5-dichloro-phenol;

(33) 3,5-dichloro-2-[6-[(2R)-2-(methoxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(34) 3,5-dichloro-2-[6-[(3S)-3-(hydroxymethyl)-1-piperidyl]pyridazin-3-yl]phenol;
(35) 3,5-dichloro-2-[6-[(2S)-2-(methoxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(36) 3,5-dichloro-2-[6-[(3R)-3-(hydroxymethyl)-1-piperidyl]pyridazin-3-yl]phenol;
(37) 7-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-7-azaspiro[3.5]nonan-2-ol;
(38) 3,5-dichloro-2-(6-morpholinopyridazin-3-yl)phenol;
(39) 3,5-dichloro-2-[6-[(2S)-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]phenol;
(40) 3,5-dichloro-2-[6-[(3S)-3-[(dimethylamino)methyl]pyrrolidin-1-yl]pyridazin-3-yl]phenol;
(41) 3,5-dichloro-2-[6-[(3R)-3-[(dimethylamino)methyl]pyrrolidin-1-yl]pyridazin-3-yl]phenol;
(42) 6-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-6-azaspiro[3.4]octan-2-ol;
(43) 3,5-dichloro-2-[6-[(2R)-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]phenol;
(44) 3-fluoro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(45) 3-fluoro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;
(46) 2-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-2-azaspiro[3.3]heptan-6-ol;
(47) N-[7-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-7-azaspiro[3.5]nonan-2-yl]acetamide;
(48) 3-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(49) 3,5-dichloro-2-[6-(4,4-difluoro-1-piperidyl)pyridazin-3-yl]phenol;
(50) 3,5-dichloro-2-[6-[(3R)-3-[(dimethylamino)methyl]-1-piperidyl]pyridazin-3-yl]phenol;
(51) 3,5-dichloro-2-[6-[(3S)-3-[(dimethylamino)methyl]-1-piperidyl]pyridazin-3-yl]phenol;
(52) 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 1;
(53) 2-[6-[-2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 2;

(54) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-(trifluoromethyl) phenol;

(55) 3,5-dichloro-2-[6-(2-methyl-2,7-diazaspiro[3.5]nonan-7-yl)pyridazin-3-yl]phenol;

(56) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(57) N-[[(3R)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl] methyl]acetamide;

(58) N-[[(3S)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl] methyl]acetamide;

(59) 2-[6-[-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 1;

(60) 2-[6-[-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 2;

(61) 1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(62) (4S)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(63) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(64) 3,5-dichloro-2-[6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridazin-3-yl]phenol;

(65) 2-[6-[(3R)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(66) 3,5-dichloro-2-[6-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyridazin-3-yl]phenol;

(67) (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-3-ol;

(68) 2-[6-[(3S)-3-(ethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(69) 2-[6-[(3S)-3-amino-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(70) (3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-3-ol;

(71) (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-3-ol;

(72) 2-[4-ethyl-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(73) 5-chloro-2-[4-ethyl-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(74) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-isopropyl-pyridazin-3-yl]-5-methyl-phenol;

(75) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-isopropyl-pyridazin-3-yl]phenol;

(76) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(77) 2-[4-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl]-5-methyl-phenol;

(78) 5-chloro-2-[4-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl]phenol;

(79) 2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(80) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4,5-dimethyl-pyridazin-3-yl]-5-methyl-phenol;

(81) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4,5-dimethyl-pyridazin-3-yl]phenol;

(82) 2-[6-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(83) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.5]nonan-7-ol;

(84) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.4]octan-6-ol;

(85) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]phenol;

(86) (4S)-4-hydroxy-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-2-one;

(87) 2-[6-[(2R)-2-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid;

(88) 2-[6-[(3R)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(89) 2-[6-[(2R)-2-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid;

(90) 6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-3-(2-hydroxy-4-methyl-phenyl)pyridazine-4-carbonitrile;

(91) 3,5-dimethyl-2-[6-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl]phenol;
(92) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;
(93) 5-fluoro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]phenol;
(94) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.4]octan-6-ol Enantiomer 1;
(95) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.4]octan-6-ol Enantiomer 2;
(96) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methoxy-3-methyl-phenol;
(97) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;
(98) 2-[6-[2-[(1S)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol Diastereoisomer 2;
(99) 2-[6-[2-[(1S)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol Diastereoisomer 1;
(102) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-4-methyl-phenol;
(103) 3-(4-chloro-2-hydroxy-phenyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile;
(105) N-[[(2S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;
(106) N-[[(2R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;
(107) 2-[6-[3-(hydroxymethyl)azepan-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(108) 2-[6-[2-[(1R)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol Diastereoisomer 1;
(109) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol;
(110) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-5-methyl-phenol;

(111) 2-[6-[rac-(4aS,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(112) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol;

(113) (4R)-2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]isoxazolidin-4-ol;

(114) 2-[6-[1-(hydroxymethyl)-6-azabicyclo[3.2.1]octan-6-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(115) 2-[6-[(2S)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(116) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methoxy-phenol;

(117) 3,5-dichloro-2-[6-[(2S)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]phenol;

(118) 2-[6-[(2R)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(119) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methoxy-3-methyl-phenol;

(120) 3,5-dimethyl-2-[6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyridazin-3-yl]phenol;

(121) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethoxy)phenol;

(122) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl) pyrrolidin-2-one;

(123) 2-[6-[(3R)-3-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, 2,2,2-trifluoroacetic acid;

(124) 2-[6-[(3S)-3-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(125) 2-[6-[(4aR,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(126) 1-[4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one;

(127) 5-chloro-2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(128) 2-[6-[(3S)-3-(dimethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(129) N-[[(3R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-3-yl]methyl]acetamide;

(130) (4S)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one;

(131) (4S)-4-amino-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-2-one;

(132) (4R)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(133) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-3-methyl-phenol;

(134) 5-(difluoromethyl)-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(135) 2-[6-[(2S)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(136) 2-[6-[(2R)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(137) (4R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl) pyrrolidin-2-one;

(138) (4S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl) pyrrolidin-2-one;

(139) (3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl) pyrrolidin-2-one;

(140) (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl) pyrrolidin-2-one;

(141) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,6-dimethylphenol;

(142) 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide;

(143) 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide;

(144) 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(145) 5-chloro-2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(146) 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl] acetamide;

(147) 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl] acetamide;

(148) 2-[6-[(3R)-3-(dimethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(149) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-3-methyl-phenol;

(150) 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N,N-dimethylacetamide;

(151) 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N,N-dimethylacetamide;

(152) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-4,6-dimethylphenol;

(153) 3-(difluoromethyl)-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(154) 3,5-dimethyl-2-[6-[rac-(4aR,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol;

(155) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-(trifluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(156) 1-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one;

(157) 1-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one;

(158) 6-(2-hydroxy-4,6-dimethyl-phenyl)-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile;

(159) 3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazine-4-carbonitrile;

(160) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-(trifluoromethyl) pyridazin-3-yl]phenol;

(161) 3,5-dichloro-2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(162) 4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3-dihydro-1,4-benzoxazin-6-ol;

(163) 6-(4-chloro-2-hydroxy-6-methyl-phenyl)-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile;

(164) N-[[(3S)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(165) 2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(166) (2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N-methylmorpholine-2-carboxamide;

(167) N-[[(3R)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(168) 2-[6-[(4aR,7aR)-4-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(169) 5-chloro-2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methylphenol;

(170) 2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(171) 5-chloro-2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(172) 3-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(173) 2-[6-[(2R,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(174) 2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(175) 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 1;

(176) 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 2;

(177) 3-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(178) 2-[6-[(2R,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(179) (4S)-2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]isoxazolidin-4-ol;

(180) 2-[6-[2-[(1R)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol Diastereoisomer 2;

(181) (2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholine-2-carboxamide;

(182) (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N-methylmorpholine-2-carboxamide;

(183) (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholine-2-carboxamide;

(184) (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N,N-dimethylmorpholine-2-carboxamide;

(185) 2-[6-[(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(186) 2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(187) 2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(188) 5-chloro-2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(189) 5-chloro-2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(190) 2-[6-[rac-(4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(191) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,4-dimethylphenol;

(192) 2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(193) 4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-2,3-dihydro-1,4-benzoxazin-7-ol;

(194) 2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(195) 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(196) 3,5-dimethyl-2-[6-(2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]phenol;

(197) 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(198) 2-[6-[(2S,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(199) 2-[6-[(2S,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(200) 2-[6-[(2R,6R)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(201) 2-[6-[(2R,6R)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(203) 3,5-dichloro-2-(6-thiomorpholinopyridazin-3-yl)phenol;

(204) 5-cyclopropyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(206) 2-[6-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(207) 2-[6-[(3aR,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(208) 2-[6-(8-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecan-4-yl)pyridazin-3-yl]-3,5-dimethylphenol;

(209) 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(210) 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(211) N-[[(3S)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(212) N-[[(3R)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(213) 1-[rac-(4aR,8aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(214) 1-[rac-(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl] ethanone;

(215) 2-[6-(2,3-dihydropyrido[3,4-b][1,4]oxazin-1-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(216) N-[[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(217) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-7-ol;

(219) 2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(220) 2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(221) 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(222) 1-[rac-(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(223) 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(224) 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(225) 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(226) 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(227) 2-[6-(6-ethyl-2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]-3,5-dimethylphenol;

(228) 1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-5-yl]ethanone;

(229) 2-[6-[rac-(3aS,6aS)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(230) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-6-ol;

(231) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-8-ol;

(232) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-5-ol;

(233) 2-[6-[(2R)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(234) 2-[6-[(2S)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(235) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-5-(hydroxymethyl) piperidin-2-one;

(236) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-5-ol;

(237) 3,5-dichloro-2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(238) 3,5-dichloro-2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(239) 1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]hexahydropyrimidin-2-one;

(240) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-4-ol;

(241) 2-[6-[4-(hydroxymethyl)indolin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(242) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-1,6-naphthyridin-5-ol;

(243) 2-[6-[rac-(3aS,6aS)-5-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(245) 5-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methylphenol;

(246) 3-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methylphenol;

(247) 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(248) 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(249) 5-chloro-2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(250) (4S)-4-amino-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(251) 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(252) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(253) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-7-ol;
(254) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-6-ol;
(255) 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(256) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(257) 1-[rac-(4aS,7aS)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;
(258) 3-methyl-2-[6-[(2R)-2-methylmorpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
(259) 3-methyl-2-[6-[(2S)-2-methylmorpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
(260) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(261) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(262) 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;
(263) 1-[(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;
(264) rac-(3aS,7aR)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one, hydrochloride;
(265) 2-[6-[rac-(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(266) 2-[6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(267) N-[[(2R)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;
(268) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(269) rac-(3aS,7aS)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one, hydrochloride;

(270) 2-[6-[(3aR,6aR)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(271) 2-[6-[(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(272) 2-[6-(3,4-dihydro-2H-quinolin-1-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(273) 3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(274) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-isopropyl-3-methyl-phenol;

(275) N-[[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(276) N-[[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]methyl]-2-methylpropanamide;

(277) N-[2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide;

(278) N-[2-[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide;

(279) N-[[(2R)-4-[6-(4-chloro-2-hydroxy-6-methylphenyl)pyridazin-3-yl]morpholin-2-yl]methyl]-2-methylpropanamide;

(280) N-[[(2S)-4-[6-(4-chloro-2-hydroxy-6-methylphenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(283) 2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(284) 2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(285) N-[[(2S)-4-[6-(4-chloro-2-hydroxy-6-methylphenyl)pyridazin-3-yl]morpholin-2-yl]methyl]-2-methylpropanamide;

(286) (4S)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(287) (3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(288) (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(289) 3-methyl-2-[6-[rac-(4aR,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(290) (4aR,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridin-8-one;

(291) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(292) (4R)-4-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(293) (4S)-4-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(295) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(296) 2-[6-[(2S,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(297) 2-[6-[(2S,6S)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(298) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(299) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(300) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridin-8-one;

(301) 2-[6-[(4aR,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(302) 2-[6-[(2R,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(303) 3,5-dimethyl-2-[6-[(2S)-2-(sulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(304) 1-[rac-(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(305) 3,5-dimethyl-2-[6-[(2R)-2-(sulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(306) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(307) 5-chloro-3-methyl-2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol;

(308) 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(309) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(310) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(311) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(312) 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(313) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(314) 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(315) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(316) (4R)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(317) 2-[6-(4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecan-8-yl)pyridazin-3-yl]-3,5-dimethylphenol;

(318) 3-methyl-2-[6-[rac-(4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride;

(320) 3-methyl-2-[6-[rac-(4aR,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride;

(321) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(322) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(323) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(324) 5-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]indan-4-ol;

(325) (3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(326) (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(327) 2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile;

(328) 2-[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile;

(329) (6R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one;

(330) (6S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one;

(331) 3-methyl-2-[6-[(2R)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(332) 3-methyl-2-[6-[(2S)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(333) 2-[6-[(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(334) 2-[6-[(4aS,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(335) 1-[rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(336) 1-[(4aR,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(337) 1-[rac-(4aR,7aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(338) 5-chloro-2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(339) 5-chloro-2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(340) 2-[6-[(rac-3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(341) 2-[6-[(rac-3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(342) 3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol;

(343) 2-[6-[(4aS,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(344) 2-[6-[(4aR,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(345) 5-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]indan-4-ol;

(346) 3-methyl-2-[6-[rac-(3aS,6aS)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride;

(348) 1-[(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(349) 1-[(4aS,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(350) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(351) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-6-fluoro-phenol;

(352) 1-[(4aS,7aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(353) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-6-fluoro-3-methyl-phenol;

(354) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(355) 2-[6-[(4aS,8aR)-6-(2,2,2-trifluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(356) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-6-fluoro-phenol;

(357) 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-phenyl)-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(358) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol;

(359) 2-[6-[(2S,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(360) 2-[6-(5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazin-7-yl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(361) 3-methyl-2-[6-[rac-(4aR,7aS)-6-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(362) 2-[6-(2,3-dihydropyrido[4,3-b][1,4]oxazin-4-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(363) 1-[(4aS,8aR)-4-[6-[2-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(364) 2-[6-[rac-(3aS,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(365) 2-[6-[(2R,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(366) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(367) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(368) 2-(hydroxymethyl)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-3-one;

(369) 1-[(3aR,7aR)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(370) 1-[(3aS,7aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(371) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(372) (4S)-1-[5-(difluoromethyl)-6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one;

(373) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(374) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(375) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(376) 3-methyl-2-[6-[rac-(4aR,7aR)-6-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(377) 1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]ethanone;

(378) 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(379) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b] [1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(380) 1-[(4aS,8aR)-4-[6-[2-ethyl-6-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(381) 1-[(4aS,8aR)-4-[6-(4-chloro-2-ethyl-6-hydroxy-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(382) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(383) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(384) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(385) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(386) 1-[(4aS,8aR)-4-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl] ethanone;

(387) 1-[(4aS,8aR)-4-[5-(difluoromethyl)-6-(2-hydroxy-4-methyl-phenyl) pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(388) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol;

(389) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(390) 2-[6-[(2S,6S)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(391) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(392) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(393) 2-[6-[(3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(394) 1-[(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(395) 1-[(3aR,7aR)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(397) 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(398) 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(399) 3,5-dichloro-2-[6-(1,1-dioxo-1,4-thiazinan-4-yl)pyridazin-3-yl]phenol;

(400) 3,5-dichloro-2-[6-(1-oxo-1,4-thiazinan-4-yl)pyridazin-3-yl]phenol;

(402) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(403) 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol;

(404) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(405) 1-[(4aS,8aR)-4-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(406) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(407) 2-[6-[(3aS,7aR)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(408) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol;

(409) 1-[(4aS,8aR)-4-[6-(2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(410) 3,5-dimethyl-2-[6-(3-methyl-3,6-diazabicyclo[3.2.2]nonan-6-yl)pyridazin-3-yl]phenol;

(411) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(412) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(413) 1-[(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(414) 1-[(3aS,7aS)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(415) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(416) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(417) 3-methyl-2-[6-(3-methyl-3,6-diazabicyclo[3.2.2]nonan-6-yl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(418) 3-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(419) (2S)-2-(hydroxymethyl)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-3-one;

(420) (2R)-2-(hydroxymethyl)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-3-one;

(421) 3,5-dimethyl-2-[6-[rac-(4aS,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol;

(422) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol;

(423) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol;

(424) 1-[(4aS,8aR)-4-[6-(2-ethyl-6-hydroxy-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(425) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-(difluoromethyl)pyridazin-3-yl]-3-ethyl-phenol;

(426) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(427) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(428) 3,5-dimethyl-2-[6-(9-methyl-1,9-diazaspiro[4.5]decan-1-yl)pyridazin-3-yl]phenol;

(429) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(430) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(431) 1-[(4aS,8aR)-4-[6-(2-hydroxy-4-methyl-phenyl)-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(432) 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol;

(433) 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(434) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol;

(435) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(436) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(437) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(438) 3-methyl-2-[6-[rac-(4aS,8aR)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(439) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-methyl-pyridazin-3-yl]-3-ethyl-phenol;

(440) 3,5-dimethyl-2-[6-(9-methyl-6-oxa-2,9-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl]phenol;

(441) 3,5-dimethyl-2-[6-(1-methyl-4-oxa-1,8-diazaspiro[5.5]undecan-8-yl)pyridazin-3-yl]phenol;

(442) 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-phenyl)-5-(difluoromethyl) pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(443) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-ethyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(444) 3,5-dimethyl-2-[6-(6-methyl-9-oxa-2,6-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl]phenol;

(445) 3,5-dimethyl-2-[6-[(5S)-9-methyl-6-oxa-2,9-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(446) 3,5-dimethyl-2-[6-[(5R)-9-methyl-6-oxa-2,9-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(448) 3-methyl-2-[6-[rac-(4aS,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(449) 3,5-dimethyl-2-[6-(8-methyl-4-oxa-1,8-diazaspiro[5.5]undecan-1-yl)pyridazin-3-yl]phenol;

(450) 3,5-dimethyl-2-[6-[(5R)-6-methyl-9-oxa-2,6-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(451) 3,5-dimethyl-2-[6-[(5S)-6-methyl-9-oxa-2,6-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(452) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(455) 3,5-dimethyl-2-[6-(2-methyl-8-oxa-2,5-diazaspiro[3.5]nonan-5-yl)pyridazin-3-yl]phenol;

(456) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(457) 1-[(3aR,7aR)-1-[6-(2-hydroxy-4-methyl-phenyl)-5-methyl-pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(458) 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(459) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol;

(460) 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(461) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol;

(462) 1-[(4aR,8aR)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]ethanone;

(463) 1-[(4aS,8aS)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]ethanone;

(466) (4aS,6S,7aR)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol;

(467) (4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol;

(468) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(469) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(470) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-ethyl-pyridazin-3-yl]-5-methyl-phenol;

(471) 5-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]indan-4-ol;

(472) 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(473) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(474) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(475) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(476) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol;

(477) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol;

(479) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-fluoro-phenol;

(480) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-fluoro-phenol;

(481) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-4-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(482) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(483) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(484) 3-methyl-2-[6-[rac-(3aS,6aS)-1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(485) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(486) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(487) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(488) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(489) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(490) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(491) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(492) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(493) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol

(494) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol;

(496) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(497) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(498) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(499) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(500) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(501) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(502) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(503) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(504) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(505) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(506) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(507) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(508) 5-ethynyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(509) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;

(510) 1-[(3aS,7aS)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(511) 1-[(3aR,7aR)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(512) 1-[(3aS,7aS)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(513) 1-[(3aR,7aR)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(514) 1-[(3aR,7aR)-1-[6-[2-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(515) 2-[6-[(4aS,8aS)-5-methyl-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(516) 2-[6-[(4aR,8aR)-5-methyl-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(517) 2-[6-[(4aR,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(518) 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(519) 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(520) 2-[6-[(4aS,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(521) 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(522) 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(523) 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(524) 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(525) 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-phenol;

(526) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol;

(527) 2-[6-[(4aS,8aR)-6-(3-fluoropropyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; and

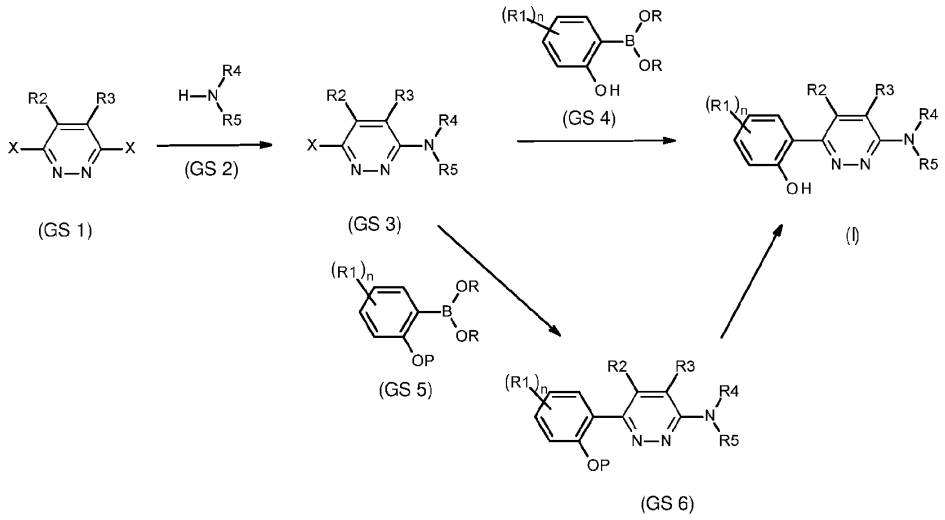
(528) 5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-isopropyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol.

Among the preceding listed compounds of formula (I) or a pharmaceutically acceptable salt thereof, the following compounds which are of interest may for example be cited: 1, 2, 5, 6, 8, 9, 14 to 31, 33 to 36, 38 to 41, 43 to 45, 48 to 54, 56 to 63, 65, 67 to 82, 85 to 90, 92, 93, 96 to 99, 102, 103, 105 to 110, 112, 113, 115 to 119, 121 to 124, 126 to 153, 155 to 161, 163 to 167, 169 to 174, 177 to 184, 186 to 189, 191, 192, 194, 198 to 201, 203, 204, 209 to 212, 216, 219, 220, 233 to 235, 237, 238, 245 to 250, 258, 259, 266, 267, 273 to 280, 283 to 288, 292, 293, 296, 297, 302, 303, 305, 324 to 332, 338, 339, 345, 359, 365, 368, 372, 390, 399, 400, 418 to 420, 508, and 509.

Preparation of the compounds of formula (I)

The compounds of formula (I) or a pharmaceutically acceptable salt thereof according to the present disclosure may be prepared according to various methods. More particularly, they can be prepared as illustrated by the schemes which follow.

Reaction scheme 1

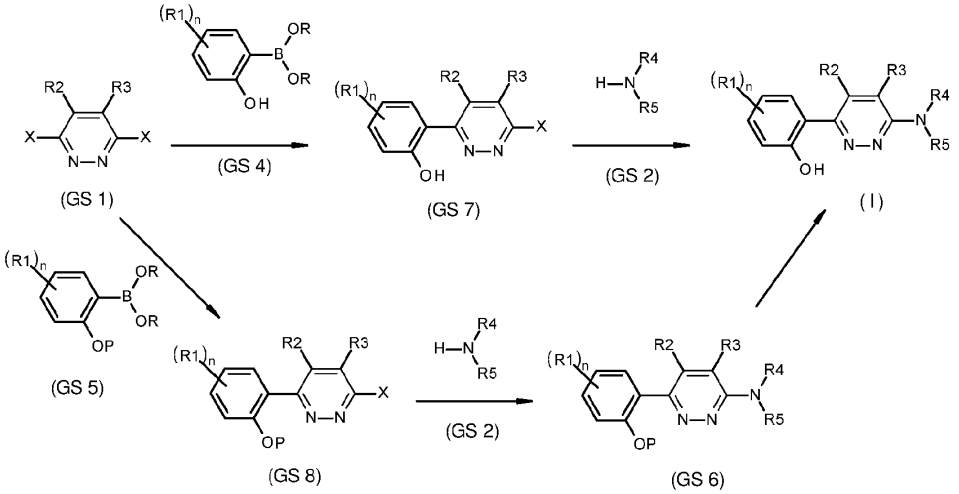


In the scheme 1 above, R1, n, R2, R3, R4 and R5 are as defined in the present disclosure, and X represent independently of each other a halogen atom, such as Cl, Br or I, P represents a protecting group like a methyl group, a paramethoxybenzyl group, a benzyl group, a methoxymethyl group or an ethoxyethyl group and $B(OR)_2$ represents either a boronic acid or a boronic ester, e.g. 4,4,5,5-tetramethyl-1,3,2-dioxaborolan.

Compounds of the invention may be prepared by the reaction scheme 1 where a dihalogenopyridazine properly substituted (GS 1) is reacted with an appropriate amine (GS 2) in a presence of a base (like K_2CO_3, DIPEA), at room temperature or elevated temperature (preferentially between 120-180°C) to give halogenopyridazine (GS 3). This reaction may be carried out in sealed tubes, and also under microwave irradiation. This reaction can be also realized by metal coupling, using Pd catalyst (like $Pd(dppf)Cl_2$) and a mineral base like K_3PO_4, at elevated temperature (typically between 100-110°C), in a non protic solvent like 1,4-dioxane to provide a compound of general formula (I) according to the present disclosure. Then, this intermediate is reacted with an appropriate phenyl boronate derivative (GS 4), where it could be under a form of boronic acid or a boronate (like 4,4,5,5-tetramethyl-1,3,2-dioxaborolan), in a Suzuki type reaction, in the presence of a Pd catalyst (like $Pd(PPh_3)_4$, or $Pd(dppf)Cl_2$) and a mineral base like $NaHCO_3$, at elevated temperature (typically between 100-140°C), in a mix of solvent like 1,4-dioxane/water or DME/water to provide a compound of general formula (I). It is to note that phenyl boronate derivative could be used also with a protected hydroxy function, with a methyl, or benzyl for example (GS 5), to give the appropriate phenyl pyridazine (GS 6), which is submitted to deprotection

conditions (BBr_3, or hydrogenation for example) to provide compound of general formula (I) according to the present disclosure.

Reaction scheme 2



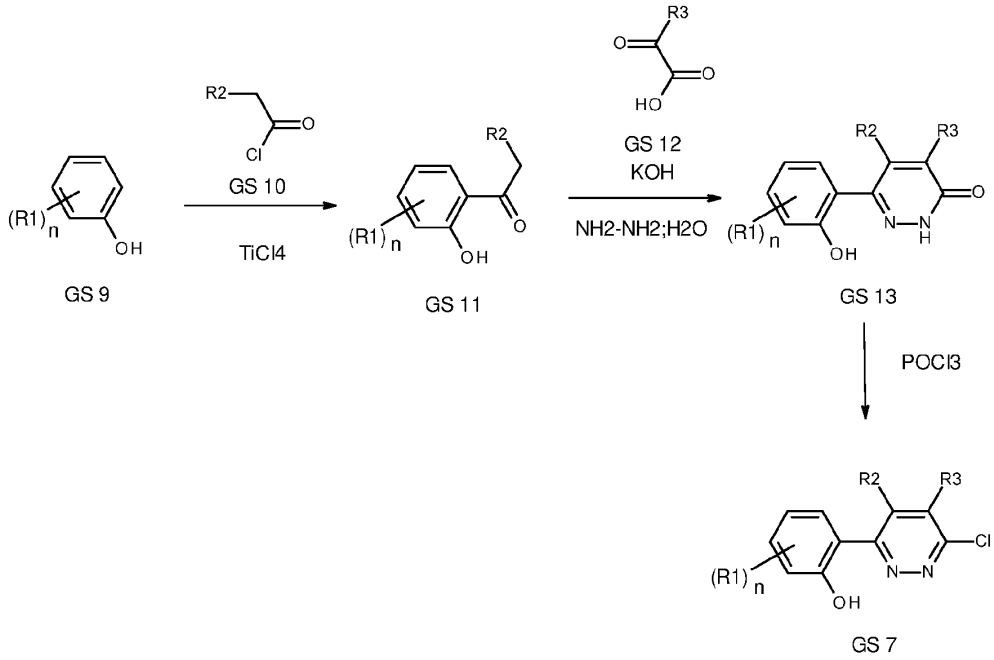
In the scheme 2 above, R1, n, R2, R3, R4 and R5 are as defined in the present disclosure, and X represent independently of each other a halogen atom, such as Cl, Br or I, P represents a protecting group like a methyl group, a paramethoxybenzyl group, a benzyl group, a methoxymethyl group or an ethoxyethyl group and $B(OR)_2$ represents either a boronic acid or a boronic ester, e.g. 4,4,5,5-tetramethyl-1,3,2-dioxaborolan.

Compounds of the invention may also be prepared by the reaction scheme 2 where a dihalogenopyridazine properly substituted (GS 1) is reacted with an appropriate phenyl boronate derivative (GS 4), where it could be under a form of boronic acid or a boronate like 4,4,5,5-tetramethyl-1,3,2-dioxaborolan, in a Suzuki type reaction, in the presence of a Pd catalyst (like $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$) and a mineral base like Na_2CO_3, in a mix of solvent like 1,4-dioxane/water or DME/water, at a temperature between 100 and 140°C, to give halogenopyridazine (GS 7). Then, this intermediate is reacted with an appropriate amine (GS 2) in a presence of a base (like $NaHCO_3$, DIPEA), at elevated temperature (preferentially between 130-180°C), also possibly carried out in sealed tubes and also under microwave irradiation, to provide a compound of general formula (I) according to the present disclosure. The suzuki reaction could also be carried out using a phenyl boronate derivative with a protected alcohol function (methyl for example) (GS 5) using similar conditions to give the appropriate halogenopyridazine (GS 8), which gives

after N-arylation using an appropriate amine (GS 2) in similar conditions as previous, and then submitted to deprotection conditions (BBr_3 for example) to provide compound of general formula (I) according to the present disclosure.

The intermediate halogenopyridazine (GS 7) may also be prepared by the reaction scheme 3 as shown below.

Reaction scheme 3



In case of n is 1, R1 represents a (C_1-C_4)alkyl group, and R2 and R3 represent independently of each other a hydrogen atom or a (C_1-C_4)alkyl group, (GS 7) may also be prepared by the reaction scheme 3 where a phenol properly substituted (GS 9) is reacted in a Friedel-Crafts acylation with an appropriate alkanoyl chloride (GS 10) in a presence of a Lewis acid such as $TiCl_4$ (Titanium (IV) chloride), at elevated temperature (for example 120°C) to give the acylated phenol GS 11. This intermediate is reacted with an a-oxo acid (GS 12) in a basic media (for example KOH (potassium hydroxide)), then after treatment, in presence of hydrazine hydrate (NH_2-NH_2, H_2O) at elevated temperature (for example 100°C) to give the pyridazone (GS 13). Then, to the intermediate (GS 13) is added a chlorinated agent like

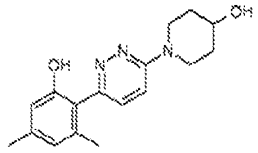
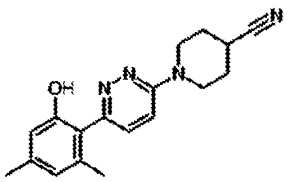
$POCl_3$ (phosphoryl chloride), in a polar solvent, for example DMF, at 80-90°C to give the chloropyridazine derivative (GS 7).

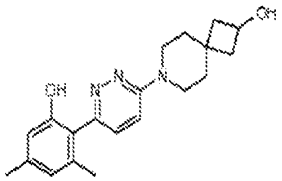
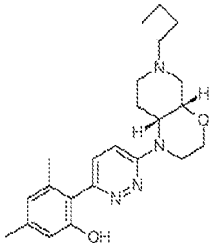
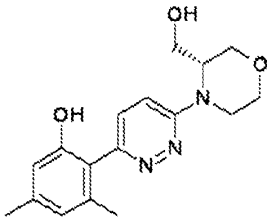
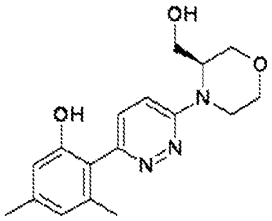
The specific compounds of formula (I) or a pharmaceutically acceptable salt thereof as defined in the present disclosure are indicated in Table 1 (number, and formula) and are further detailed hereafter. In Table 1, ^{1}H NMR, and liquid chromatography/mass spectra are also indicated.

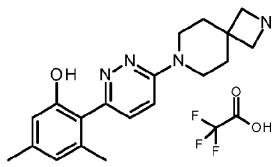
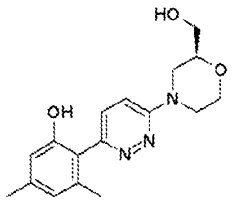
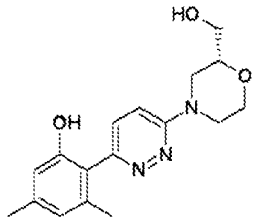
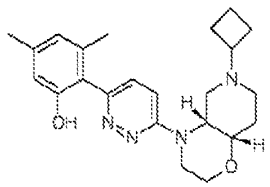
The ^{1}H NMR of Table 1 is ^{1}H NMR Spectra (400 MHz or 500 MHz, δ in ppm, DMSO-d6, CD_3OD or $CDCl_3$) as defined in the Experimental part.

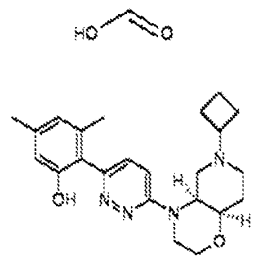
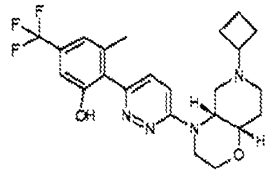
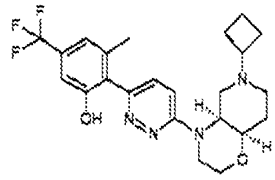
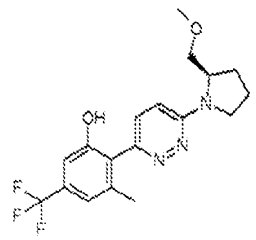
The liquid chromatography/mass spectra (LC/MS) of Table 1 were obtained according to one of the six methods described in the Experimental part.

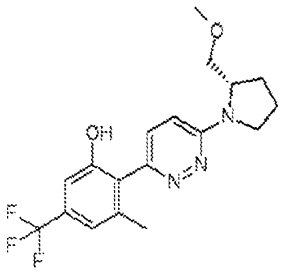
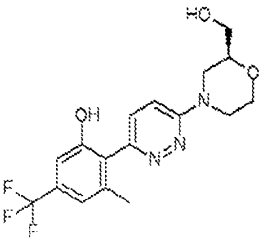
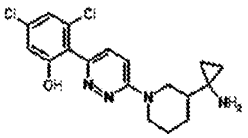
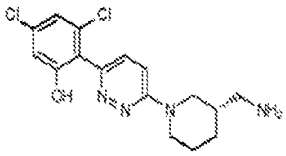
Table 1:

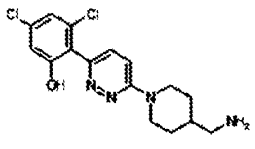
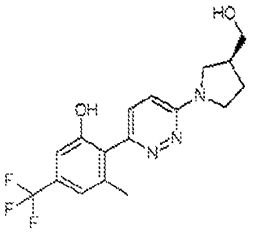
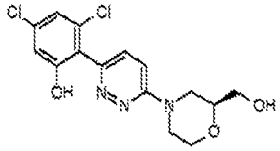
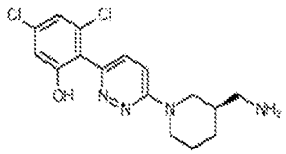
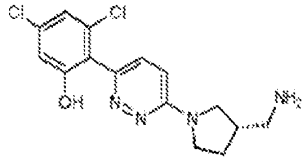
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
1		300.1 0.55 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.42 (dtd, J=12.9, 9.3, 9.3, 3.8 Hz, 2 H), 1.76 - 1.93 (m, 2 H), 2.04 (s, 3 H), 2.22 (s, 3 H), 3.21 (ddd, J=13.2, 10.1, 3.1 Hz, 2 H), 3.75 (tq, J=8.5, 4.1 Hz, 1 H), 4.09 (dt, J=13.3, 4.2 Hz, 2 H), 4.71 (d, J=4.3 Hz, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 7.21 - 7.36 (m, 2 H), 9.40 (s, 1 H)
2		309.2 1.05 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.70 - 1.85 (m, 2 H), 1.93 - 2.03 (m, 2 H), 2.03 (s, 3 H), 2.22 (s, 3 H), 3.10 - 3.21 (m, 1 H), 3.42 - 3.56 (m, 2 H), 3.86 - 4.00 (m, 2 H), 6.56 - 6.57(br s, 1 H), 6.57 - 6.59 (br s, 1 H), 7.23 - 7.42 (m, 2 H), 9.37 (s, 1 H)

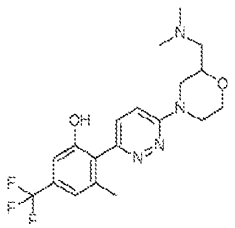
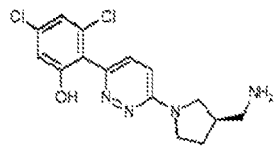
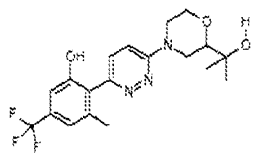
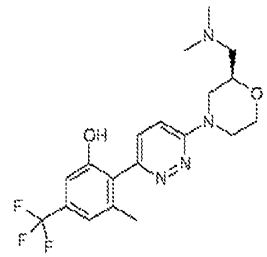
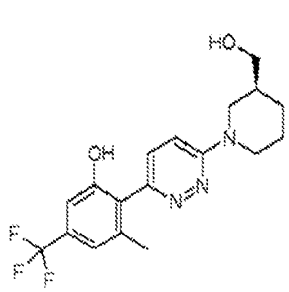
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
3		340.2 1.00 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.58 - 1.71 (m, 6 H), 2.09 (s, 3 H), 2.16 - 2.25 (m, 2 H), 2.24 (s, 3 H), 3.62 (dt, J=19.2, 5.4 Hz, 4 H), 4.10 - 4.23 (m, 1 H), 4.68 - 5.21 (m, 1 H), 6.63 (s, 2 H), 7.67 - 7.95 (m, 2 H), 9.49 - 10.33 (m, 1 H)
4		395 0.395 C	1H NMR (400 MHz, CD3OD) δ ppm 7.47 (d, *J* = 9.4 Hz, 1H), 7.31 (d, *J* = 9.6 Hz, 1H), 6.64 (s, 1H), 6.59 (s, 1H), 4.67 (br d, *J* = 11.2 Hz, 1H), 4.21 (dd, *J* = 3.2, 11.4 Hz, 1H), 3.98 (br s, 1H), 3.94 - 3.79 (m, 2H), 3.54 - 3.43 (m, 2H), 3.35 (br dd, *J* = 4.0, 12.4 Hz, 2H), 3.02 - 2.91 (m, 1H), 2.79 - 2.67 (m, 1H), 2.37 - 2.20 (m, 7H), 2.18 - 2.11 (m, 1H), 2.08 (s, 3H), 1.96 - 1.77 (m, 3H)
5		316.3 0.91 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.04 (s, 3 H), 2.22 (s, 3 H), 3.15 (td, J=12.8, 3.9 Hz, 1 H), 3.43 - 3.64 (m, 3 H), 3.69 - 3.81 (m, 1 H), 3.95 (dd, J=11.3, 3.6 Hz, 1 H), 4.04 - 4.23 (m, 3 H), 4.85 (dd, J=6.2, 4.9 Hz, 1 H), 6.56 - 6.57 (m, 1 H), 6.57 - 6.59 (m, 1 H), 7.19 (d, J=9.5 Hz, 1 H), 7.32 (d, J=9.5 Hz, 1 H), 9.39 (s, 1 H)
6		316.3 0.91 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.04 (s, 3 H), 2.22 (s, 3 H), 3.15 (td, J=12.7, 3.6 Hz, 1 H), 3.44 - 3.62 (m, 3 H), 3.74 (td, J=9.6, 6.4 Hz, 1 H), 3.95 (br dd, J=11.3, 3.1 Hz, 1 H), 4.00 - 4.26 (m, 3 H), 4.87 (t, J=5.5 Hz, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 7.20 (d, J=9.5 Hz, 1 H), 7.32 (d, J=9.5 Hz, 1 H), 9.41 (s, 1 H)

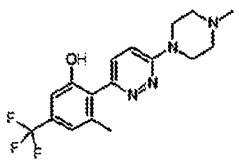
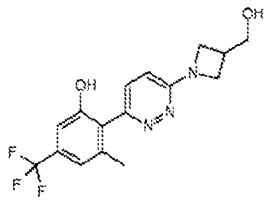
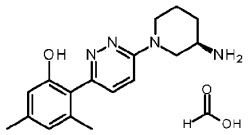
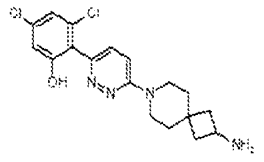
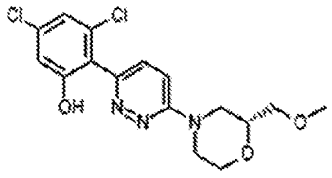
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
7		325.3 0.38 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.86 - 1.94 (m, 4 H), 2.08 (s, 3 H), 2.25 (s, 3 H), 3.65 - 3.71 (m partially hidden, 4 H), 3.81 (t, J=6.3 Hz, 4 H), 6.64 (s, 2 H), 7.69 - 7.96 (m, 2 H), 8.67 - 8.90 (m, 2 H), 9.55 - 10.23 (m, 1 H)
8		316.2 0.92 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.04 (s, 3 H), 2.23 (s, 3 H), 2.71 (dd, J=12.8, 9.9 Hz, 1 H), 2.97 (td, J=12.3, 3.5 Hz, 1 H), 3.41 - 3.58 (m, 3 H), 3.62 (td, J=11.6, 2.6 Hz, 1 H), 4.00 (dd, J=11.5, 2.3 Hz, 1 H), 4.13 (br d, J=12.9 Hz, 1 H), 4.32 (br d, J=12.6 Hz, 1 H), 4.82 (t, J=5.5 Hz, 1 H), 6.58 (br s, 1 H), 6.59 (br s, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 7.35 (d, J=9.5 Hz, 1 H), 9.39 (s, 1 H)
9		316.3 0.93 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 2.71 (dd, J=12.7, 9.8 Hz, 1 H) 2.97 (td, J=12.3, 3.4 Hz, 1 H) 3.41 - 3.56 (m, 3 H) 3.61 (td, J=11.6, 2.7 Hz, 1 H) 3.99 (dd, J=11.5, 2.2 Hz, 1 H) 4.12 (br d, J=12.8 Hz, 1 H) 4.31 (br d, J=12.7 Hz, 1 H) 4.82 (br s, 1 H) 6.53 - 6.64 (m, 2 H) 7.27 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.25 - 9.47 (m, 1 H)
10		395 0.421 C	1H NMR (400 MHz, CD3OD) δ ppm 7.45 (d, *J* = 9.6 Hz, 1H), 7.26 (d, *J* = 9.6 Hz, 1H), 6.65 (s, 1H), 6.60 (s, 1H), 4.47 (br d, *J* = 10.6 Hz, 1H), 4.12 (dd, *J* = 3.6, 11.6 Hz, 1H), 4.06 - 3.96 (m, 1H), 3.87 (br d, *J* = 2.6 Hz, 1H), 3.78 (dt, *J* = 3.4, 11.8 Hz, 1H), 3.31 - 3.25 (m, 1H), 2.95 - 2.85 (m, 1H), 2.79 - 2.65 (m, 2H), 2.40 (br t, *J* = 11.0 Hz, 1H), 2.29 (s, 3H), 2.21 - 2.02 (m, 6H), 2.00 - 1.85 (m, 4H), 1.80 - 1.66 (m, 2H)

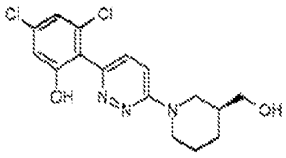
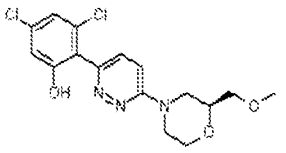
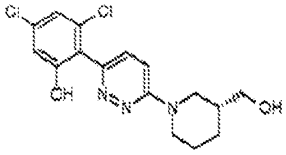
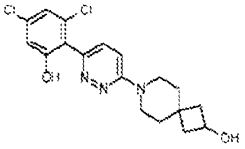
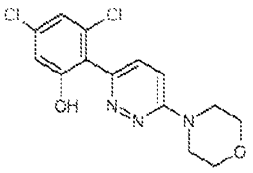
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
11		395 0.419 C	1H NMR (400 MHz, DMSO-d6) δ ppm 9.53 - 9.26 (m, 1H), 8.23 (br d, *J* = 1.2 Hz, 1H), 7.33 (d, *J* = 9.6 Hz, 1H), 7.19 (d, *J* = 9.6 Hz, 1H), 6.57 (br d, *J* = 5.4 Hz, 2H), 4.35 (br d, *J* = 10.0 Hz, 1H), 4.08 - 4.00 (m, 1H), 3.94 (br d, *J* = 12.6 Hz, 1H), 3.74 (br s, 1H), 3.65 - 3.58 (m, 1H), 3.14 (dt, *J* = 3.4, 12.6 Hz, 1H), 2.74 (quin, *J* = 7.6 Hz, 1H), 2.54 (br d, *J* = 4.6 Hz, 2H), 2.26 - 2.14 (m, 4H), 2.02 (s, 3H), 1.98 - 1.84 (m, 3H), 1.84 - 1.65 (m, 4H), 1.59 (br d, *J* = 6.4 Hz, 2H)
12		449 0.48 D	1H NMR (400 MHz, CD3OD) δ ppm 7.47 (d, *J* = 9.6 Hz, 1H), 7.28 (d, *J* = 9.6 Hz, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 4.55 - 4.45 (m, 1H), 4.11 (dd, *J* = 3.6, 11.6 Hz, 1H), 4.06 - 3.97 (m, 1H), 3.89 - 3.83 (m, 1H), 3.81 - 3.72 (m, 1H), 3.30 - 3.24 (m, 1H), 2.96 - 2.81 (m, 1H), 2.79 - 2.62 (m, 2H), 2.40 (t, *J* = 11.2 Hz, 1H), 2.18 (s, 3H), 2.16 - 2.01 (m, 3H), 1.98 - 1.84 (m, 4H), 1.77 - 1.65 (m, 2H).
13		449 0.516 D	1H NMR (400 MHz, CD3OD) δ ppm 7.47 (d, *J* = 9.6 Hz, 1H), 7.28 (d, *J* = 9.6 Hz, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 4.55 - 4.45 (m, 1H), 4.11 (dd, *J* = 3.6, 11.6 Hz, 1H), 4.06 - 3.97 (m, 1H), 3.89 - 3.83 (m, 1H), 3.81 - 3.72 (m, 1H), 3.30 - 3.24 (m, 1H), 2.96 - 2.81 (m, 1H), 2.79 - 2.62 (m, 2H), 2.40 (t, *J* = 11.2 Hz, 1H), 2.18 (s, 3H), 2.16 - 2.01 (m, 3H), 1.98 - 1.84 (m, 4H), 1.77 - 1.65 (m, 2H).
14		368.2 1.19 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.91 - 2.11 (m, 4 H) 2.14 (s, 3 H) 3.29 (s, 3 H) 3.32 - 3.42 (m, 2 H) 3.50 - 3.62 (m, 2 H) 4.24 - 4.36 (m, 1 H) 6.98 (d, J=9.4 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.34 (d, J=9.4 Hz, 1 H) 10.07 - 10.13 (m, 1 H)

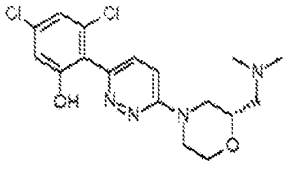
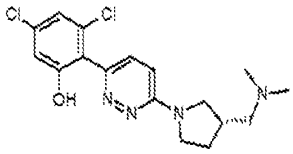
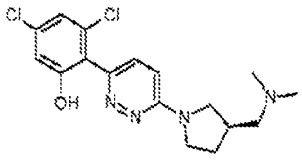
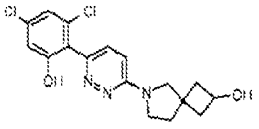
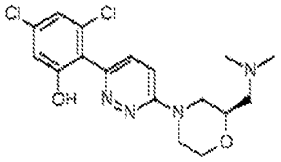
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
15		368.2 1.20 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.90 - 2.10 (m, 4 H) 2.14 (s, 3 H) 3.29 (s, 3 H) 3.32 - 3.43 (m, 2 H) 3.50 - 3.62 (m, 2 H) 4.25 - 4.36 (m, 1 H) 6.98 (d, J=9.4 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.34 (d, J=9.4 Hz, 1 H) 10.11 (s, 1 H)
16		370.2 1.21 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H), 2.74 (dd, J=12.8, 9.9 Hz, 1 H), 2.95 - 3.08 (m, 1 H), 3.41 - 3.58 (m, 3 H), 3.62 (td, J=11.6, 2.8 Hz, 1 H), 3.97 - 4.05 (m, 1 H), 4.15 (br d, J=13.0 Hz, 1 H), 4.34 (br d, J=12.6 Hz, 1 H), 4.80 (t, J=5.6 Hz, 1 H), 7.06 (br s, 1 H), 7.12 (br s, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 7.41 (d, J=9.5 Hz, 1 H), 10.45 (s, 1 H)
17		379.2 0.64 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.42 - 0.66 (m, 4 H) 1.12 - 1.29 (m, 1 H) 1.39 - 1.57 (m, 2 H) 1.69 - 1.86 (m, 2 H) 2.73 - 2.90 (m, 2 H) 4.40 (br d, J=12.8 Hz, 1 H) 4.48 (br d, J=12.5 Hz, 1 H) 6.96 (d, J=2.0 Hz, 1 H) 7.13 (d, J=2.0 Hz, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H)
18		353.2 0.59 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.17 - 1.34 (m, 1 H), 1.41 - 1.66 (m, 2 H), 1.68 - 1.79 (m, 1 H), 1.81 - 1.91 (m, 1 H), 2.56 (br d, J=6.1 Hz, 2 H), 2.73 (dd, J=12.9, 10.4 Hz, 1 H), 2.94 - 3.04 (m, 1 H), 4.21 - 4.32 (m, 1 H), 4.33 - 4.43 (m, 1 H), 6.88 (br s, 1 H), 7.02 (br s, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 7.32 (d, J=9.5 Hz, 1 H)

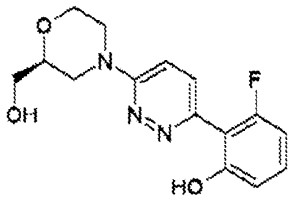
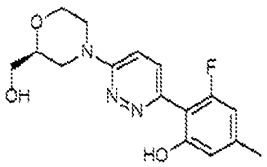
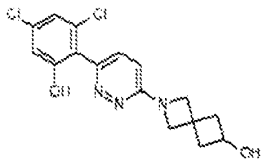
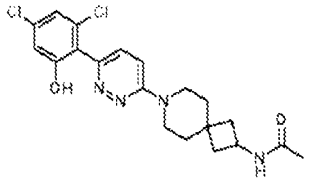
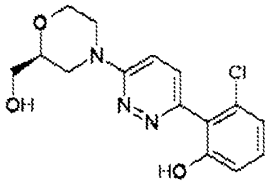
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
19		353.2 0.53 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.06 - 1.22 (m, 2 H) 1.51 - 1.66 (m, 1 H) 1.81 (br d, J=11.0 Hz, 2 H) 2.37 - 2.58 (m hidden, 2 H) 2.89 (td, J=12.6, 2.2 Hz, 2 H) 4.42 (br d, J=13.3 Hz, 2 H) 6.83 (d, J=2.0 Hz, 1 H) 6.96 (d, J=2.0 Hz, 1 H) 7.27 (d, J=9.5 Hz, 1 H) 7.30 (d, J=9.5 Hz, 1 H)
20		354.3 1.00 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.80 (dq, J=12.4, 7.6 Hz, 1 H), 2.07 (dtd, J=12.3, 7.2, 7.2, 5.3 Hz, 1 H), 2.14 (s, 3 H), 2.40 - 2.54 (m partially hidden, 1 H), 3.22 - 3.34 (m partially hidden, 1 H), 3.38 - 3.53 (m, 3 H), 3.55 - 3.67 (m, 2 H), 4.73 (t, J=5.3 Hz, 1 H), 6.90 (d, J=9.5 Hz, 1 H), 7.06 (br s, 1 H), 7.11 (br s, 1 H), 7.33 (d, J=9.5 Hz, 1 H), 10.10 (s, 1 H)
21		356.2 1.28 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.74 (dd, J=12.8, 9.8 Hz, 1 H), 2.95 - 3.06 (m, 1 H), 3.40 - 3.57 (m, 3 H), 3.61 (td, J=11.6, 2.8 Hz, 1 H), 3.95 - 4.07 (m, 1 H), 4.15 (br d, J=13.1 Hz, 1 H), 4.34 (br d, J=12.8 Hz, 1 H), 4.75 - 4.91 (m, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.12 (d, J=2.0 Hz, 1 H), 7.30 (d, J=9.5 Hz, 1 H), 7.39 (d, J=9.5 Hz, 1 H), 9.89 - 11.08 (m, 1 H)
22		353.2 0.94 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.15 - 1.31 (m, 1 H), 1.40 - 1.62 (m, 2 H), 1.66 - 1.79 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.32 - 2.62 (m hidden, 2 H), 2.72 (dd, J=12.7, 10.4 Hz, 1 H), 2.93 - 3.03 (m, 1 H), 4.27 (br d, J=13.0 Hz, 1 H), 4.32 - 4.39 (m, 1 H), 6.84 (br s, 1 H), 6.96 (br s, 1 H), 7.26 (d, J=9.5 Hz, 1 H), 7.31 (d, J=9.5 Hz, 1 H)
23		339.2 0.78 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.72 - 1.86 (m, 1 H) 2.05 - 2.21 (m, 1 H) 2.36 - 2.48 (m, 2 H) 2.77 (br d, J=6.8 Hz, 2 H) 3.26 (dd, J=10.7, 6.8 Hz, 1 H) 3.42 - 3.53 (m, 1 H) 3.54 - 3.63 (m, 1 H) 3.68 (br dd, J=10.6, 7.6 Hz, 1 H) 6.87 (d, J=9.5 Hz, 1 H) 6.92 (d, J=2.0 Hz, 1 H) 7.08 (d, J=2.0 Hz, 1 H) 7.32 (d, J=9.5 Hz, 1 H)

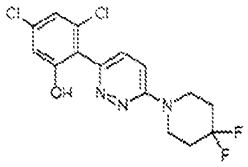
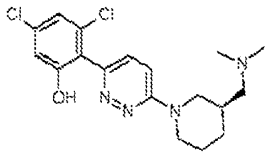
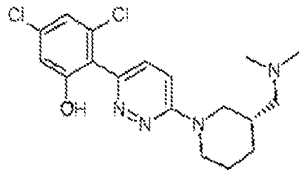
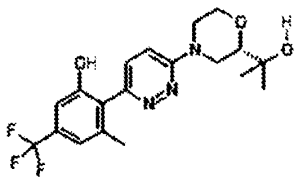
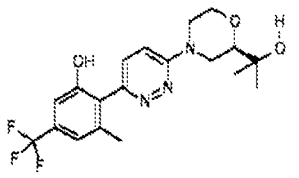
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
24		397.3 0.96 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.21 (s, 6 H) 2.33 - 2.46 (m, 2 H) 2.70 (dd, J=12.9, 10.4 Hz, 1 H) 2.99 (td, J=12.3, 3.5 Hz, 1 H) 3.55 - 3.72 (m, 2 H) 3.98 (dd, J=11.6, 2.2 Hz, 1 H) 4.13 (br d, J=12.6 Hz, 1 H) 4.34 (br d, J=12.4 Hz, 1 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.06 - 10.22 (m, 1 H)
25		339.2 0.78 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.67 - 1.83 (m, 1 H), 2.01 - 2.17 (m, 1 H), 2.28 - 2.42 (m, 1 H), 2.61 - 2.75 (m, 2 H), 3.23 (dd, J=10.6, 6.8 Hz, 2 H), 3.33 - 3.82 (m partially hidden, 3 H), 6.82 - 6.87 (m, 2 H), 6.98 (d, J=2 Hz, 1 H), 7.29 (d, J=9.5 Hz, 1 H)
26		398.3 1.35 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.14 (s, 3 H), 1.18 (s, 3 H), 2.13 (s, 3 H), 2.80 (dd, J=12.7, 11.1 Hz, 1 H), 2.95 (td, J=12.4, 3.4 Hz, 1 H), 3.20 - 3.35 (m partially hidden, 1 H), 3.60 (td, J=11.7, 2.5 Hz, 1 H), 4.04 (dd, J=11.4, 2.9 Hz, 1 H), 4.16 (br d, J=12.6 Hz, 1 H), 4.44 (br d, J=13.0 Hz, 1 H), 4.53 (s, 1 H), 7.06 (br s, 1 H), 7.12 (br s, 1 H), 7.30 (d, J=9.5 Hz, 1 H), 7.40 (d, J=9.5 Hz, 1 H), 10.15 (br s, 1 H)
27		397.3 0.96 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.24 (s, 6 H) 2.35 - 2.50 (m, 2 H) 2.70 (dd, J=12.9, 10.4 Hz, 1 H) 3.00 (td, J=12.3, 3.4 Hz, 1 H) 3.55 - 3.72 (m, 2 H) 3.98 (dd, J=11.6, 2.2 Hz, 1 H) 4.13 (br d, J=13.0 Hz, 1 H) 4.34 (br d, J=13.0 Hz, 1 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 10.14 (br s, 1 H)
28		368.3 1.15 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.19 - 1.33 (m, 1 H), 1.43 - 1.58 (m, 1 H), 1.61 - 1.85 (m, 3 H), 2.14 (s, 3 H), 2.74 (dd, J=13.0, 10.4 Hz, 1 H), 2.93 - 3.08 (m, 1 H), 3.23 - 3.49 (m partially hidden, 2 H), 4.25 (br d, J=13.0 Hz, 1 H), 4.34 - 4.46 (m, 1 H), 4.56 (br t, J=4.8 Hz, 1 H), 7.06 (br s, 1 H), 7.11 (br s, 1 H), 7.26 (d, J=9.5 Hz, 1 H), 7.34 (d, J=9.5 Hz, 1 H), 10.14 (br s, 1 H)

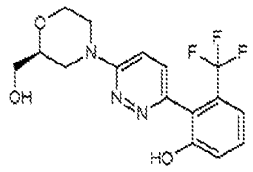
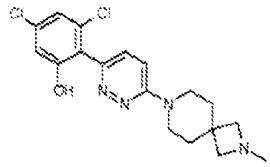
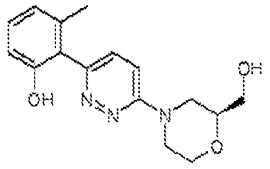
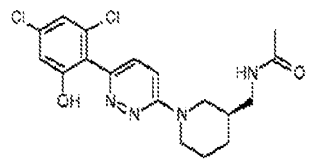
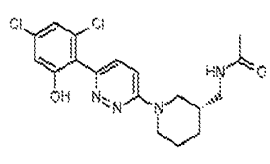
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
29		353.3 0.92 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.25 (s, 3 H) 2.38 - 2.47 (m, 4 H) 3.56 - 3.67 (m, 4 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 10.03 - 10.20 (m, 1 H)
30		340.2 0.99 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.11 (s, 3 H) 2.80 - 2.95 (m, 1 H) 3.62 (br d, J=6.1 Hz, 2 H) 3.83 (dd, J=8.3, 5.5 Hz, 2 H) 4.10 (t, J=8.2 Hz, 2 H) 4.68 - 4.97 (m, 1 H) 6.81 (d, J=9.5 Hz, 1 H) 7.05 (br s, 1 H) 7.11 (br s, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.95 - 10.26 (m, 1 H)
31		299.3 0.56 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.38 - 1.62 (m, 2 H) 1.73 - 1.88 (m, 1 H) 1.90 - 2.00 (m, 1 H) 2.04 (s, 3 H) 2.22 (s, 3 H) 2.93 - 3.04 (m, 2 H) 3.08 (ddd, J=13.0, 10.3, 2.8 Hz, 1 H) 3.96 - 4.06 (m, 1 H) 4.29 - 4.40 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.26 (d, J=9.5 Hz, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 8.15 - 8.42 (m, 1 H) 9.10 - 9.83 (m, 1 H)
32		379.2 1.05 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.43 - 1.66 (m, 6 H), 2.16 (ddd, J=9.7, 7.8, 2.4 Hz, 2 H), 3.31 - 3.47 (m partially hidden, 1 H), 3.48 - 3.67 (m partially hidden, 4 H), 6.82 (d, J=2.0 Hz, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.26 (d, J=9.5 Hz, 1 H), 7.29 (d, J=9.5 Hz, 1 H)
33		354.2 0.82 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.77 (dd, J=12.8, 10.7 Hz, 1 H), 3.00 (td, J=12.3, 3.4 Hz, 1 H), 3.31 (s, 3 H), 3.38 - 3.53 (m partially hidden, 2 H), 3.61 (td, J=11.6, 2.6 Hz, 1 H), 3.69 (dtd, J=10.4, 5.1, 5.1, 2.7 Hz, 1 H), 3.99 (br dd, J=11.6, 2.3 Hz, 1 H), 4.15 (br d, J=12.8 Hz, 1 H), 4.29 (br d, J=12.5 Hz, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.12 (d, J=2.0 Hz, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 7.39 (d, J=9.5 Hz, 1 H), 9.74 - 11.74 (m, 1 H)

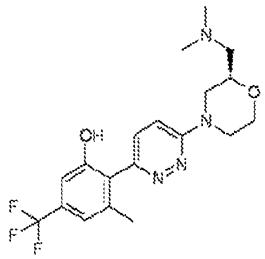
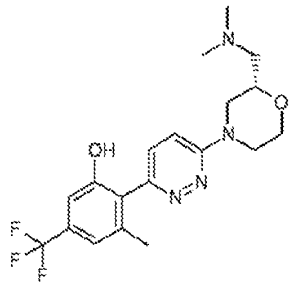
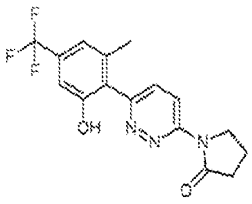
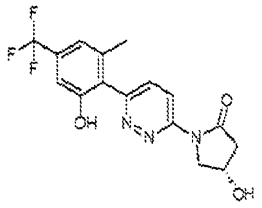
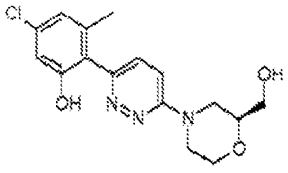
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
34		354.2 0.82 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.26 - 1.40 (m, 1 H), 1.49 - 1.64 (m, 1 H), 1.66 - 1.93 (m, 3 H), 2.81 (dd, J=13.0, 10.3 Hz, 1 H), 3.00 - 3.10 (m, 1 H), 3.26 - 3.61 (m hidden, 2 H), 4.32 (br d, J=13.0 Hz, 1 H), 4.46 (br dd, J=12.7, 3.1 Hz, 1 H), 4.61 - 4.71 (m, 1 H), 7.01 (d, J=2.0 Hz, 1 H), 7.18 (d, J=2.0 Hz, 1 H), 7.32 (d, J=9.5 Hz, 1 H), 7.39 (d, J=9.5 Hz, 1 H), 10.03 - 11.42 (m, 1 H)
35		370.2 1.05 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.77 (dd, J=12.8, 10.8 Hz, 1 H) 3.00 (td, J=12.3, 3.5 Hz, 1 H) 3.31 (s partially hidden, 3 H) 3.40 - 3.53 (m partially hidden, 2 H) 3.61 (td, J=11.6, 2.6 Hz, 1 H) 3.66 - 3.74 (m, 1 H) 3.99 (dd, J=11.6, 2.1 Hz, 1 H) 4.15 (br d, J=12.8 Hz, 1 H) 4.29 (br d, J=12.5 Hz, 1 H) 6.95 (d, J=2.0 Hz, 1 H) 7.13 (d, J=2.0 Hz, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.39 (d, J=9.5 Hz, 1 H) 9.60 - 11.29 (m, 1 H)
36		354.2 0.82 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.20 - 1.34 (m, 1 H), 1.43 - 1.57 (m, 1 H), 1.60 - 1.85 (m, 3 H), 2.75 (dd, J=13.0, 10.4 Hz, 1 H), 2.96 - 3.05 (m, 1 H), 3.21 - 3.43 (m hidden, 2 H), 4.25 (br d, J=12.9 Hz, 1 H), 4.35 - 4.43 (m, 1 H), 4.50 - 4.67 (m, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.11 (d, J=2.0 Hz, 1 H), 7.25 (d, J=9.5 Hz, 1 H), 7.32 (d, J=9.5 Hz, 1 H), 9.55 - 11.35 (m, 1 H)
37		380.2 0.88 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.52 - 1.71 (m, 6 H), 2.15 - 2.28 (m, 2 H), 3.51 - 3.67 (m, 4 H), 4.07 - 4.24 (m, 1 H), 4.85 - 4.99 (m, 1 H), 6.93 (d, J=2.0 Hz, 1 H), 7.09 (d, J=2.0 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 10.04 - 11.61 (m, 1 H)
38		326.2 0.99 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 3.55 - 3.63 (m, 4 H), 3.72 - 3.86 (m, 4 H), 6.95 (d, J=2.0 Hz, 1 H), 7.12 (d, J=2.0 Hz, 1 H), 7.30 (d, J=9.5 Hz, 1 H), 7.39 (d, J=9.5 Hz, 1 H), 10.13 - 11.28 (m, 1 H)

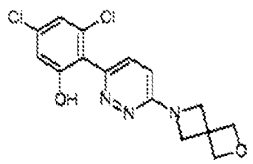
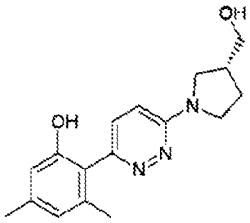
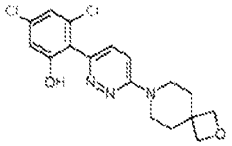
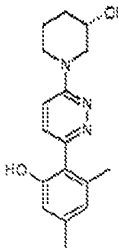
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
39		383.2 0.60 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.21 (s, 6 H), 2.34 - 2.46 (m, 2 H), 2.70 (dd, J=13.0, 10.5 Hz, 1 H), 3.00 (td, J=12.3, 3.5 Hz, 1 H), 3.57 - 3.71 (m, 2 H), 3.93 - 4.01 (m, 1 H), 4.13 (br d, J=12.6 Hz, 1 H), 4.33 (br d, J=12.4 Hz, 1 H), 6.96 (d, J=2.0 Hz, 1 H), 7.13 (d, J=2.0 Hz, 1 H), 7.30 (d, J=9.5 Hz, 1 H), 7.38 (d, J=9.5 Hz, 1 H), 9.64 - 11.57 (m, 1 H)
40		367.2 0.48 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.73 (dq, J=12.2, 7.8 Hz, 1 H), 2.06 - 2.16 (m, 1 H), 2.18 (s, 6 H), 2.23 - 2.38 (m, 2 H), 2.48 - 2.61 (m partially hidden, 1 H), 3.20 (br dd, J=10.5, 6.8 Hz, 1 H), 3.41 - 3.53 (m, 1 H), 3.56 - 3.75 (m, 2 H), 6.89 (d, J=9.3 Hz, 1 H), 6.94 (d, J=2.0 Hz, 1 H), 7.11 (d, J=2.0 Hz, 1 H), 7.30 (d, J=9.3 Hz, 1 H), 9.78 - 11.70 (m, 1 H)
41		367.2 0.48 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.73 (dq, J=12.3, 7.8 Hz, 1 H), 2.03 - 2.17 (m, 1 H), 2.18 (s, 6 H), 2.23 - 2.36 (m, 2 H), 2.48 - 2.59 (m partially hidden, 1 H), 3.20 (br dd, J=10.5, 6.8 Hz, 1 H), 3.38 - 3.52 (m, 1 H), 3.55 - 3.69 (m, 2 H), 6.89 (d, J=9.4 Hz, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.11 (d, J=2.0 Hz, 1 H), 7.30 (d, J=9.4 Hz, 1 H), 9.49 - 11.46 (m, 1 H)
42		366.2 0.70 A	1H NMR (400 MHz, DMSO-d6, 30°C, mixture of diastereoisomer 50/50) δ ppm 1.84 - 2.04 (m, 4 H), 2.20 - 2.34 (m, 2 H), 3.37 - 3.59 (m, 4 H), 4.11 - 4.26 (m, 1 H), 4.99 - 5.14 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.94 (d, J=2.0 Hz, 1 H), 7.10 (d, J=2.0 Hz, 1 H), 7.26 - 7.33 (m, 1 H), 9.72 - 11.84 (m, 1 H)
43		383.2 0.60 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.21 (s, 6 H), 2.34 - 2.45 (m, 2 H), 2.70 (dd, J=12.9, 10.4 Hz, 1 H), 3.00 (td, J=12.3, 3.5 Hz, 1 H), 3.57 - 3.70 (m, 2 H), 3.98 (br dd, J=11.6, 2.1 Hz, 1 H), 4.13 (br d, J=12.9 Hz, 1 H), 4.33 (br d, J=12.6 Hz, 1 H), 6.96 (d, J=2.0 Hz, 1 H), 7.13 (d, J=2.0 Hz, 1 H), 7.30 (d, J=9.5 Hz, 1 H), 7.38 (d, J=9.5 Hz, 1 H), 9.86 - 11.64 (m, 1 H)

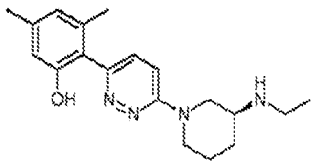
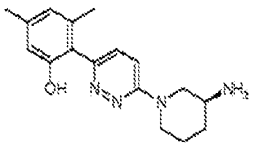
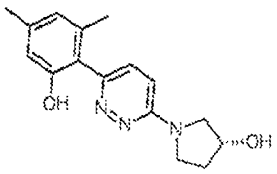
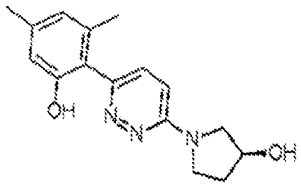
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
44		306.2 0.82 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.79 (dd, J=12.9, 9.7 Hz, 1 H), 3.03 (ddd, J=12.8, 11.9, 3.6 Hz, 1 H), 3.42 - 3.69 (m, 6 H), 3.95 - 4.04 (m, 1 H), 4.16 (br d, J=13.1 Hz, 1 H), 4.34 (br d, J=12.8 Hz, 1 H), 6.75 (ddd, J=11.4, 8.3, 0.9 Hz, 1 H), 6.80 (d, J=8.3 Hz, 1 H), 7.26 (td, J=8.3, 6.8 Hz, 1 H), 7.44 (d, J=9.8 Hz, 1 H), 7.81 (d, J=9.8 Hz, 1 H)
45		320.2 0.95 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.28 (s, 3 H), 2.78 (dd, J=12.9, 9.8 Hz, 1 H), 3.03 (td, J=12.3, 3.5 Hz, 1 H), 3.40 - 3.56 (m, 3 H), 3.60 (td, J=11.6, 2.7 Hz, 1 H), 3.99 (dd, J=11.5, 2.3 Hz, 1 H), 4.15 (br d, J=13.0 Hz, 1 H), 4.33 (br d, J=12.8 Hz, 1 H), 4.81 - 4.89 (m, 1 H), 6.58 - 6.66 (m, 2 H), 7.46 (d, J=9.8 Hz, 1 H), 7.84 (d, J=9.8 Hz, 1 H), 12.78 (br s, 1 H)
46		352.2 0.70 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.98 - 2.19 (m, 2 H), 2.42 - 2.62 (m hidden, 2 H), 3.95 - 4.20 (m, 5 H), 5.09 (d, J=6.2 Hz, 1 H), 6.79 (d, J=9.2 Hz, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.13 (d, J=2.0 Hz, 1 H), 7.33 (d, J=9.2 Hz, 1 H), 10.59 (br s, 1 H)
47		421.2 0.89 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.53 - 1.73 (m, 6 H), 1.78 (s, 3 H), 2.16 - 2.26 (m, 2 H), 3.53 - 3.67 (m, 4 H), 4.21 (sxt, J=8.1 Hz, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.12 (d, J=2.0 Hz, 1 H), 7.26 - 7.37 (m, 2 H), 8.09 (d, J=7.5 Hz, 1 H), 10.63 (br s, 1 H)
48		322.1 0.63 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.74 (dd, J=12.8, 9.8 Hz, 1 H) 2.99 (td, J=12.3, 3.5 Hz, 1 H) 3.43 - 3.57 (m, 3 H) 3.61 (td, J=11.6, 2.7 Hz, 1 H) 4.00 (dd, J=11.6, 2.3 Hz, 1 H) 4.15 (br d, J=13.0 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.76 - 4.90 (m, 1 H) 6.92 (dd, J=8.2, 0.9 Hz, 1 H) 6.99 (dd, J=8.0, 0.9 Hz, 1 H) 7.20 - 7.27 (m, 1 H) 7.30 (d, J=9.4 Hz, 1 H) 7.39 (d, J=9.4 Hz, 1 H) 9.90 - 10.21 (m, 1 H)

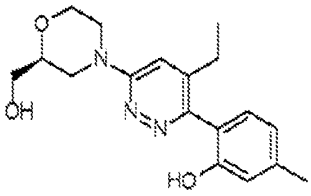
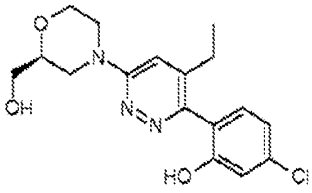
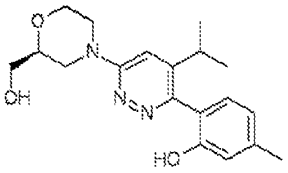
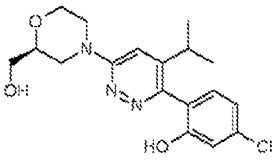
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
49		360.1 1.29 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.99 - 2.15 (m, 4 H), 3.79 - 3.87 (m, 4 H), 6.96 (d, J=2.0 Hz, 1 H), 7.13 (d, J=2.0 Hz, 1 H), 7.38 - 7.46 (m, 2 H), 10.24 - 11.20 (m, 1 H)
50		381.2 0.64 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.14 - 1.30 (m, 1 H) 1.42 - 1.59 (m, 1 H) 1.68 - 1.88 (m, 3 H) 2.05 (dd, J=12.0, 6.0 Hz, 1 H) 2.15 (s, 6 H) 2.17 - 2.26 (m, 1 H) 2.70 (dd, J=13.1, 9.9 Hz, 1 H) 3.01 - 3.12 (m, 1 H) 4.19 (br d, J=12.9 Hz, 1 H) 4.34 - 4.42 (m, 1 H) 6.95 (d, J=2.0 Hz, 1 H) 7.12 (d, J=2.0 Hz, 1 H) 7.24 (d, J=9.4 Hz, 1 H) 7.32 (d, J=9.4 Hz, 1 H)
51		381.2 0.64 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.16 - 1.27 (m, 1 H), 1.44 - 1.57 (m, 1 H), 1.67 - 1.87 (m, 3 H), 2.05 (dd, J=12.0, 6.1 Hz, 1 H), 2.14 (s, 6 H), 2.20 (dd, J=12.0, 8.6 Hz, 1 H), 2.70 (dd, J=13.1, 9.9 Hz, 1 H), 3.00 - 3.15 (m, 1 H), 4.14 - 4.28 (m, 1 H), 4.31 - 4.46 (m, 1 H), 6.95 (d, J=2.0 Hz, 1 H), 7.11 (d, J=2.0 Hz, 1 H), 7.24 (d, J=9.5 Hz, 1 H), 7.32 (d, J=9.5 Hz, 1 H), 9.80 - 11.46 (m, 1 H)
52		398.1 1.34 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.14 (s, 3 H) 1.18 (s, 3 H) 2.12 (s, 3 H) 2.79 (dd, J=12.8, 10.9 Hz, 1 H) 2.94 (td, J=12.4, 3.4 Hz, 1 H) 3.21 - 3.30 (m partially hidden, 1 H) 3.60 (td, J=11.7, 2.8 Hz, 1 H) 4.04 (dd, J=11.3, 2.8 Hz, 1 H) 4.15 (br d, J=13.0 Hz, 1 H) 4.43 (br d, J=12.8 Hz, 1 H) 4.46 - 4.59 (m, 1 H) 6.98 (s, 2 H) 7.27 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.4 Hz, 1 H)
53		398.1 1.34 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.14 (s, 3 H), 1.18 (s, 3 H), 2.13 (s, 3 H), 2.79 (dd, J=12.8, 10.9 Hz, 1 H), 2.94 (td, J=12.4, 3.5 Hz, 1 H), 3.18 - 3.31 (m partially hidden, 1 H), 3.60 (td, J=11.6, 2.6 Hz, 1 H), 4.04 (dd, J=11.4, 2.8 Hz, 1 H), 4.15 (br d, J=12.6 Hz, 1 H), 4.44 (br d, J=12.8 Hz, 1 H), 4.52 (br s, 1 H), 7.03 (br s, 1 H), 7.06 (br s, 1 H), 7.29 (d, J=9.5 Hz, 1 H), 7.40 (d, J=9.5 Hz, 1 H), 9.80 - 11.06 (m, 1 H)

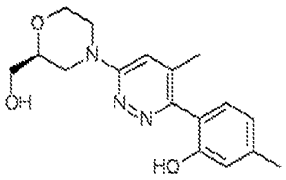
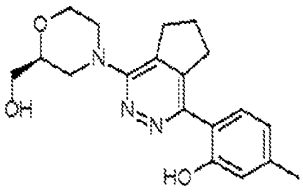
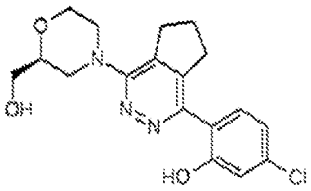
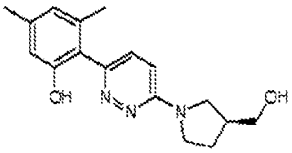
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
54		356.2 0.68 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.73 (dd, J=12.9, 9.9 Hz, 1 H) 2.93 - 3.05 (m, 1 H) 3.42 - 3.57 (m, 3 H) 3.62 (td, J=11.6, 2.8 Hz, 1 H) 3.95 - 4.04 (m, 1 H) 4.14 (br d, J=13.4 Hz, 1 H) 4.33 (br d, J=12.8 Hz, 1 H) 4.73 - 4.86 (m, 1 H) 7.19 - 7.30 (m, 3 H) 7.36 (d, J=9.4 Hz, 1 H) 7.41 - 7.49 (m, 1 H) 10.02 - 10.27 (m, 1 H)
55		379.2 0.52 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.98 - 2.23 (m, 4 H), 2.75 (br s, 3 H), 3.04 - 3.41 (m partially hidden, 4 H), 3.51 - 3.69 (m, 4 H), 6.89 (d, J=9.3 Hz, 1 H), 6.99 (d, J=2.0 Hz, 1 H), 7.13 (d, J=2.0 Hz, 1 H), 7.35 (d, J=9.3 Hz, 1 H), 10.35 - 11.12 (m, 1 H)
56		302.2 0.49 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H) 2.72 (dd, J=12.7, 9.9 Hz, 1 H) 2.98 (td, J=12.2, 3.3 Hz, 1 H) 3.41 - 3.57 (m, 3 H) 3.62 (td, J=11.5, 2.4 Hz, 1 H) 3.99 (br dd, J=11.4, 2.0 Hz, 1 H) 4.13 (br d, J=12.8 Hz, 1 H) 4.32 (br d, J=12.6 Hz, 1 H) 4.80 (br s, 1 H) 6.71 - 6.79 (m, 2 H) 7.10 (t, J=7.8 Hz, 1 H) 7.28 (d, J=9.4 Hz, 1 H) 7.37 (d, J=9.4 Hz, 1 H) 9.43 (br s, 1 H)
57		395.2 0.83 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.17 - 1.30 (m, 1 H), 1.40 - 1.57 (m, 1 H), 1.61 - 1.89 (m, 3 H), 1.82 (s, 3 H), 2.66 - 2.77 (m, 1 H), 2.90 - 3.12 (m, 3 H), 4.18 - 4.28 (m, 1 H), 4.30 - 4.37 (m, 1 H), 6.94 (d, J=2.1 Hz, 1 H), 7.10 (d, J=2.1 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 7.33 (d, J=9.5 Hz, 1 H), 7.90 (br t, J=5.7 Hz, 1 H), 10.02 - 11.37 (m, 1 H)
58		395.2 0.83 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.15 - 1.33 (m, 1 H) 1.39 - 1.57 (m, 1 H) 1.59 - 1.85 (m, 3 H) 1.84 (s, 3 H) 2.70 (dd, J=13.1, 10.4 Hz, 1 H) 2.91 - 3.10 (m, 3 H) 4.22 (br d, J=13.3 Hz, 1 H) 4.33 (br dd, J=13.0, 3.9 Hz, 1 H) 6.95 (d, J=2.0 Hz, 1 H) 7.12 (d, J=2.0 Hz, 1 H) 7.27 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 7.90 (br t, J=5.6 Hz, 1 H)

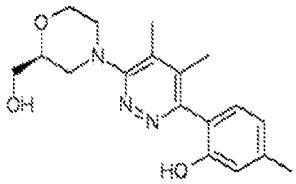
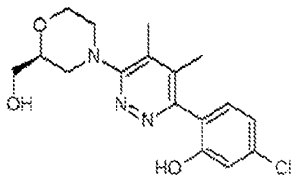
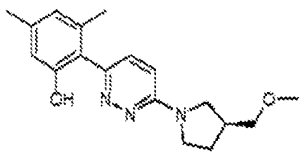
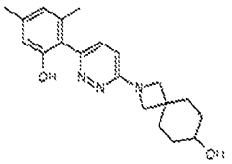
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
59		397.2 0.95 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H), 2.21 (s, 6 H), 2.34 - 2.45 (m, 2 H), 2.70 (dd, J=13.0, 10.4 Hz, 1 H), 2.93 - 3.05 (m, 1 H), 3.54 - 3.74 (m, 2 H), 3.94 - 4.03 (m, 1 H), 4.13 (br d, J=12.9 Hz, 1 H), 4.34 (br d, J=12.3 Hz, 1 H), 7.06 (br s, 1 H), 7.11 (br s, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 7.40 (d, J=9.5 Hz, 1 H), 9.90 - 10.45 (m, 1 H)
60		397.2 0.95 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.21 (s, 6 H) 2.32 - 2.46 (m, 2 H) 2.70 (dd, J=13, 10 Hz, 1 H) 2.99 (td, J=12, 4 Hz, 1 H) 3.52 - 3.73 (m, 2 H) 3.92 - 4.04 (m, 1 H) 4.13 (br d, J=13 Hz, 1 H) 4.34 (br d, J=12 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.31 (d, J=9.4 Hz, 1 H) 7.40 (d, J=9.4 Hz, 1 H) 10.02 - 10.30 (m, 1 H)
61		338.1 1.50 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.07 - 2.23 (m, 2 H), 2.11 (s, 3 H), 2.64 (t, J=8.0 Hz, 2 H), 4.16 (t, J=7.1 Hz, 2 H), 7.09 (br s, 1 H), 7.16 (br s, 1 H), 7.71 (d, J=9.3 Hz, 1 H), 8.61 (d, J=9.3 Hz, 1 H), 10.09 - 10.45 (m, 1 H)
62		354.1 1.33 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.11 (s, 3 H), 2.42 (br d, J=17.5 Hz, 1 H), 2.99 (dd, J=17.2, 5.9 Hz, 1 H), 4.11 (br d, J=11.8 Hz, 1 H), 4.22 (dd, J=11.8, 4.8 Hz, 1 H), 4.44 - 4.53 (m, 1 H), 5.31 - 5.49 (m, 1 H), 7.09 (br s, 1 H), 7.15 (br s, 1 H), 7.72 (d, J=9.3 Hz, 1 H), 8.63 (d, J=9.3 Hz, 1 H), 9.94 - 10.64 (m, 1 H)
63		336.2 0.67 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.05 (s, 3 H), 2.72 (dd, J=12.8, 9.8 Hz, 1 H), 2.98 (td, J=12.3, 3.4 Hz, 1 H), 3.42 - 3.57 (m, 3 H), 3.61 (td, J=11.5, 2.6 Hz, 1 H), 3.99 (dd, J=11.5, 2.3 Hz, 1 H), 4.13 (br d, J=12.9 Hz, 1 H), 4.32 (br d, J=12.8 Hz, 1 H), 4.74 - 4.87 (m, 1 H), 6.81 (br s, 1 H), 6.84 (br s, 1 H), 7.28 (d, J=9.4 Hz, 1 H), 7.36 (d, J=9.4 Hz, 1 H), 9.70 - 10.28 (m, 1 H)

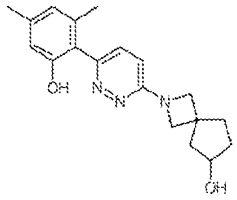
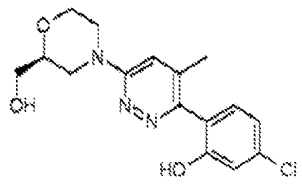
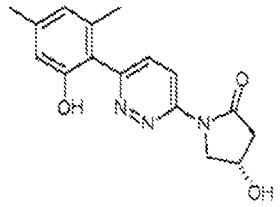
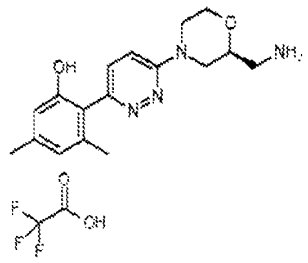
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
64		338.1 0.74 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 4.27 (s, 4 H), 4.76 (s, 4 H), 6.84 (d, J=9.1 Hz, 1 H), 6.94 (d, J=1.9 Hz, 1 H), 7.10 (br s, 1 H), 7.34 (d, J=9.1 Hz, 1 H), 10.01 - 11.43 (m, 1 H)
65		300.2 0.83 B	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.70 - 1.85 (m, 1 H), 1.99 - 2.13 (m, 1 H), 2.04 (s, 3 H), 2.22 (s, 3 H), 2.40 - 2.52 (m partially hidden, 1 H), 3.27 (dd, J=10.2, 6.5 Hz, 1 H), 3.38 - 3.52 (m, 3 H), 3.53 - 3.66 (m, 2 H), 4.73 (t, J=5.4 Hz, 1 H), 6.56 (br s, 1 H), 6.58 (br s, 1 H), 6.86 (d, J=9.5 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 9.40 (s, 1 H)
66		366.2 0.96 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.84 - 1.91 (m, 4 H), 3.55 - 3.64 (m, 4 H), 4.38 (s, 4 H), 6.95 (s, 1 H), 7.12 (s, 1 H), 7.27 - 7.41 (m, 2 H), 10.20 - 11.04 (m, 1 H)
67		300.2 0.55 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.36 - 1.58 (m, 2 H), 1.72 - 1.83 (m, 1 H), 1.87 - 1.98 (m, 1 H), 2.04 (s, 3 H), 2.22 (s, 3 H), 2.90 (dd, J=12.6, 8.8 Hz, 1 H), 3.07 - 3.18 (m, 1 H), 3.52 - 3.64 (m, 1 H), 3.94 - 4.03 (m, 1 H), 4.21 (dd, J=12.4, 3.7 Hz, 1 H), 4.87 (d, J=4.4 Hz, 1 H), 6.56 (br s, 1 H), 6.58 (br s, 1 H), 7.22 (d, J=9.5 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 9.42 (s, 1 H)

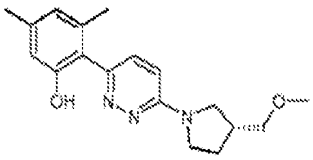
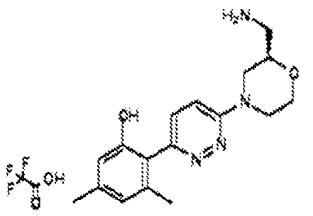
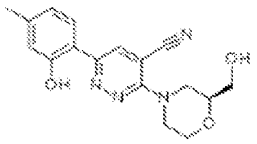
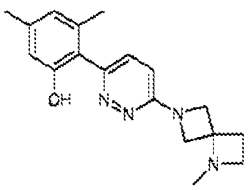
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
68		327.3 0.45 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.02 (t, J=7 Hz, 3 H), 1.25 - 1.36 (m, 1 H), 1.42 - 1.56 (m, 1 H), 1.54 - 1.72 (m, 1 H), 1.71 - 1.82 (m, 1 H), 1.91 - 2.00 (m, 1 H), 2.04 (s, 3 H), 2.22 (s, 3 H), 2.50 - 2.71 (m, 3 H), 2.76 (dd, J=13, 9 Hz, 1 H), 2.95 - 3.07 (m, 1 H), 4.10 - 4.17 (m, 1 H), 4.30 - 4.38 (m, 1 H), 6.56 (br s, 1 H), 6.58 (br s, 1 H), 7.22 (d, J=9.5 Hz, 1 H), 7.28 (d, J=9.5 Hz, 1 H), 9.33 - 9.52 (m, 1 H)
69		299.2 0.42 A	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.20 - 1.35 (m, 1 H), 1.41 - 1.58 (m, 1 H), 1.65 - 2.34 (m, 2 H), 1.69 - 1.80 (m, 1 H), 1.85 - 1.95 (m, 1 H), 2.04 (s, 3 H), 2.22 (s, 3 H), 2.62 - 2.78 (m, 2 H), 2.94 (ddd, J=13, 11, 3 Hz, 1 H), 4.11 - 4.22 (m, 1 H), 4.27 (br dd, J=10, 1 Hz, 1 H), 6.56 (br s, 1 H), 6.58 (br s, 1 H), 7.22 (d, J=9.5 Hz, 1 H), 7.28 (d, J=9.5 Hz, 1 H), 9.07 - 9.87 (m, 1 H)
70		286.3 1.03 E	1H NMR (500 MHz, DMSO) δ (ppm): 9.51 (s, 1H), 7.27 (d, J = 9.3 Hz, 1H), 6.86 (d, J = 9.3 Hz, 1H), 6.55 (d, J = 13.7 Hz, 2H), 5.03 (s, 1H), 4.44 (s, 1H), 3.60 – 3.50 (m, 3H), 3.41 (d, J = 11.2 Hz, 1H), 2.21 (s, 3H), 2.07 (m, 1H), 2.03 (s, 3H), 1.98 – 1.91 (m, 1H).
71		286.3 1.04 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.41 (s, 1H), 7.27 (d, J = 9.2 Hz, 1H), 6.87 (d, J = 9.3 Hz, 1H), 6.56 (d, J = 4.2 Hz, 2H), 5.02 (d, J = 3.6 Hz, 1H), 4.44 (s, 1H), 3.56 (td, J = 12.7, 7.3 Hz, 3H), 3.41 (d, J = 11.1 Hz, 1H), 2.22 (s, 3H), 2.08 (m, J = 9.0, 4.5 Hz, 1H), 2.03 (s, 3H), 2.00 – 1.89 (m, 1H)

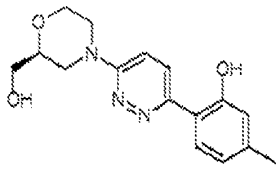
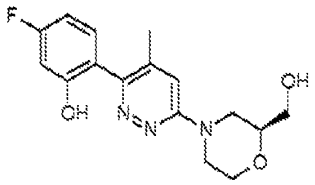
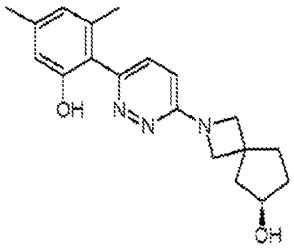
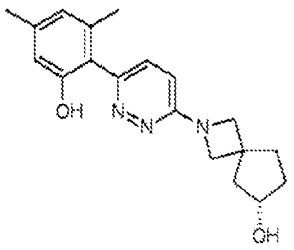
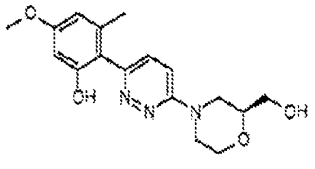
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
72		330.1 0.95 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.99 (t, J=7.5 Hz, 3 H), 2.28 (s, 3 H), 2.42 (q, J=7.5 Hz, 2 H), 2.69 (dd, J=12.7, 9.7 Hz, 1 H), 2.94 (td, J=12.3, 3.5 Hz, 1 H), 3.42 - 3.57 (m, 3 H), 3.61 (td, J=11.6, 2.8 Hz, 1 H), 3.95 - 4.02 (m, 1 H), 4.14 (br d, J=13.0 Hz, 1 H), 4.29 (br d, J=12.6 Hz, 1 H), 4.79 (t, J=5.6 Hz, 1 H), 6.70 (br d, J=7.5 Hz, 1 H), 6.73 (br s, 1 H), 7.02 (d, J=7.5 Hz, 1 H), 7.07 (s, 1 H), 9.45 (s, 1 H)
73		350.1 1.06 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.01 (t, J=7.5 Hz, 3 H), 2.40 (q, J=7.5 Hz, 2 H), 2.70 (dd, J=12.8, 9.8 Hz, 1 H), 2.95 (td, J=12.3, 3.5 Hz, 1 H), 3.42 - 3.57 (m, 3 H), 3.60 (td, J=11.6, 2.6 Hz, 1 H), 3.99 (br dd, J=11.5, 2.3 Hz, 1 H), 4.16 (br d, J=12.9 Hz, 1 H), 4.31 (br d, J=12.6 Hz, 1 H), 4.76 - 4.83 (m, 1 H), 6.93 - 6.98 (m, 2 H), 7.10 (br s, 1 H), 7.17 (d, J=8.6 Hz, 1 H), 10.12 (br s, 1 H)
74		344.1 1.02 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.04 - 1.12 (m, 6 H), 2.28 (s, 3 H), 2.60 - 2.80 (m, 2 H), 2.93 (td, J=12.3, 3.5 Hz, 1 H), 3.42 - 3.59 (m, 3 H), 3.61 (td, J=11.5, 2.7 Hz, 1 H), 3.95 - 4.05 (m, 1 H), 4.16 (br d, J=13.0 Hz, 1 H), 4.31 (br d, J=12.6 Hz, 1 H), 4.78 (t, J=5.4 Hz, 1 H), 6.67 - 6.74 (m, 2 H), 7.01 (d, J=7.5 Hz, 1 H), 7.09 (s, 1 H), 9.37 (s, 1 H)
75		364.1 1.14 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.07 - 1.12 (m, 6 H), 2.60 - 2.74 (m, 2 H), 2.94 (td, J=12.3, 3.5 Hz, 1 H), 3.42 - 3.57 (m, 3 H), 3.61 (td, J=11.6, 2.7 Hz, 1 H), 3.96 - 4.03 (m, 1 H), 4.18 (br d, J=12.9 Hz, 1 H), 4.32 (br d, J=12.6 Hz, 1 H), 4.79 (t, J=5.5 Hz, 1 H), 6.93 - 6.98 (m, 2 H), 7.11 (s, 1 H), 7.17 (d, J=8.6 Hz, 1 H), 10.07 (br s, 1 H)

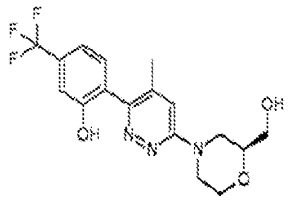
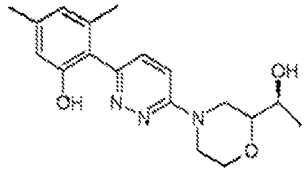
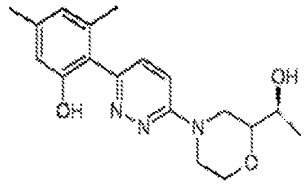
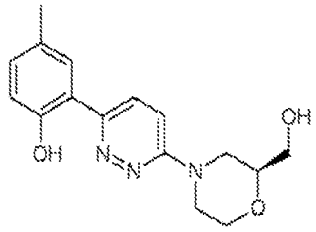
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
76		316.1 0.88 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.11 (s, 3 H), 2.28 (s, 3 H), 2.69 (br dd, J=12.7, 9.7 Hz, 1 H), 2.94 (td, J=12.3, 3.4 Hz, 1 H), 3.41 - 3.56 (m, 3 H), 3.60 (td, J=11.6, 2.6 Hz, 1 H), 3.98 (br dd, J=11.4, 2.1 Hz, 1 H), 4.12 (br d, J=12.8 Hz, 1 H), 4.28 (br d, J=12.6 Hz, 1 H), 4.82 (br t, J=5.1 Hz, 1 H), 6.71 (d, J=7.8 Hz, 1 H), 6.74 (s, 1 H), 7.06 (d, J=7.6 Hz, 1 H), 7.13 (s, 1 H), 9.67 (br s, 1 H)
77		342.1 1.13 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.02 (quin, J=7.1 Hz, 2 H), 2.29 (s, 3 H), 2.79 (dd, J=12.9, 10.3 Hz, 1 H), 2.91 - 3.08 (m, 5 H), 3.39 - 3.47 (m, 1 H), 3.48 - 3.55 (m, 1 H), 3.59 (ddd, J=10.1, 5.4, 2.1 Hz, 1 H), 3.67 (td, J=11.4, 2.4 Hz, 1 H), 3.79 (br d, J=12.6 Hz, 1 H), 3.94 (br dd, J=12.7, 1.4 Hz, 2 H), 4.80 (t, J=5.7 Hz, 1 H), 6.74 (d, J=8.0 Hz, 1 H), 6.78 (s, 1 H), 7.41 (d, J=8.0 Hz, 1 H), 12.23 (s, 1 H)
78		362.1 1.33 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.02 (quin, J=7.2 Hz, 2 H), 2.81 (dd, J=12.9, 10.3 Hz, 1 H), 2.92 - 3.10 (m, 5 H), 3.40 - 3.47 (m, 1 H), 3.48 - 3.55 (m, 1 H), 3.56 - 3.63 (m, 1 H), 3.67 (td, J=11.4, 2.3 Hz, 1 H), 3.83 (br d, J=12.9 Hz, 1 H), 3.91 - 4.02 (m, 2 H), 4.80 (br t, J=5.5 Hz, 1 H), 6.98 (dd, J=8.3, 2.1 Hz, 1 H), 7.01 (d, J=2.0 Hz, 1 H), 7.50 (d, J=8.3 Hz, 1 H), 12.28 (br s, 1 H)
79		300.1 0.85 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.70 - 1.87 (m, 1 H) 2.04 (s, 3 H) 2.05 - 2.13 (m, 1 H) 2.22 (s, 3 H) 2.38 - 2.49 (m, 1 H) 3.17 - 3.31 (m partially hidden, 1 H) 3.34 - 3.52 (m, 3 H) 3.53 - 3.67 (m, 2 H) 4.71 (t, J=5.2 Hz, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.85 (d, J=9.4 Hz, 1 H) 7.27 (d, J=9.4 Hz, 1 H) 9.39 (s, 1 H)

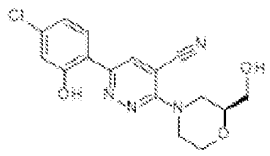
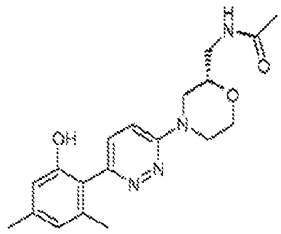
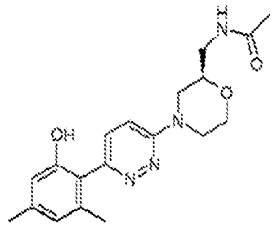
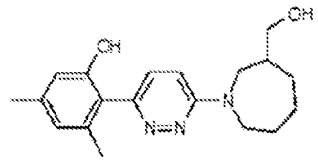
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
80		330.1 0.98 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.24 (s, 3 H) 2.29 (s, 3 H) 2.69 - 2.80 (m, 1 H) 2.88 - 3.03 (m, 1 H) 3.21 - 3.32 (m partially hidden, 1 H) 3.35 - 3.46 (m, 2 H) 3.46 - 3.57 (m, 1 H) 3.58 - 3.69 (m, 1 H) 3.74 (br t, J=10.4 Hz, 1 H) 3.94 (br d, J=11.1 Hz, 1 H) 4.75 (br s, 1 H) 6.72 (br d, J=7.6 Hz, 1 H) 6.75 (br s, 1 H) 7.05 (d, J=7.6 Hz, 1 H) 9.53 (br s, 1 H)
81		350.1 1.12 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H), 2.24 (s, 3 H), 2.75 (dd, J=12.4, 10.3 Hz, 1 H), 2.96 (td, J=11.9, 3.0 Hz, 1 H), 3.27 - 3.47 (m partially hidden, 3 H), 3.48 - 3.55 (m, 1 H), 3.61 - 3.70 (m, 1 H), 3.74 (td, J=11.3, 2.1 Hz, 1 H), 3.94 (br d, J=10.8 Hz, 1 H), 4.76 (br t, J=4.9 Hz, 1 H), 6.92 - 7.00 (m, 2 H), 7.20 (d, J=8.8 Hz, 1 H), 10.25 (br s, 1 H)
82		314 5.97 F	1H NMR (400 MHz, $CDCl_3$) δ ppm 11.22 (s, 1H), 7.47 (d, J = 9.6 Hz, 1H), 6.80 – 6.73 (m, 2H), 6.65 – 6.60 (m, 1H), 3.72 (m, 2H), 3.61 (m, 1H), 3.51 – 3.41 (m, 2H), 3.39 (s, 3H), 3.38 – 3.34 (m, 1H), 2.70 (m, 1H), 2.38 (s, 3H), 2.30 (s, 3H), 2.21 (m, 1H), 1.97 – 1.84 (m, 1H)
83		340.1 0.96 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.22 - 1.36 (m, 2 H), 1.47 - 1.61 (m, 2 H), 1.66 - 1.77 (m, 2 H), 1.82 - 1.96 (m, 2 H), 2.02 (s, 3 H), 2.22 (s, 3 H), 3.41 - 3.57 (m, 1 H), 3.73 (s, 2 H), 3.77 (s, 2 H), 4.49 (d, J=4.0 Hz, 1 H), 6.52 - 6.60 (m, 2 H), 6.77 (d, J=9.1 Hz, 1 H), 7.27 (d, J=9.1 Hz, 1 H), 9.34 (s, 1 H)

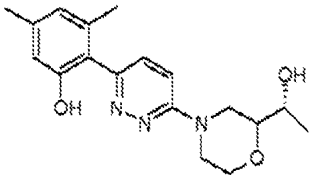
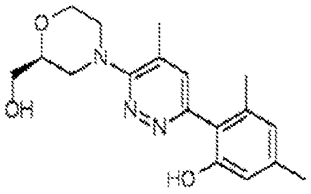
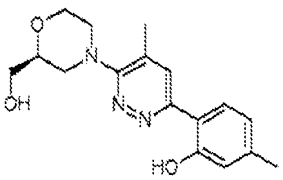
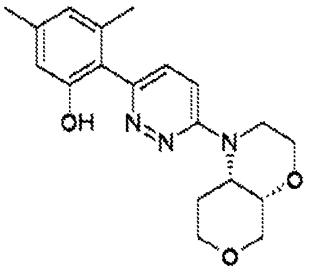
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
84		326.2 0.94 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.50 - 1.61 (m, 1 H), 1.76 - 1.90 (m, 3 H), 1.99 - 2.12 (m, 2 H), 2.02 (s, 3 H), 2.22 (s, 3 H), 3.92 (s, 2 H), 3.94 (d, J=8.1 Hz, 1 H), 4.04 (d, J=8.1 Hz, 1 H), 4.14 - 4.23 (m, 1 H), 4.53 (br d, J=3.0 Hz, 1 H), 6.56 - 6.57 (m, 1 H), 6.57 - 6.59 (m, 1 H), 6.77 (d, J=9.1 Hz, 1 H), 7.28 (d, J=9.1 Hz, 1 H), 9.24 - 9.50 (m, 1 H)
85		336 0.98 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.09 (s, 3 H), 2.70 (dd, J=12.8, 9.9 Hz, 1 H), 2.96 (td, J=12.3, 3.4 Hz, 1 H), 3.40 - 3.56 (m, 3 H), 3.60 (td, J=11.6, 2.6 Hz, 1 H), 3.98 (br dd, J=11.6, 2.1 Hz, 1 H), 4.13 (br d, J=13.0 Hz, 1 H), 4.29 (br d, J=12.8 Hz, 1 H), 4.75 - 4.85 (m, 1 H), 6.93 - 6.98 (m, 2 H), 7.15 (br s, 1 H), 7.18 - 7.22 (m, 1 H), 10.26 (br s, 1 H)
86		300.1 1.16 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H), 2.24 (s, 3 H), 2.41 (br d, J=17.5 Hz, 1 H), 2.98 (dd, J=17.3, 5.9 Hz, 1 H), 4.10 (br d, J=11.8 Hz, 1 H), 4.21 (dd, J=11.8, 5.0 Hz, 1 H), 4.43 - 4.54 (m, 1 H), 5.38 (d, J=3.6 Hz, 1 H), 6.61 (br d, J=3.6 Hz, 2 H), 7.63 (d, J=9.3 Hz, 1 H), 8.56 (d, J=9.3 Hz, 1 H), 9.39 (s, 1 H)
87		315.2 0.69-071 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H), 2.23 (s, 3 H), 2.79 (dd, J=12.9, 10.5 Hz, 1 H), 2.87 - 3.19 (m, 3 H), 3.62 - 3.72 (m, 1 H), 3.74 - 3.85 (m, 1 H), 4.05 - 4.18 (m, 2 H), 4.40 (br d, J=12.6 Hz, 1 H), 6.57 - 6.58 (m, 1 H), 6.59 - 6.60 (m, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 7.41 (d, J=9.5 Hz, 1 H), 7.92 (br s, 3 H), 9.39 (br s, 1 H)

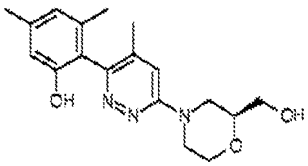
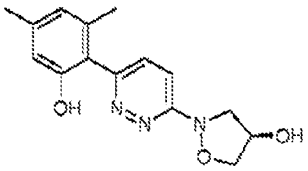
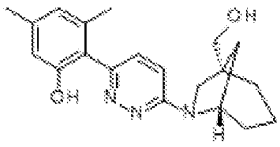
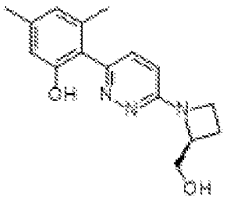
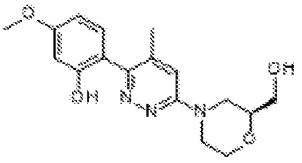
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
88		314 2.96 E	1H NMR (400 MHz, DMSO-d6) δ ppm 9.41 (s, 1H), 7.28 (d, J = 9.2 Hz, 1H), 6.89 (s, 1H), 6.57 (d, J = 5.5 Hz, 2H), 3.67 – 3.56 (m, 2H), 3.51 – 3.45 (m, 1H), 3.43 – 3.36 (m, 2H), 3.30 (s, 3H), 3.24 (dd, J = 10.5, 6.6 Hz, 1H), 2.62 (m, 1H), 2.23 (s, 3H), 2.11 (h, J = 7.0 Hz, 1H), 2.04 (s, 3H), 1.83 – 1.73 (m, 1H).
89		315.2 0.72 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.05 (s, 3 H), 2.24 (s, 3 H), 2.85 (dd, J=12.8, 10.6 Hz, 1 H), 2.91 - 3.03 (m, 1 H), 3.06 - 3.17 (m, 2 H), 3.53 - 3.90 (m partially hidden, 2 H), 4.06 - 4.19 (m, 2 H), 4.38 (br d, J=12.5 Hz, 1 H), 6.56 - 6.67 (m, 2 H), 7.44 - 7.66 (m, 2 H), 7.94 (br s, 3 H), 9.23 - 9.92 (m, 1 H)
90		327.1 1.45 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.30 (s, 3 H) 3.01 (dd, J=12.9, 10.4 Hz, 1 H) 3.19 - 3.29 (m, 1 H) 3.38 - 3.47 (m, 1 H) 3.48 - 3.57 (m, 1 H) 3.59 - 3.74 (m, 2 H) 3.95 - 4.03 (m, 1 H) 4.12 (br d, J=12.3 Hz, 1 H) 4.28 (br d, J=13.0 Hz, 1 H) 4.86 (t, J=5.8 Hz, 1 H) 6.74 - 6.84 (m, 2 H) 7.81 (d, J=8.0 Hz, 1 H) 8.70 (s, 1 H) 11.79 (s, 1 H)
91		311.2 0.74 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H), 2.22 (s, 3 H), 2.28 (s, 3 H), 2.32 (t, J=6.7 Hz, 2 H), 3.07 (t, J=6.7 Hz, 2 H), 4.03 (d, J=10.0 Hz, 2 H), 4.21 (d, J=10.0 Hz, 2 H), 6.54 - 6.59 (m, 2 H), 6.82 (d, J=9.1 Hz, 1 H), 7.29 (d, J=9.1 Hz, 1 H), 9.33 (s, 1 H)

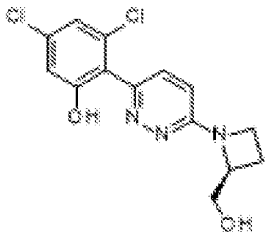
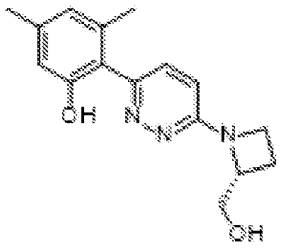
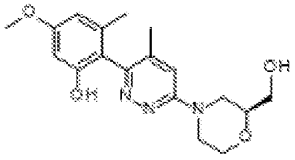
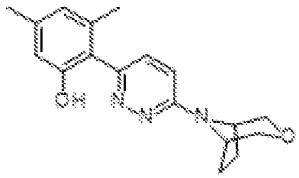
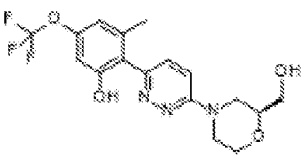
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
92		302.1 1.22 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.29 (s, 3 H), 2.77 (dd, J=12.9, 9.8 Hz, 1 H), 3.02 (ddd, J=12.9, 11.8, 3.5 Hz, 1 H), 3.43 - 3.57 (m, 3 H), 3.60 (td, J=11.6, 2.8 Hz, 1 H), 3.94 - 4.07 (m, 1 H), 4.10 - 4.22 (m, 1 H), 4.32 (br d, J=12.9 Hz, 1 H), 4.67 - 5.00 (m, 1 H), 6.71 - 6.82 (m, 2 H), 7.52 (d, J=10.0 Hz, 1 H), 7.77 (d, J=7.9 Hz, 1 H), 8.22 (d, J=10.0 Hz, 1 H), 13.46 (br s, 1 H)
93		320.1 0.86 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.10 (s, 3 H), 2.69 (dd, J=12.8, 9.9 Hz, 1 H), 2.95 (td, J=12.3, 3.4 Hz, 1 H), 3.41 - 3.56 (m, 3 H), 3.60 (td, J=11.6, 2.8 Hz, 1 H), 3.98 (dd, J=11.5, 2.1 Hz, 1 H), 4.13 (br d, J=12.9 Hz, 1 H), 4.29 (br d, J=12.6 Hz, 1 H), 4.76 - 4.88 (m, 1 H), 6.67 - 6.77 (m, 2 H), 7.15 (s, 1 H), 7.17 - 7.27 (m, 1 H), 10.12 - 10.47 (m, 1 H)
94		326.2 0.93 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.50 - 1.61 (m, 1 H), 1.76 - 1.90 (m, 3 H), 2.01 (s, 3 H), 2.00 - 2.11 (m, 2 H), 2.22 (s, 3 H), 3.89 - 3.97 (m, 3 H), 4.03 (d, J=8.0 Hz, 1 H), 4.13 - 4.22 (m, 1 H), 4.51 (d, J=3.5 Hz, 1 H), 6.55 - 6.59 (m, 2 H), 6.76 (d, J=9.2 Hz, 1 H), 7.28 (d, J=9.2 Hz, 1 H), 9.33 (s, 1 H)
95		326.2 0.94 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.50 - 1.62 (m, 1 H), 1.76 - 1.89 (m, 3 H), 1.97 - 2.12 (m, 2 H), 2.01 (s, 3 H), 2.22 (s, 3 H), 3.90 - 3.97 (m, 3 H), 4.03 (d, J=8.0 Hz, 1 H), 4.14 - 4.21 (m, 1 H), 4.51 (d, J=3.5 Hz, 1 H), 6.54 - 6.60 (m, 2 H), 6.76 (d, J=9.1 Hz, 1 H), 7.28 (d, J=9.1 Hz, 1 H), 9.33 (s, 1 H)
96		332.1 0.86 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H), 2.71 (dd, J=12.8, 9.9 Hz, 1 H), 2.91 - 3.03 (m, 1 H), 3.42 - 3.57 (m, 3 H), 3.61 (td, J=11.6, 2.8 Hz, 1 H), 3.72 (s, 3 H), 3.93 - 4.02 (m, 1 H), 4.11 (br d, J=13.0 Hz, 1 H), 4.30 (br d, J=12.6 Hz, 1 H), 4.79 (t, J=5.6 Hz, 1 H), 6.34 - 6.37 (m, 2 H), 7.25 (d, J=9.6 Hz, 1 H), 7.35 (d, J=9.6 Hz, 1 H), 9.62 (s, 1 H)

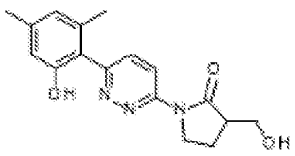
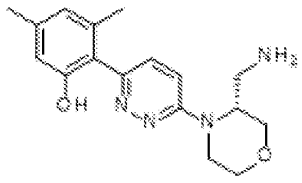
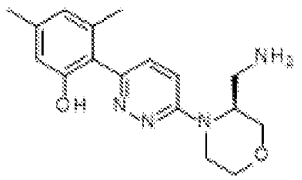
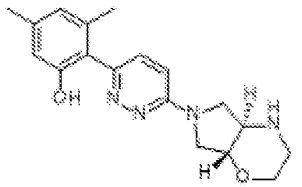
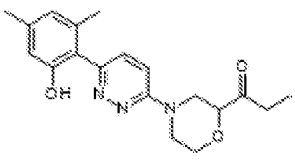
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
97		370.1 1.12 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.10 (s, 3 H), 2.72 (dd, J=12.8, 9.9 Hz, 1 H), 2.93 - 3.02 (m, 1 H), 3.41 - 3.56 (m, 3 H), 3.60 (td, J=11.6, 2.8 Hz, 1 H), 3.96 - 4.03 (m, 1 H), 4.15 (br d, J=13.0 Hz, 1 H), 4.31 (br d, J=12.8 Hz, 1 H), 4.73 - 4.87 (m, 1 H), 7.17 (s, 1 H), 7.22 (br s, 1 H), 7.24 (br d, J=8.0 Hz, 1 H), 7.41 (br d, J=7.6 Hz, 1 H), 10.28 - 10.55 (m, 1 H)
98		330.4 2.53 E	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 7.53 (d, *J* = 9.6 Hz, 1H), 7.06 (d, *J* = 9.7 Hz, 1H), 6.76 (s, 1H), 6.65 (s, 1H), 4.29 – 4.22 (m, 1H), 4.21 – 4.14 (m, 1H), 4.14 – 4.08 (m, 1H), 4.01 – 3.88 (m, 1H), 3.84 – 3.72 (m, 1H), 3.54 – 3.48 (m, 1H), 3.21 – 3.12 (m, 1H), 3.07 (dd, *J* = 12.8, 10.5 Hz, 1H), 2.38 (s, 3H), 2.30 (s, 3H), 2.01 (br. s, 1H), 1.30 (d, *J* = 6.5 Hz, 3H). (proton of phenol not visible)
99		330.4 2.5 E	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 10.97 (s, 1H), 7.54 (d, *J* = 9.7 Hz, 1H), 7.04 (d, *J* = 9.7 Hz, 1H), 6.76 (s, 1H), 6.65 (s, 1H), 4.28 – 4.21 (m, 1H), 4.18 – 4.12 (m, 1H), 4.12 – 4.05 (m, 1H), 3.85 – 3.79 (m, 1H), 3.79 – 3.73 (m, 1H), 3.45 – 3.39 (m, 1H), 3.20 – 3.11 (m, 1H), 2.98 – 2.91 (m, 1H), 2.48 (br. s, 1H), 2.38 (s, 3H), 2.30 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H).
102		302.1 1.23 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.29 (s, 3 H), 2.78 (dd, J=12.9, 9.9 Hz, 1 H), 2.98 - 3.08 (m, 1 H), 3.41 - 3.57 (m, 3 H), 3.61 (td, J=11.6, 2.8 Hz, 1 H), 3.98 (br dd, J=11.6, 2.2 Hz, 1 H), 4.17 (br d, J=13.0 Hz, 1 H), 4.34 (br d, J=12.9 Hz, 1 H), 4.81 (br t, J=4.7 Hz, 1 H), 6.83 (d, J=8.3 Hz, 1 H), 7.08 (dd, J=8.3, 1.5 Hz, 1 H), 7.53 (d, J=9.9 Hz, 1 H), 7.71 (d, J=1.5 Hz, 1 H), 8.24 (d, J=9.9 Hz, 1 H), 13.18 (s, 1 H)

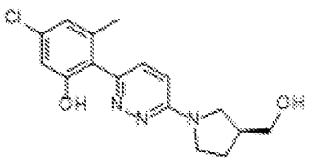
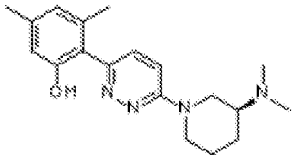
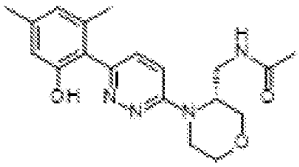
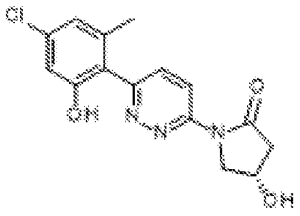
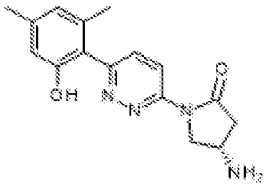
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
103		347.1 1.52 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 3.04 (dd, J=13.0, 10.4 Hz, 1 H), 3.23 - 3.31 (m partially hidden, 1 H), 3.40 - 3.48 (m, 1 H), 3.50 - 3.57 (m, 1 H), 3.62 (ddd, J=10.4, 5.3, 2.3 Hz, 1 H), 3.68 (td, J=11.6, 2.5 Hz, 1 H), 4.00 (dd, J=11.5, 1.5 Hz, 1 H), 4.18 (br dd, J=13.0, 1.4 Hz, 1 H), 4.34 (br d, J=13.0 Hz, 1 H), 4.86 (t, J=5.7 Hz, 1 H), 7.01 - 7.12 (m, 2 H), 7.92 (d, J=8.4 Hz, 1 H), 8.64 (s, 1 H), 11.91 (br s, 1 H)
105		357.2 0.96 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.85 (s, 3 H), 2.03 (s, 3 H), 2.22 (s, 3 H), 2.67 (dd, J=12.8, 10.6 Hz, 1 H), 2.97 (td, J=12.2, 3.4 Hz, 1 H), 3.23 (t, J=5.8 Hz, 2 H), 3.50 - 3.67 (m, 2 H), 4.00 (br dd, J=11.5, 2.0 Hz, 1 H), 4.10 (br d, J=12.9 Hz, 1 H), 4.28 (br d, J=12.3 Hz, 1 H), 6.54 - 6.62 (m, 2 H), 7.28 (d, J=9.5 Hz, 1 H), 7.35 (d, J=9.5 Hz, 1 H), 8.03 (br t, J=5.8 Hz, 1 H), 9.37 (s, 1 H)
106		357.2 0.96 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.85 (s, 3 H), 2.03 (s, 3 H), 2.22 (s, 3 H), 2.67 (dd, J=12.8, 10.6 Hz, 1 H), 2.97 (td, J=12.2, 3.4 Hz, 1 H), 3.23 (t, J=5.9 Hz, 2 H), 3.51 - 3.70 (m, 2 H), 4.00 (br dd, J=11.5, 2.0 Hz, 1 H), 4.10 (br d, J=12.8 Hz, 1 H), 4.28 (br d, J=12.4 Hz, 1 H), 6.55 - 6.62 (m, 2 H), 7.28 (d, J=9.5 Hz, 1 H), 7.35 (d, J=9.5 Hz, 1 H), 8.03 (t, J=5.8 Hz, 1 H), 9.37 (s, 1 H)
107		328.2 0.98 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.20 - 1.41 (m, 2 H), 1.55 - 1.81 (m, 3 H), 1.85 - 1.99 (m, 2 H), 2.06 (s, 3 H), 2.23 (s, 3 H), 3.21 (br dd, J=14.3, 10.1 Hz, 1 H), 3.28 - 3.42 (m, 2 H), 3.43 - 3.57 (m, 1 H), 3.89 - 4.08 (m, 2 H), 4.68 (br t, J=5.0 Hz, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 7.07 (d, J=9.4 Hz, 1 H), 7.28 (d, J=9.4 Hz, 1 H), 9.46 (s, 1 H)

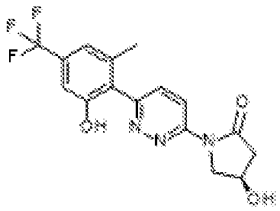
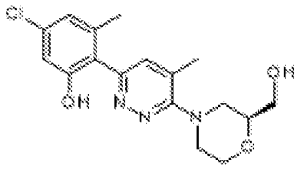
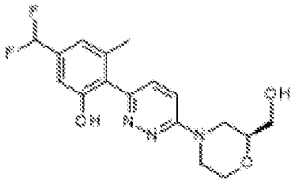
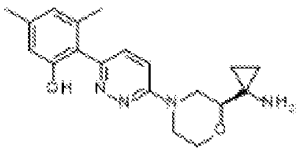
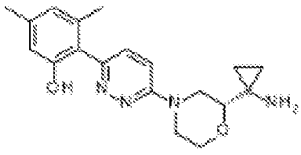
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
108		330.4 2.39 E	^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.99 (s, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.04 (d, *J* = 9.6 Hz, 1H), 6.77 (s, 1H), 6.65 (s, 1H), 4.31 – 4.20 (m, 1H), 4.19 – 4.11 (m, 1H), 4.12 – 4.06 (m, 1H), 3.84 – 3.79 (m, 1H), 3.78 – 3.74 (m, 1H), 3.48 – 3.37 (m, 1H), 3.16 (td, *J* = 12.3, 3.6 Hz, 1H), 2.95 (dd, *J* = 12.8, 10.8 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 1.30 (d, *J* = 6.4 Hz, 3H).
109		330.1 1.05 B	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.00 (s, 3 H), 2.23 (s, 3 H), 2.30 (s, 3 H), 2.78 (dd, J=12.1, 10.6 Hz, 1 H), 2.99 (td, J=12.0, 2.5 Hz, 1 H), 3.40 - 3.47 (m, 2 H), 3.48 - 3.53 (m, 1 H), 3.55 (br d, J=12.9 Hz, 1 H), 3.61 - 3.68 (m, 1 H), 3.69 - 3.78 (m, 1 H), 3.94 (br d, J=11.0 Hz, 1 H), 4.75 (t, J=5.8 Hz, 1 H), 6.58 (br s, 1 H), 6.59 (br s, 1 H), 7.32 (s, 1 H), 9.37 (s, 1 H)
110		316.1 1.36 B	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.30 (s, 3 H), 2.40 (s, 3 H), 2.78 (dd, J=12.5, 10.2 Hz, 1 H), 2.95 - 3.04 (m, 1 H), 3.41 - 3.55 (m, 3 H), 3.57 - 3.68 (m, 2 H), 3.72 (td, J=11.3, 1.9 Hz, 1 H), 3.93 (br d, J=11.3 Hz, 1 H), 4.73 - 4.82 (m, 1 H), 6.73 - 6.81 (m, 2 H), 7.82 (d, J=7.9 Hz, 1 H), 8.23 (s, 1 H), 13.52 (s, 1 H)
111		342.4 2.63 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.89 (br. s, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 6.98 (d, *J* = 9.7 Hz, 1H), 6.77 (s, 1H), 6.65 (s, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.20 (dd, *J* = 11.3, 3.9 Hz, 1H), 4.16 – 4.01 (m, 2H), 3.84 – 3.73 (m, 2H), 3.67 (s, 1H), 3.65 – 3.62 (m, 1H), 3.57 (td, *J* = 12.1, 2.1 Hz, 1H), 3.41 (td, *J* = 12.7, 3.9 Hz, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 2.26 (dd, *J* = 12.5, 4.9 Hz, 1H), 1.68 (d, *J* = 13.1 Hz, 1H).

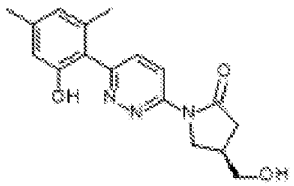
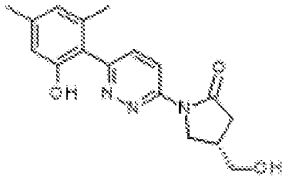
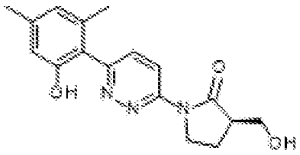
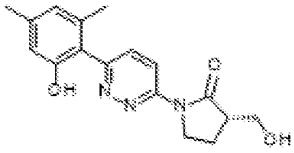
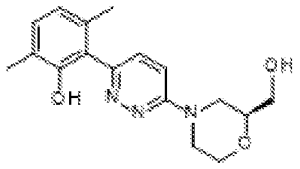
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
112		330.2 0.92 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.85 (s, 3 H), 1.95 (br s, 3 H), 2.23 (s, 3 H), 2.68 (dd, J=12.6, 9.8 Hz, 1 H), 2.87 - 3.02 (m, 1 H), 3.42 - 3.56 (m, 3 H), 3.61 (td, J=11.6, 2.8 Hz, 1 H), 3.94 - 4.02 (m, 1 H), 4.08 - 4.17 (m, 1 H), 4.24 - 4.36 (m, 1 H), 4.74 - 4.85 (m, 1 H), 6.49 - 6.65 (m, 2 H), 7.14 (s, 1 H), 9.12 (s, 1 H)
113		288.1 1.04 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H), 2.23 (s, 3 H), 3.79 - 3.86 (m, 2 H), 3.90 (dd, J=8.9, 5.1 Hz, 1 H), 4.11 (dd, J=11.4, 6.1 Hz, 1 H), 4.71 - 4.80 (m, 1 H), 5.35 (br s, 1 H), 6.58 (br s, 1 H), 6.60 (br s, 1 H), 7.42 (d, J=9.1 Hz, 1 H), 7.47 (d, J=9.1 Hz, 1 H), 9.30 - 9.46 (m, 1 H)
114		340 0.96 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.27 - 1.50 (m, 4 H) 1.55 - 1.66 (m, 2 H) 1.82 - 2.01 (m, 2 H) 2.05 (s, 3 H) 2.22 (s, 3 H) 3.33 - 3.49 (m, 4 H) 4.30 - 4.50 (m, 1 H) 4.67 - 4.72 (m, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.84 (br d, J=9.0 Hz, 1 H) 7.24 (d, J=9.0 Hz, 1 H) 9.44 (br s, 1 H)
115		286 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.20 - 2.28 (m, 1 H) 2.21 (s, 3 H) 2.29 - 2.43 (m, 1 H) 3.65 - 3.76 (m, 2 H) 3.87 - 4.02 (m, 2 H) 4.34 - 4.43 (m, 1 H) 5.19 (br t, J=5.3 Hz, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.97 (d, J=9.3 Hz, 1 H) 7.29 (d, J=9.3 Hz, 1 H) 9.35 (s, 1 H)
116		332 0.83 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.64 - 2.73 (m, 1 H) 2.88 - 3.00 (m, 1 H) 3.43 - 3.63 (m, 4 H) 3.75 (s, 3 H) 3.94 - 4.05 (m, 1 H) 4.12 (br d, J=12.7 Hz, 1 H) 4.27 (br d, J=12.7 Hz, 1 H) 4.81 (br t, J=5.4 Hz, 1 H) 6.45 - 6.53 (m, 2 H) 7.08 - 7.16 (m, 2 H) 9.97 (br s, 1 H)

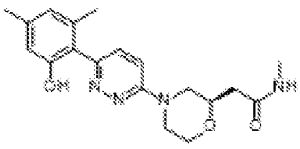
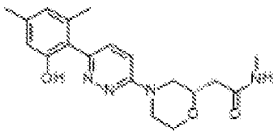
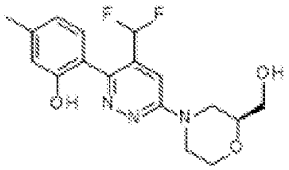
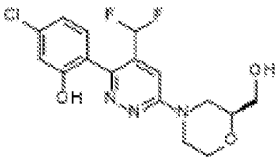
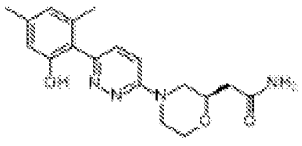
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
117		326 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.19 - 2.30 (m, 1 H) 2.31 - 2.45 (m, 1 H) 3.66 - 3.77 (m, 2 H) 3.91 - 4.04 (m, 2 H) 4.38 - 4.46 (m, 1 H) 5.15 (br t, J=5.0 Hz, 1 H) 6.95 (d, J=2.0 Hz, 1 H) 7.00 (d, J=9.4 Hz, 1 H) 7.12 (d, J=2.0 Hz, 1 H) 7.34 (d, J=9.4 Hz, 1 H) 9.77 - 11.05 (m, 1 H)
118		286 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.02 (s, 3 H) 2.17 - 2.29 (m, 1 H) 2.22 (s, 3 H) 2.29 - 2.40 (m, 1 H) 3.67 - 3.75 (m, 2 H) 3.91 - 3.98 (m, 2 H) 4.35 - 4.43 (m, 1 H) 5.18 (br t, J=5.3 Hz, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.97 (d, J=9.4 Hz, 1 H) 7.29 (d, J=9.4 Hz, 1 H) 9.34 (s, 1 H)
119		346 0.86 U	1H NMR (500 MHz, DMSO-d6, 25°C) δ ppm 1.86 (s, 3 H) 1.96 (s, 3 H) 2.67 (dd, J=12.7, 10.0 Hz, 1 H) 2.90 - 2.97 (m, 1 H) 3.42 - 3.49 (m, 1 H) 3.49 - 3.56 (m, 2 H) 3.60 (td, J=11.6, 2.6 Hz, 1 H) 3.72 (s, 3 H) 3.98 (br d, J=11.6 Hz, 1 H) 4.08 - 4.16 (m, 1 H) 4.24 - 4.31 (m, 1 H) 4.77 - 4.87 (m, 1 H) 6.33 (d, J=2.2 Hz, 1 H) 6.36 (d, J=2.2 Hz, 1 H) 7.14 (s, 1 H) 9.33 (br s, 1 H)
120		312 1.01 U	1H NMR (500 MHz, DMSO-d6, 25°C) δ ppm 1.88 - 2.05 (m, 4 H) 2.04 (s, 3 H) 2.22 (s, 3 H) 3.57 (d, J=11.0 Hz, 2 H) 3.70 (d, J=11.0 Hz, 2 H) 4.58 - 4.62 (m, 2 H) 6.57 (br s, 1 H) 6.59 (br s, 1 H) 7.22 (d, J=9.4 Hz, 1 H) 7.33 (d, J=9.4 Hz, 1 H) 9.42 (br s, 1 H)
121		386.3 2.57 E	1H NMR (500 MHz, CDCl3) δ (ppm) : 11.47 (s, 1H), 7.54 (d, J = 9.6 Hz, 1H), 7.06 (d, J = 9.7 Hz, 1H), 6.81 (s, 1H), 6.67 (s, 1H), 4.23 (d, J = 12.8 Hz, 1H), 4.18 – 4.11 (m, 2H), 3.85 – 3.69 (m, 4H), 3.20 (td, J = 12.3, 3.6 Hz, 1H), 3.03 (dd, J = 12.8, 10.1 Hz, 1H), 2.43 (s, 3H), 1.93 (s, 1H).

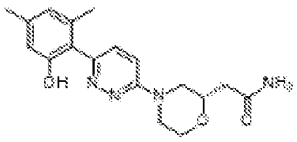
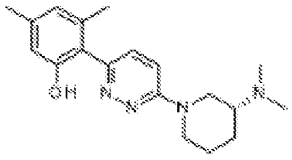
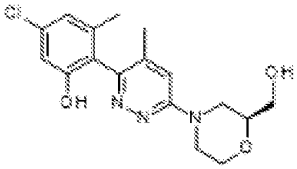
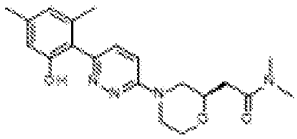
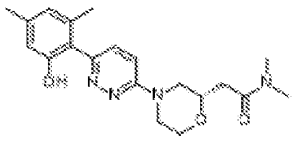
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
122		314 1.22 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.08 - 2.20 (m, 1 H) 2.23 - 2.30 (m, 1 H) 2.24 (s, 3 H) 2.73 - 2.94 (m, 1 H) 3.63 - 3.72 (m, 1 H) 3.72 - 3.82 (m, 1 H) 3.96 - 4.10 (m, 1 H) 4.11 - 4.23 (m, 1 H) 4.85 (t, J=5.3 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.63 (d, J=9.5 Hz, 1 H) 8.56 (d, J=9.5 Hz, 1 H) 9.39 (br s, 1 H)
123	 CF_3COOH	315 0.79 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H) 2.23 (s, 3 H) 3.10 - 3.40 (m, 3 H) 3.50 - 3.60 (m partially hidden, 1 H) 3.62 - 3.70 (m, 1 H) 3.90 - 4.06 (m, 3 H) 4.74 (br t, J=7.0 Hz, 1 H) 6.58 - 6.62 (m, 2 H) 7.35 - 7.55 (m, 2 H) 7.89 (br s, 3 H) 9.35 - 9.60 (m, 1 H)
124		315 0.79 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.04 (s, 3 H) 2.22 (s, 3 H) 2.74 (dd, J=12.4, 5.5 Hz, 1 H) 3.01 (dd, J=12.4, 9.0 Hz, 1 H) 3.17 (td, J=12.9, 3.5 Hz, 1 H) 3.47 - 3.59 (m, 2 H) 3.94 (dd, J=11.5, 3.5 Hz, 1 H) 4.08 - 4.17 (m, 3 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 9.25 - 9.50 (m, 1 H)
125		326.9 4.52 F	1H NMR (400 MHz, CDCl3) δ (ppm): 7.42 (d, J = 9.5 Hz, 1H), 6.80 – 6.62 (m, 2H), 6.57 (s, 1H), 4.05 – 3.80 (m, 3H), 3.75 (td, J = 11.7, 3.0 Hz, 1H), 3.72 – 3.62 (m, 1H), 3.32 (t, J = 9.5 Hz, 1H), 3.25 (t, J = 10.1 Hz, 1H), 3.12 – 3.00 (m, 2H), 2.99 – 2.89 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H). (OH and NH not visible)
126		342.3 2.81 E	1H NMR (500 MHz, DMSO-d6) δ (ppm): 9.37 (s, 1H), 7.35 (q, J = 9.4 Hz, 2H), 6.58 (d, J = 5.7 Hz, 2H), 4.40 – 4.33 (m, 1H), 4.19 (dd, J = 9.9, 3.2 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.77 – 3.68 (m, 1H), 3.12 (ddd, J = 13.8, 10.9, 3.7 Hz, 1H), 3.02 (dd, J = 13.0, 10.0 Hz, 1H), 2.67 (qt, J = 6.9, 3.5 Hz, 2H), 2.23 (s, 3H), 2.03 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H).

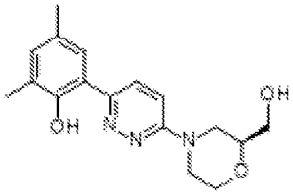
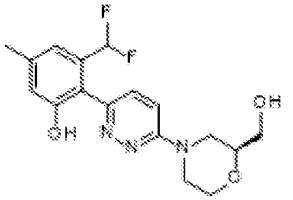
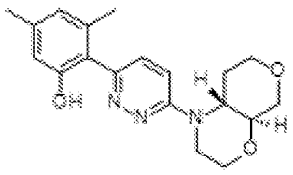
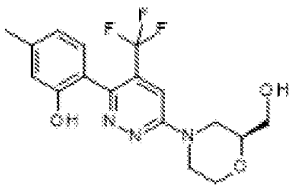
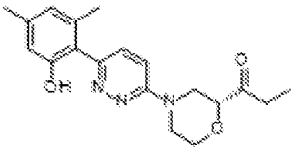
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
127		320 0.90 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.74 - 1.85 (m, 1 H) 2.01 - 2.11 (m, 1 H) 2.05 (s, 3 H) 2.43 - 2.48 (m, 1 H) 3.25 - 3.66 (m partially hidden, 1 H) 3.41 - 3.51 (m, 3 H) 3.54 - 3.62 (m, 2 H) 4.65 - 4.80 (m, 1 H) 6.80 - 6.844 (m, 2 H) 6.87 (d, J=9.5 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.90 - 10.20 (m, 1 H)
128		327 0.77 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.41 - 1.54 (m, 2 H) 1.76 - 1.84 (m, 1 H) 1.89 - 1.98 (m, 1 H) 2.04 (s, 3 H) 2.22 (s, 3 H) 2.22 - 2.26 (m, 1 H) 2.27 (s, 6 H) 2.79 - 2.94 (m, 2 H) 4.22 (br d, J=12.7 Hz, 1 H) 4.46 (br d, J=12.7 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.41 (s, 1 H)
129		357 0.80 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.65 (s, 3 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 3.20 - 3.30 (m partially hidden, 1 H) 3.36 (br t, J=6.2 Hz, 2 H) 3.51 (br td, J=11.5, 3.0 Hz, 1 H) 3.59 (dd, J=11.5, 3.0 Hz, 1 H) 3.89 (d, J=11.5 Hz, 1 H) 3.97 (br dd, J=11.5, 3.0 Hz, 1 H) 4.16 - 4.27 (m, 2 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 8.00 (t, J=6.2 Hz, 1 H) 9.37 (br s, 1 H)
130		320 1.13 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.04 (s, 3 H) 2.42 (br d, J=17.5 Hz, 1 H) 2.98 (dd, J=17.5, 6.0 Hz, 1 H) 4.10 (br d, J=11.5 Hz, 1 H) 4.22 (dd, J=11.5, 5.0 Hz, 1 H) 4.44 - 4.50 (m, 1 H) 5.38 (d, J=3.5 Hz, 1 H) 6.84 (br s, 1 H) 6.87 (br s, 1 H) 7.67 (d, J=9.5 Hz, 1 H) 8.59 (d, J=9.5 Hz, 1 H) 9.95 - 10.10 (m, 1 H)
131		299 0.82 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.97 - 2.05 (m, 2 H) 2.01 (s, 3 H) 2.24 (s, 3 H) 2.30 (br dd, J=17.0, 2.9 Hz, 1 H) 2.86 (dd, J=17.0, 6.5 Hz, 1 H) 3.66 - 3.78 (m, 1 H) 3.88 (br dd, J=11.0, 2.9 Hz, 1 H) 4.18 (dd, J=11.0, 6.0 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.62 (d, J=9.5 Hz, 1 H) 8.55 (d, J=9.5 Hz, 1 H) 9.38 (br s, 1 H)

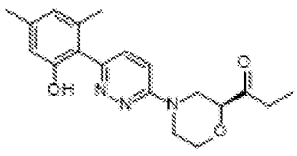
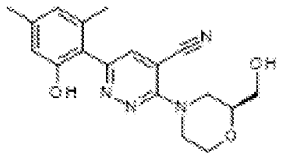
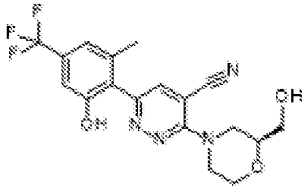
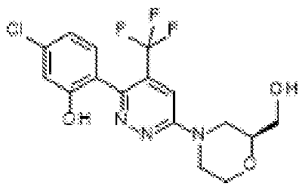
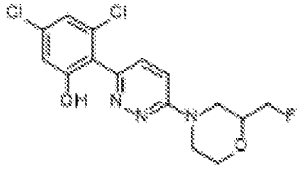
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
132		354 1.33 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.11 (s, 3 H) 2.42 (br d, J=17.5 Hz, 1 H) 2.99 (dd, J=17.5, 6.0 Hz, 1 H) 4.11 (br d, J=11.5 Hz, 1 H) 4.23 (dd, J=11.5, 5.0 Hz, 1 H) 4.45 - 4.50 (m, 1 H) 4.95 - 5.65 (m, 1 H) 7.10 (br s, 1 H) 7.16 (br s, 1 H) 7.72 (d, J=9.5 Hz, 1 H) 8.63 (d, J=9.5 Hz, 1 H) 10.24 (s, 1 H)
133		350 1.20 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.32 (s, 3 H) 2.74 - 2.85 (m, 1 H) 2.96 - 3.06 (m, 1 H) 3.42 - 3.61 (m, 4 H) 3.62 - 3.69 (m, 1 H) 3.73 (td, J=11.3, 2.5 Hz, 1 H) 3.90 - 3.99 (m, 1 H) 4.74 (br t, J=5.4 Hz, 1 H) 6.84 (br s, 1 H) 6.86 (br s, 1 H) 7.35 (s, 1 H) 9.96 (br s, 1 H)
134		352 1.01 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.10 (s, 3 H) 2.73 (br dd, J=12.7, 10.0 Hz, 1 H) 2.99 (td, J=12.7, 2.6 Hz, 1 H) 3.41 - 3.58 (m, 3 H) 3.62 (td, J=11.6, 2.6 Hz, 1 H) 4.00 (dd, J=11.6, 2.6 Hz, 1 H) 4.15 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.82 (t, J=5.4 Hz, 1 H) 6.79 - 7.11 (m, 3 H) 7.30 (d, J=9.5 Hz, 1 H) 7.39 (d, J=9.5 Hz, 1 H) 9.88 (s, 1 H)
135		341 0.79 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.41 - 0.62 (m, 4 H) 2.03 (s, 3 H) 2.05 - 2.30 (m, 2H) 2.22 (s, 3 H) 2.84 - 3.00 (m, 2 H) 3.09 (dd, J=11.5, 2.5 Hz, 1 H) 3.59 (td, J=11.5, 2.5 Hz, 1 H) 4.01 (dd, J=11.5, 2.5 Hz, 1 H) 4.15 (br d, J=12.0 Hz, 1 H) 4.33 (br d, J=12.0 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.30 (d, J=9.3 Hz, 1 H) 7.35 (d, J=9.3 Hz, 1 H) 9.38 (s, 1 H)
136		341 0.79 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.41 - 0.62 (m, 4 H) 1.90 - 2.20 (m, 2H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.84 - 3.00 (m, 2 H) 3.09 (dd, J=11.5, 2.5 Hz, 1 H) 3.59 (td, J=11.5, 2.5 Hz, 1 H) 4.01 (dd, J=11.5, 2.5 Hz, 1 H) 4.15 (br d, J=12.0 Hz, 1 H) 4.33 (br d, J=12.0 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.30 (d, J=9.3 Hz, 1 H) 7.35 (d, J=9.3 Hz, 1 H) 9.38 (s, 1 H)

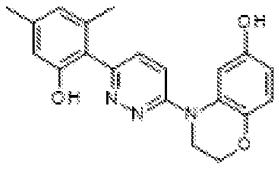
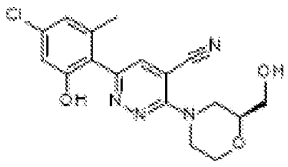
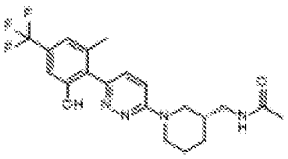
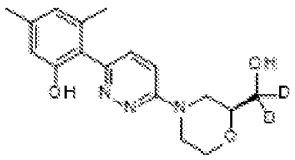
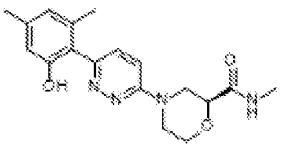
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
137		314 1.20 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.24 (s, 3 H) 2.44 (dd, J=17.0, 5.5 Hz, 1 H) 2.54 - 2.63 (m, 1 H) 2.75 (dd, J=17.0, 8.3 Hz, 1 H) 3.47 - 3.54 (m, 2 H) 3.97 (dd, J=11.3, 5.5 Hz, 1 H) 4.20 (dd, J=11.3, 8.3 Hz, 1 H) 4.87 (t, J=5.5 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.62 (d, J=9.3 Hz, 1 H) 8.54 (d, J=9.3 Hz, 1 H) 9.39 (s, 1 H)
138		314 1.20 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.24 (s, 3 H) 2.44 (dd, J=17.0, 5.5 Hz, 1 H) 2.54 - 2.64 (m, 1 H) 2.74 (dd, J=17.0, 8.3 Hz, 1 H) 3.47 - 3.55 (m, 2 H) 3.97 (dd, J=11.3, 5.5 Hz, 1 H) 4.20 (dd, J=11.3, 8.3 Hz, 1 H) 4.87 (t, J=5.5 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.62 (d, J=9.3 Hz, 1 H) 8.54 (d, J=9.3 Hz, 1 H) 9.39 (s, 1 H)
139		314 1.21 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.09 - 2.20 (m, 1 H) 2.21 - 2.30 (m, 1 H) 2.24 (s, 3 H) 2.80 - 2.88 (m, 1 H) 3.62 - 3.72 (m, 1 H) 3.72 - 3.83 (m, 1 H) 3.97 - 4.09 (m, 1 H) 4.13 - 4.21 (m, 1 H) 4.85 (t, J=5.3 Hz, 1 H) 6.60 (br s, 1 H) 6.62 (br s, 1 H) 7.63 (d, J=9.0 Hz, 1 H) 8.56 (d, J=9.0 Hz, 1 H) 9.39 (s, 1 H)
140		314 1.22 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.09 - 2.20 (m, 1 H) 2.21 - 2.30 (m, 1 H) 2.24 (s, 3 H) 2.80 - 2.88 (m, 1 H) 3.62 - 3.72 (m, 1 H) 3.72 - 3.83 (m, 1 H) 3.97 - 4.09 (m, 1 H) 4.13 - 4.21 (m, 1 H) 4.85 (t, J=5.3 Hz, 1 H) 6.60 (br s, 1 H) 6.62 (br s, 1 H) 7.63 (d, J=9.0 Hz, 1 H) 8.56 (d, J=9.0 Hz, 1 H) 9.39 (s, 1 H)
141		316.3 2.42 E	1H NMR (400 MHz, CDCl3) δ (ppm): 10.97 (s, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.75 (d, J = 7.6 Hz, 1H), 4.24 (d, J = 12.8 Hz, 1H), 4.16 (ddt, J = 11.5, 3.4, 2.0 Hz, 2H), 3.89 – 3.68 (m, 4H), 3.27 – 3.15 (m, 1H), 3.04 (dd, J = 12.8, 9.9 Hz, 1H), 2.39 (s, 3H), 2.31 (s, 3H), 2.00 (s, 1H).

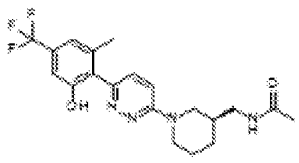
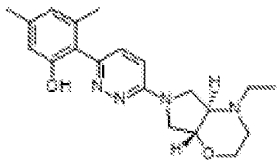
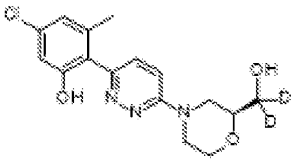
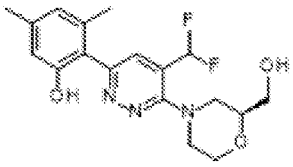
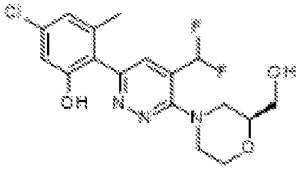
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
142		316.4 2.25 E	1H-NMR (500 MHz, DMSO-d6) δ (ppm): 9.31 (s, 1H), 7.80 (d, J = 4.8 Hz, 1H), 7.29 (d, J = 9.4 Hz, 1H), 7.19 (d, J = 9.5 Hz, 1H), 6.57 – 6.48 (m, 2H), 4.22 (d, J = 12.7 Hz, 1H), 4.03 (d, J = 12.7 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.81 (qd, J = 7.3, 2.5 Hz, 1H), 3.59 – 3.46 (m, 1H), 2.89 (td, J = 12.3, 3.5 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.53 (d, J = 4.6 Hz, 3H), 2.31 – 2.23 (m, 2H), 2.16 (s, 3H), 1.96 (s, 3H).
143		357.4 2.25 E	1H-NMR (400 MHz, DMSO-d6) δ (ppm): 9.31 (s, 1H), 7.80 (d, J = 4.8 Hz, 1H), 7.29 (d, J = 9.4 Hz, 1H), 7.19 (d, J = 9.5 Hz, 1H), 6.53 – 6.48 (m, 2H), 4.22 (dd, J = 12.8, 2.4 Hz, 1H), 4.03 (d, J = 12.8 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.81 (dtd, J = 13.0, 6.4, 2.5 Hz, 1H), 3.52 (td, J = 11.6, 2.7 Hz, 1H), 2.89 (td, J = 12.3, 3.5 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.53 (d, J = 4.6 Hz, 3H), 2.28 (d, J = 3.2 Hz, 2H), 2.15 (s, 3H), 1.96 (s, 3H).
144		352 1.23 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.29 (s, 3 H) 2.79 (dd, J=12.7, 10.0 Hz, 1 H) 3.03 (td, J=12.7, 2.6 Hz, 1 H) 3.44 - 3.66 (m, 4 H) 3.99 (dd, J=11.6, 2.6 Hz, 1 H) 4.24 (br d, J=12.7 Hz, 1 H) 4.38 (br d, J=12.7 Hz, 1 H) 4.82 (t, J=5.4 Hz, 1 H) 6.60 - 6.92 (m, 3 H) 7.15 (d, J=7.8 Hz, 1 H) 7.38 (s, 1 H) 9.82 (br s, 1 H)
145		372 1.31 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.80 (dd, J=12.7, 10.0 Hz, 1 H) 2.98 - 3.12 (m, 1 H) 3.45 - 3.57 (m, 3 H) 3.61 (td, J=11.6, 2.6 Hz, 1 H) 3.95 - 4.04 (m, 1 H) 4.25 (br d, J=12.7 Hz, 1 H) 4.39 (br d, J=12.7 Hz, 1 H) 4.83 (br t, J=5.4 Hz, 1 H) 6.80 (t, J=54.3 Hz, 1 H) 6.95 - 7.02 (m, 2 H) 7.29 (d, J=7.8 Hz, 1 H) 7.40 (s, 1 H) 10.40 - 10.55 (m, 1 H)
146		343.2 2.32 E	1H NMR (500 MHz, DMSO-d6) δ (ppm): 9.38 (s, 1H), 7.40 (s, 1H), 7.36 (d, J = 9.3 Hz, 1H), 7.26 (d, J = 9.4 Hz, 1H), 6.90 (s, 1H), 6.58 (d, J = 4.4 Hz, 2H), 4.31 (d, J = 12.9 Hz, 1H), 4.10 (d, J = 12.7 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.93 – 3.82 (m, 1H), 3.61 (td, J = 11.6, 2.7 Hz, 1H), 2.97 (td, J = 12.3, 3.5 Hz, 1H), 2.71 (dd, J = 12.8, 10.3 Hz, 1H), 2.42 – 2.26 (m, 2H), 2.23 (s, 3H), 2.03 (s, 3H).

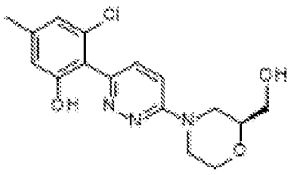
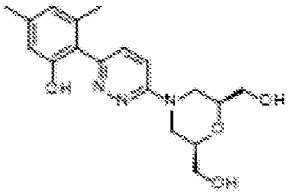
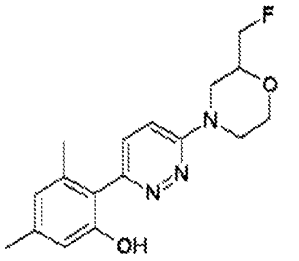
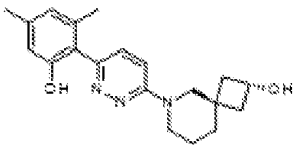
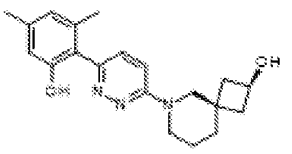
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
147		343.2 2.32 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.38 (s, 1H), 7.40 (s, 1H), 7.36 (d, J = 9.4 Hz, 1H), 7.26 (d, J = 9.4 Hz, 1H), 6.90 (s, 1H), 6.58 (d, J = 4.2 Hz, 2H), 4.31 (d, J = 12.7 Hz, 1H), 4.10 (d, J = 12.8 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.87 (q, J = 7.9 Hz, 1H), 3.61 (td, J = 12.8, 3.5 Hz, 1H), 2.97 (td, J = 12.3, 3.4 Hz, 1H), 2.71 (dd, J = 12.8, 10.3 Hz, 1H), 2.42 – 2.25 (m, 2H), 2.23 (s, 3H), 2.04 (s, 3H).
148		327 0.77 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.41 - 1.54 (m, 2 H) 1.75 - 1.84 (m, 1 H) 1.88 - 1.98 (m, 1 H) 2.04 (s, 3 H) 2.22 (s, 3 H) 2.22 - 2.26 (m, 1 H) 2.27 (s, 6 H) 2.79 - 2.94 (m, 2 H) 4.22 (br d, J=12.7 Hz, 1 H) 4.46 (br d, J=12.7 Hz, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.39 (br s, 1 H)
149		350 1.01 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.89 (s, 3 H) 1.96 (s, 3 H) 2.70 (dd, J=12.7, 10.0 Hz, 1 H) 2.90 - 3.02 (m, 1 H) 3.42 - 3.64 (m, 4 H) 3.95 - 4.02 (m, 1 H) 4.09 - 4,18 (m, 1 H) 4.25 - 4.33 (m, 1 H) 4.79 (t, J=5.4 Hz, 1 H) 6.80 (d, J=2.0 Hz, 1 H) 6.85 (d, J=2.0 Hz, 1 H) 7.17 (s, 1 H) 9.81 (s, 1 H)
150		371.3 2.59 E	1H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.38 (s, 1H), 7.36 (d, J = 9.3 Hz, 1H), 7.25 (d, J = 9.4 Hz, 1H), 6.58 (d, J = 5.4 Hz, 2H), 4.35 (d, J = 12.6 Hz, 1H), 4.13 (d, J = 12.7 Hz, 1H), 3.99 – 3.88 (m, 2H), 3.66 – 3.57 (m, 1H), 3.01 (s, 3H), 2.96 (td, J = 12.2, 3.5 Hz, 1H), 2.85 (s, 3H), 2.76 – 2.65 (m, 2H), 2.23 (s, 3H), 2.04 (s, 3H) + 1H hidden under DMSO peak (confirmed by HSQC and NMR in $CDCl_3$)
151		371.3 2.56 E	δ (ppm): 9.38 (s, 1H), 7.36 (d, J = 9.3 Hz, 1H), 7.25 (d, J = 9.4 Hz, 1H), 6.58 (d, J = 5.4 Hz, 2H), 4.35 (d, J = 12.7 Hz, 1H), 4.13 (d, J = 12.7 Hz, 1H), 3.95 (ddd, J = 17.0, 11.3, 5.4 Hz, 2H), 3.61 (td, J = 11.6, 2.7 Hz, 1H), 3.01 (s, 3H), 2.99 – 2.94 (m, 1H), 2.85 (s, 3H), 2.81 – 2.64 (m, 2H), 2.23 (s, 3H), 2.04 (s, 3H) + 1H hidden under DMSO peak (confirmed by HSQC and NMR in $CDCl_3$)

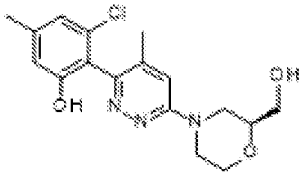
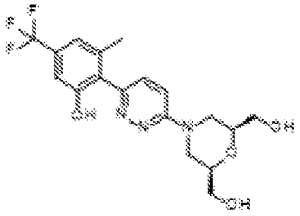
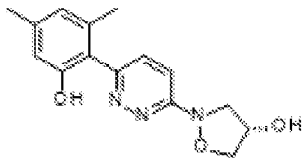
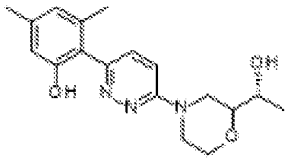
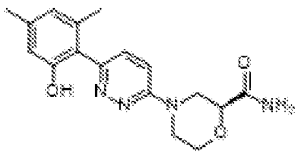
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
152		316.2 2.98 E	1H NMR (500 MHz, CDCl3) δ (ppm): 13.34 (s, 1H), 7.88 (d, J = 9.8 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.09 (d, J = 9.8 Hz, 1H), 7.00 (s, 1H), 4.21 – 4.07 (m, 3H), 3.85 – 3.68 (m, 4H), 3.21 – 3.13 (m, 1H), 3.00 (dd, J = 12.7, 10.1 Hz, 1H), 2.31 (s, 6H), 1.93 (t, J = 5.9 Hz, 1H).
153		352 1.06 U	1H NMR (500 MHz, DMSO-d6, 25°C) δ ppm 2.34 (s, 3 H) 2.73 (dd, J=12.7, 10.0 Hz, 1 H) 2.99 (td, J=12.7, 2.6 Hz, 1 H) 3.42 - 3.57 (m, 3 H) 3.61 (td, J=11.6, 2.6 Hz, 1 H) 3.99 (dd, J=11.6, 2.6 Hz, 1 H) 4.15 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.83 (t, J=5.5 Hz, 1 H) 6.82 (t, J=55.6 Hz, 1 H) 6.92 (br s, 1 H) 7.01 (br s, 1 H) 7.30 (d, J=9.5 Hz, 1 H) 7.48 (d, J=9.5 Hz, 1 H) 9.90 (s, 1 H)
154		342 1.21 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.34 - 1.46 (m, 1 H) 2.02 (s, 3 H) 2.23 (s, 3 H) 2.45 - 2.53 (m partially hidden, 1 H) 3.22 - 3.38 (m partially hidden, 2 H) 3.46 - 3.58 (m , 2 H) 3.66 (dt, J=12.5, 3.0 Hz, 1 H) 3.82 - 3.92 (m, 3 H) 3.93 - 4.00 (m, 1 H) 6.59 (br s, 1 H) 6.60 (br s, 1 H) 7.39 (d, J=9.0 Hz, 1 H) 7.45 (d, J=9.0 Hz, 1 H) 9.39 (s, 1 H)
155		370 1.33 U	1H NMR (500 MHz, DMSO-d6, 25°C) δ ppm 2.28 (s, 3 H) 2.82 (dd, J=12.7, 10.0 Hz, 1 H) 3.03 - 3.10 (m, 1 H) 3.46 - 3.58 (m, 3 H) 3.61 (td, J=11.6, 2.6 Hz, 1 H) 4.00 (dd, J=11.6, 2.6 Hz, 1 H) 4.28 (br d, J=12.7 Hz, 1 H) 4.43 (br d, J=12.7 Hz, 1 H) 4.83 (t, J=5.5 Hz, 1 H) 6.68 (br d, J=7.7 Hz, 1 H) 6.71 (br s, 1 H) 7.00 (d, J=7.7 Hz, 1 H) 7.54 (s, 1 H) 9.37 (s, 1 H)
156		342.2 3.01 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.37 (s, 1H), 7.35 (q, J = 9.4 Hz, 2H), 6.58 (d, J = 5.3 Hz, 2H), 4.40 – 4.33 (m, 1H), 4.19 (dd, J = 9.9, 3.2 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.77 – 3.68 (m, 1H), 3.12 (s, 1H), 3.02 (dd, J = 13.0, 9.9 Hz, 1H), 2.67 (qd, J = 7.2, 3.0 Hz, 2H), 2.23 (s, 3H), 2.03 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H).

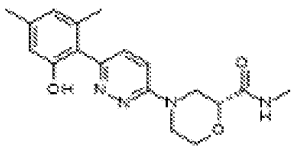
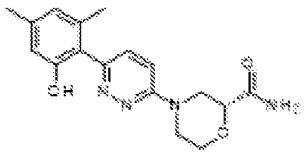
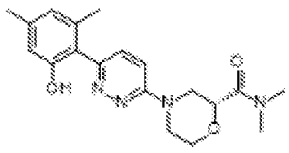
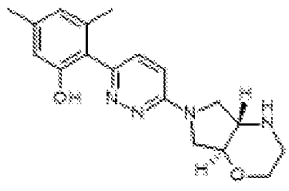
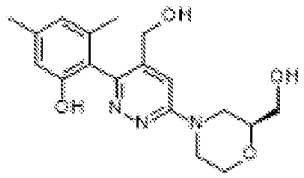
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
157		342.2 2.99 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.37 (s, 1H), 7.35 (q, J = 9.4 Hz, 2H), 6.58 (d, J = 5.2 Hz, 2H), 4.40 – 4.33 (m, 1H), 4.19 (dd, J = 10.0, 3.2 Hz, 1H), 4.13 – 4.02 (m, 2H), 3.77 – 3.68 (m, 1H), 3.12 (ddd, J = 13.7, 10.9, 3.7 Hz, 1H), 3.02 (dd, J = 13.0, 10.0 Hz, 1H), 2.68 (qt, J = 7.3, 3.7 Hz, 2H), 2.23 (s, 3H), 2.03 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H).
158		341 1.32 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.05 (s, 3 H) 2.24 (s, 3 H) 3.01 (dd, J=12.7, 10.0 Hz, 1 H) 3.19 - 3.27 (m partially hidden, 1 H) 3.42 - 3.73 (m, 4 H) 4.00 (br d, J=11.6 Hz, 1 H) 4.14 (br d, J=12.7 Hz, 1 H) 4.30 (br d, J=12.7 Hz, 1 H) 4.83 (br t, J=5.4 Hz, 1 H) 6.58 - 6.65 (m, 2 H) 7.96 (s, 1 H) 9.46 (br s, 1 H)
159		395 1.46 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.15 (s, 3 H) 3.05 (dd, J=12.7, 10.0 Hz, 1 H) 3.24 - 3.27 (m partially hidden, 1 H) 3.42 - 3.49 (m, 1 H) 3.50 - 3.58 (m, 1 H) 3.59 - 3.75 (m, 2 H) 4.01 (br d, J=11.6 Hz, 1 H) 4.21 (br d, J=12.7 Hz, 1 H) 4.37 (br d, J=12.7 Hz, 1 H) 4.79 - 4.88 (m, 1 H) 7.09 (br s, 1 H) 7.16 (br s, 1 H) 8.07 (s, 1 H) 10.20 - 10.45 (m, 1 H)
160		390 1.39 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.84 (dd, J=12.7, 10.0 Hz, 1 H) 3.03 - 3.13 (m, 1 H) 3.45 - 3.64 (m, 4 H) 4.00 (dd, J=11.6, 2.6 Hz, 1 H) 4.29 (br d, J=12.7 Hz, 1 H) 4.44 (br d, J=12.7 Hz, 1 H) 4.84 (br t, J=5.4 Hz, 1 H) 6.91 - 6.96 (m, 2 H) 7.17 (d, J=8.5 Hz, 1 H) 7.57 (s, 1 H) 10.09 (br s, 1 H)
161		358 1.50 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.85 (dd, J=12.7, 10.8 Hz, 1 H) 2.97 - 3.07 (m, 1 H) 3.65 (td, J=11.6, 2.6 Hz, 1 H) 3.73 - 3.88 (m, 1 H) 4.00 - 4.07 (m, 1 H) 4.16 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 6.93 (d, J=2.0 Hz, 1 H) 7.08 (d, J=2.0 Hz, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 10.30 - 10.80 (m, 1 H)

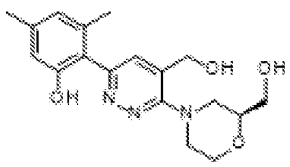
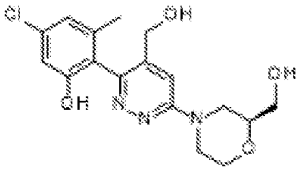
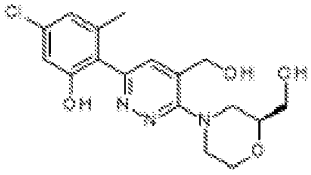
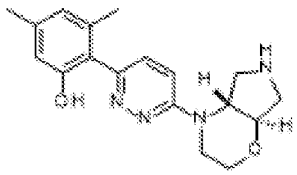
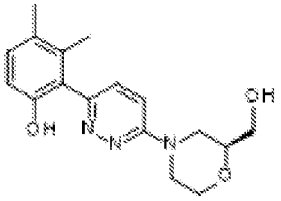
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
162		350 1.50 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.23 (s, 3 H) 3.26 - 3.33 (m, 2 H) 4.08 - 4.16 (m, 2 H) 6.31 (dd, J=8.5, 2.8 Hz, 1 H) 6.43 (d, J=2.8 Hz, 1 H) 6.59 (br s, 1 H) 6.61 (br s, 1 H) 6.69 (d, J=8.5 Hz, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.62 (d, J=9.5 Hz, 1 H) 9.30 - 9.50 (br s, 1 H)
163		361 1.39 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.07 (s, 3 H) 3.03 (dd, J=12.7, 10.0 Hz, 1 H) 3.22 - 3.28 (m partially hidden, 1 H) 3.41 - 3.48 (m, 1 H) 3.51 - 3.57 (m, 1 H) 3.60 - 3.73 (m, 2 H) 3.97 - 4.04 (m, 1 H) 4.15 - 4.21 (m, 1 H) 4.29 - 4.38 (m, 1 H) 4.83 (t, J=5.4 Hz, 1 H) 6.84 (d, J=2.0 Hz, 1 H) 6.88 (d, J=2.0 Hz, 1 H) 8.01 (s, 1 H) 10.12 (br s, 1 H)
164		409 1.16 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.17 - 1.30 (m, 1 H) 1.42 - 1.55 (m, 1 H) 1.61 - 1.85 (m, 3 H) 1.84 (s, 3 H) 2.13 (s, 3 H) 2.64 - 2.76 (m, 1 H) 2.94 - 3.09 (m, 3 H) 4.23 (br d, J=12.7 Hz, 1 H) 4.33 (br dd, J=12.7, 2.6 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 7.90 (br t, J=5.8 Hz, 1 H) 10.13 (br s, 1 H)
165		318.4 2.26 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.38 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 7.26 (d, J = 9.5 Hz, 1H), 6.63 – 6.46 (m, 2H), 4.78 (s, 1H), 4.34 – 4.27 (m, 1H), 4.20 – 4.05 (m, 1H), 4.08 – 3.90 (m, 1H), 3.61 (td, J = 11.6, 2.8 Hz, 1H), 3.53 (dd, J = 10.6, 2.6 Hz, 1H), 3.18 – 2.81 (m, 1H), 2.70 (dd, J = 12.8, 10.6 Hz, 1H), 2.22 (s, 3H), 2.03 (s, 3H).
166		343.3 2.41 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.39 (s, 1H), 7.89 (d, J = 4.9 Hz, 1H), 7.46 – 7.11 (m, 2H), 6.58 (d, J = 4.6 Hz, 2H), 4.43 (dd, J = 12.2, 2.6 Hz, 1H), 4.18 – 3.93 (m, 3H), 3.71 (td, J = 11.1, 2.5 Hz, 1H), 3.16 – 3.02 (m, 1H), 2.94 (dd, J = 13.0, 10.2 Hz, 1H), 2.64 (d, J = 4.7 Hz, 3H), 2.22 (s, 3H), 2.03 (s, 3H).

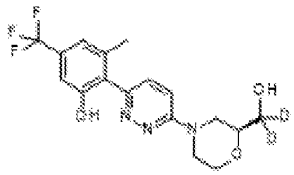
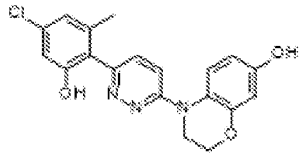
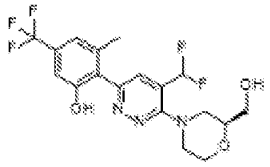
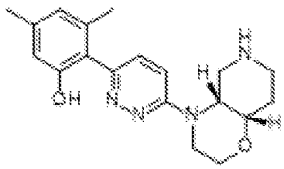
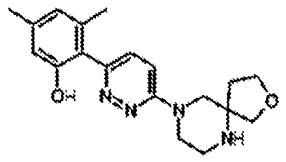
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
167		409 1.15 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.18 - 1.31 (m, 2 H) 1.42 - 1.55 (m, 1 H) 1.66 - 1.85 (m, 2 H) 1.84 (s, 3 H) 2.13 (s, 3 H) 2.70 (dd, J=12.7, 10.0 Hz, 1 H) 2.93 - 3.09 (m, 3 H) 4.23 (br d, J=12.7 Hz, 1 H) 4.30 - 4.37 (m, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 7.92 (br t, J=5.8 Hz, 1 H) 10.15 (br s, 1 H)
168		355.5 2.54 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.36 (s, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.91 (d, J = 9.3 Hz, 1H), 6.67 – 6.41 (m, 2H), 4.05 – 3.91 (m, 2H), 3.92 – 3.80 (m, 1H), 3.77 – 3.61 (m, 2H), 3.25 (t, J = 9.5 Hz, 1H), 3.13 (t, J = 10.0 Hz, 1H), 2.97 – 2.85 (m, 1H), 2.74 – 2.59 (m, 1H), 2.41 – 2.35 (m, 1H), 2.29 – 2.23 (m, 1H), 2.22 (s, 3H), 2.17 – 2.06 (m, 1H), 2.02 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H).
169		338.4 3.38 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.97 (s, 1H), 7.37 (d, J = 9.4 Hz, 1H), 7.28 (d, J = 9.5 Hz, 1H), 6.91 – 6.72 (m, 2H), 4.78 (s, 1H), 4.45 – 4.21 (m, 1H), 4.17 – 4.06 (m, 1H), 4.07 – 3.88 (m, 1H), 3.71 – 3.56 (m, 1H), 3.52 (dd, J = 10.6, 2.6 Hz, 1H), 3.08 – 2.88 (m, 1H), 2.78 – 2.64 (m, 1H), 2.05 (s, 3H).
170		366 1.40 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.04 (s, 3 H) 2.24 (s, 3 H) 2.94 (dd, J=12.7, 10.0 Hz, 1 H) 3.12 - 3.18 (m, 1 H) 3.41 - 3.54 (m, 3 H) 3.62 (dt, J=12.7, 2.3 Hz, 1 H) 3.64 - 3.71 (m, 1 H) 3.76 (td, J=11.6, 2.5 Hz, 1 H) 3.93 - 3.96 (m, 1 H) 4.77 (t, J=5.4 Hz, 1 H) 6.62 (s, 2 H) 7.22 (t, J=53.6 Hz, 1 H) 7.67 (s, 1 H) 9.47 (s, 1 H)
171		386 1.46 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H) 2.95 (dd, J=12.7, 10.0 Hz, 1 H) 3.11 - 3.22 (m, 1 H) 3.41 - 3.55 (m, 3 H) 3.63 - 3.79 (m, 3 H) 3.92 - 3.98 (m, 1 H) 4.76 (t, J=5.4 Hz, 1 H) 6.85 (d, J=2.0 Hz, 1 H) 6.89 (d, J=2.0 Hz, 1 H) 7.22 (t, J=53.6 Hz, 1 H) 7.71 (s, 1 H) 10.09 (s, 1 H)

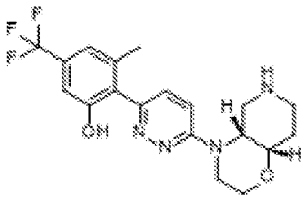
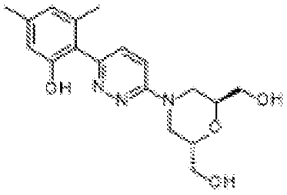
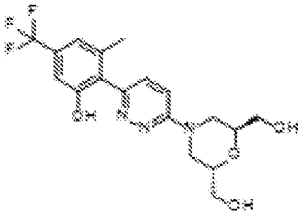
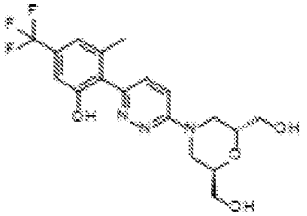
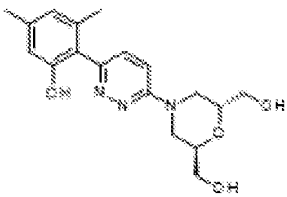
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
172		336 1.13 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.27 (s, 3 H) 2.73 (dd, J=12.7, 10.0 Hz, 1 H) 2.99 (td, J=12.7, 2.6 Hz, 1 H) 3.44 - 3.65 (m, 4 H) 3.99 (dd, J=11.6, 2.6 Hz, 1 H) 4.14 (br d, J=12.7 Hz, 1 H) 4.33 (br d, J=12.7 Hz, 1 H) 4.79 - 4.88 (m, 1 H) 6.73 (s, 1 H) 6.83 (s, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 9.94 (br s, 1 H)
173		346 0.92 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 2.60 - 2.69 (m, 2 H) 3.44 - 3.63 (m, 6 H) 4.33 (br d, J=12.7 Hz, 2 H) 4.77 (br t, J=5.5 Hz, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 9.37 (br s, 1 H)
174		318 1.10 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 2.82 (dd, J=12.7, 10.8 Hz, 1 H) 2.93 - 3.04 (m, 1 H) 3.66 (td, J=11.6, 2.6 Hz, 1 H) 3.75 - 3.87 (m, 1 H) 4.00 - 4.06 (m, 1 H) 4.13 (br d, J=12.7 Hz, 1 H) 4.31 (br d, J=11.5 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 9.37 (br s, 1 H)
175		340 1.01 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.49 - 1.63 (m, 6 H) 2.04 (s, 3 H) 2.09 - 2.17 (m, 2 H) 2.22 (s, 3 H) 3.49 (s, 2 H) 3.53 (br t, J=5.1 Hz, 2 H) 4.18 - 4.30 (m, 1 H) 4.94 (d, J=6.3 Hz, 1 H) 6.56 (br s, 1 H) 6.58 (br s, 1 H) 7.26 (d, J=9.5 Hz, 1 H) 7.30 (d, J=9.5 Hz, 1 H) 9.41 (br s, 1 H)
176		340 1.02 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.57 - 1.62 (m, 4 H) 1.63 - 1.70 (m, 2 H) 2.04 (s, 3 H) 2.04 - 2.10 (m, 2 H) 2.22 (s, 3 H) 3.49 - 3.53 (m, 2 H) 3.53 (s, 2 H) 4.06 - 4.17 (m, 1 H) 4.94 (d, J=6.3 Hz, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.42 (br s, 1 H)

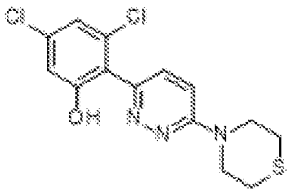
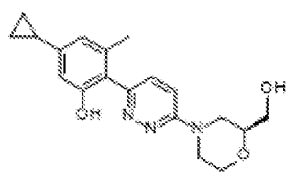
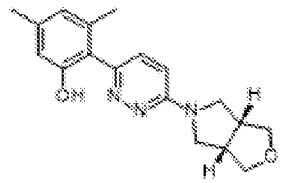
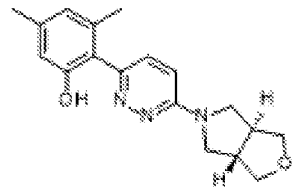
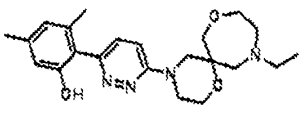
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
177		350 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.96 (s, 3 H) 2.28 (s, 3 H) 2.70 (dd, J=12.7, 10.0 Hz, 1 H) 2.96 (td, J=12.7, 2.6 Hz, 1 H) 3.36 - 3.64 (m, 4 H) 3.99 (dd, J=11.6, 2.6 Hz, 1 H) 4.10 - 4.18 (m, 1 H) 4.25 - 4.35 (m, 1 H) 4.82 (br t, J=5.4 Hz, 1 H) 6.72 (br s, 1 H) 6.84 (br s, 1 H) 7.17 (br s, 1 H) 9.77 (br s, 1 H)
178		400 1.18 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.67 (dd, J=12.7, 10.6 Hz, 2 H) 3.42 - 3.63 (m, 6 H) 4.32 - 4.40 (m, 2 H) 4.77 - 4.85 (m, 2 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.30 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 10.10 - 10.35 (m, 1 H)
179		288 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.23 (s, 3 H) 3.78 - 3.85 (m, 2 H) 3.90 (dd, J=9.0, 5.0 Hz, 1 H) 4.11 (dd, J=11.0, 6.0 Hz, 1 H) 4.71 - 4.76 (m, 1 H) 5.35 (br d, J=4.0 Hz, 1 H) 6.58 (br s, 1 H) 6.60 (br s, 1 H) 7.41 (d, J=9.0 Hz, 1 H) 7.48 (d, J=9.0 Hz, 1 H) 9.35 (br s, 1 H)
180		330.4 2.41 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.40 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 7.26 (d, J = 9.4 Hz, 1H), 6.61 – 6.55 (m, 2H), 4.85 (d, J = 5.5 Hz, 1H), 4.52 – 4.39 (m, 1H), 4.16 – 4.06 (m, 1H), 4.04 – 3.96 (m, 1H), 3.67 – 3.54 (m, 2H), 3.27 – 3.18 (m, 1H), 3.01 – 2.92 (m, 1H), 2.72 (dd, J = 13.0, 10.4 Hz, 1H), 2.23 (s, 3H), 2.04 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H).
181		329.4 2.22 E	1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 9.45 (s, 1H), 7.47 – 7.24 (m, 4H), 6.67 – 6.51 (m, 2H), 4.48 – 4.34 (m, 1H), 4.16 – 3.95 (m, 3H), 3.78 – 3.66 (m, 1H), 3.15 – 3.05 (m, 1H), 2.96 (dd, J = 13.0, 10.2 Hz, 1H), 2.23 (s, 3H), 2.03 (s, 3H).

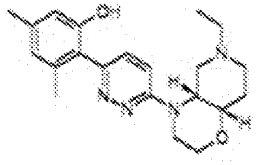
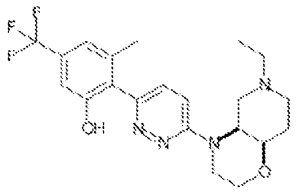
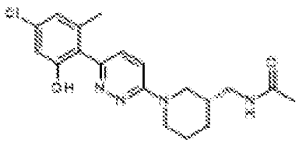
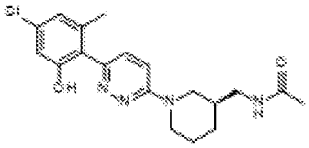
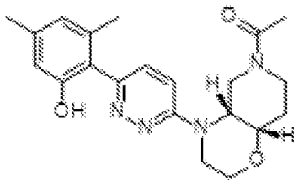
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
182		343.2 1.24 P	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.39 (s, 1H), 7.88 (d, J = 5.1 Hz, 1H), 7.36 (d, J = 9.4 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.59 (s, 1H), 6.57 (s, 1H), 4.43 (d, J = 12.6 Hz, 1H), 4.13 – 4.03 (m, 3H), 3.75 – 3.67 (m, 1H), 3.09 (t, J = 11.0 Hz, 1H), 2.94 (dd, J = 13.0, 10.2 Hz, 1H), 2.64 (d, J = 4.7 Hz, 3H), 2.22 (s, 3H), 2.03 (s, 3H).
183		329.2 2.33 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.39 (s, 1H), 7.40 – 7.28 (m, 4H), 6.58 (s, 1H), 6.57 (s, 1H), 4.40 (d, J = 13.1 Hz, 1H), 4.11 – 3.99 (m, 3H), 3.74 – 3.66 (m, 1H), 3.15 – 3.06 (m, 1H), 2.96 (dd, J = 13.0, 10.2 Hz, 1H), 2.22 (s, 3H), 2.03 (s, 3H).
184		357.2 1.22 P	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.39 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 7.31 (d, J = 9.4 Hz, 1H), 6.58 (s, 1H), 6.57 (s, 1H), 4.39 (dd, J = 10.0, 2.8 Hz, 1H), 4.24 (d, J = 13.2 Hz, 1H), 4.17 (d, J = 13.1 Hz, 1H), 4.00 (d, J = 12.0 Hz, 1H), 3.73 (td, J = 11.4, 2.8 Hz, 1H), 3.19 – 3.02 (m, 2H), 3.07 (s, 3H), 2.86 (s, 3H), 2.22 (s, 3H), 2.03 (s, 3H).
185		327.2 2.37 E	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (d, J = 9.5 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.68 – 6.59 (m, 1H), 4.07 – 3.86 (m, 3H), 3.81 (td, J = 11.7, 2.9 Hz, 1H), 3.76 – 3.67 (m, 1H), 3.40 (t, J = 9.5 Hz, 1H), 3.30 (t, J = 10.1 Hz, 1H), 3.18 – 3.05 (m, 2H), 3.05 – 2.97 (m, 1H), 2.37 (s, 3H), 2.30 (s, 3H).
186		346 0.84 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.84 (s, 3 H) 2.23 (s, 3 H) 2.72 (dd, J=12.7, 10.0 Hz, 1 H) 2.94 - 3.01 (m, 1 H) 3.44 - 3.65 (m, 4 H) 3.95 - 4.02 (m, 2 H) 4.12 - 4.18 (m, 1 H) 4.24 - 4.30 (m, 2 H) 4.84 (t, J=5.4 Hz, 1 H) 5.34 (br t, J=5.4 Hz, 1 H) 6.56 (br s, 1 H) 6.58 (br s, 1 H) 7.21 (br s, 1 H) 9.20 (s, 1 H)

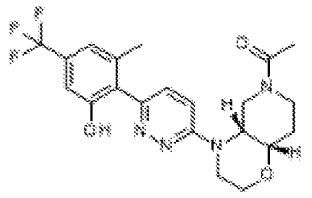
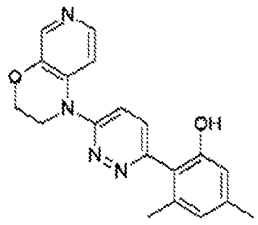
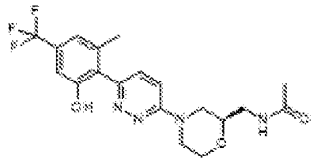
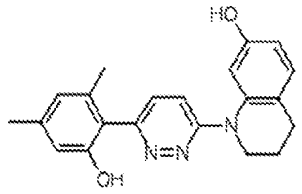
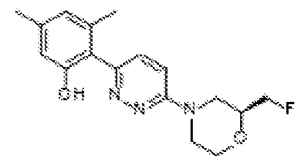
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
187		346 0.97 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.01 (s, 3 H) 2.24 (s, 3 H) 2.79 (dd, J=12.7, 10.0 Hz, 1 H) 2.98 - 3.04 (m, 1 H) 3.35 - 3.53 (m, 4 H) 3.60 - 3.66 (m, 1 H) 3.71 (td, J=11.6, 2.6 Hz, 1 H) 3.90 - 3.94 (m, 1 H) 4.53 (d, J=5.4 Hz, 2 H) 4.75 (t, J=5.4 Hz, 1 H) 5.55 (t, J=5.4 Hz, 1 H) 6.59 (br s, 1 H) 6.60 (br s, 1 H) 7.53 (s, 1 H) 9.39 (s, 1 H)
188		366 0.92 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.88 (s, 3 H) 2.73 (dd, J=12.7, 10.0 Hz, 1 H) 2.95 - 3.02 (m, 1 H) 3.44 - 3.65 (m, 4 H) 3.97 - 4.02 (m, 2 H) 4.13 - 4.19 (m, 1 H) 4.23 - 4.31 (m, 2 H) 4.84 (t, J=5.4 Hz, 1 H) 5.30 - 5.55 (m, 1 H) 6.79 (d, J=2.0 Hz, 1 H) 6.85 (d, J=2.0 Hz, 1 H) 7.23 (s, 1 H) 9.75 - 10.0 (m, 1 H)
189		366 1.10 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.03 (s, 3 H) 2.80 (dd, J=12.7, 10.2 Hz, 1 H) 2.97 - 3.05 (m, 1 H) 3.36 - 3.52 (m, 4 H) 3.60 - 3.66 (m, 1 H) 3.68 - 3.74 (m, 1 H) 3.89 - 3.96 (m, 1 H) 4.53 (br d, J=5.4 Hz, 2 H) 4.76 (br t, J=5.4 Hz, 1 H) 5.57 (t, J=5.4 Hz, 1 H) 6.84 (d, J=2.0 Hz, 1 H) 6.86 (d, J=2.0 Hz, 1 H) 7.54 (s, 1 H) 9.90 - 10.10 (m, 1 H)
190		327.3 2.20 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.37 (br. s, 1H), 7.38 (d, *J* = 9.3 Hz, 1H), 7.32 (d, *J* = 9.3 Hz, 1H), 6.57 (d, *J* = 6.8 Hz, 2H), 4.13 – 4.04 (m, 1H), 3.94 – 3.75 (m, 3H), 3.70 – 3.60 (m, 1H), 3.13 – 3.01 (m, 1H), 3.01 – 2.90 (m, 2H), 2.81 – 2.69 (m, 2H), 2.22 (s, 3H), 2.00 (s, 3H). (NH not visible)
191		316.2 2.33 E	^{1}H NMR (400 MHz, DMSO) δ (ppm): 10.97 (s, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.75 (d, J = 7.6 Hz, 1H), 4.24 (d, J = 12.8 Hz, 1H), 4.16 (ddt, J = 11.5, 3.4, 2.0 Hz, 2H), 3.89 – 3.68 (m, 4H), 3.27 – 3.15 (m, 1H), 3.04 (dd, J = 12.8, 9.9 Hz, 1H), 2.39 (s, 3H), 2.31 (s, 3H), 2.00 (s, 1H).

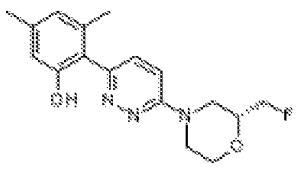
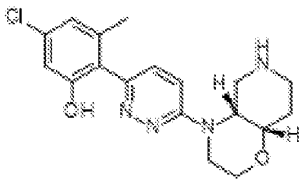
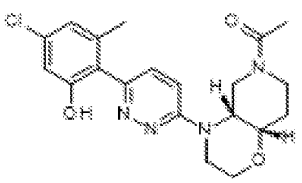
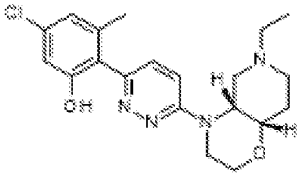
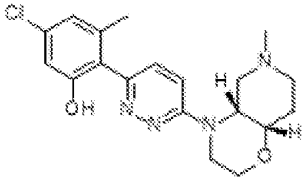
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
192		372.2 2.68 E	^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm): 10.15 (s, 1H), 7.41 (d, J = 9.4 Hz, 1H), 7.31 (d, J = 9.5 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.79 (s, 1H), 4.37 – 4.28 (m, 1H), 4.21 – 4.10 (m, 1H), 4.06 – 3.93 (m, 1H), 3.67 – 3.56 (m, 1H), 3.53 (dd, J = 10.4, 2.6 Hz, 1H), 3.07 – 2.92 (m, 1H), 2.82 – 2.64 (m, 1H), 2.13 (s, 3H).
193		370 1.53 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 3.26 - 3.33 (m hidden, 2 H) 4.12 - 4.18 (m, 2 H) 6.56 - 6.63 (m, 3 H) 6.83 (d, J=2.0 Hz, 1 H) 6.85 (d, J=2.0 Hz, 1 H) 7.30 (d, J=9.5 Hz, 1 H) 7.63 (d, J=9.5 Hz, 1 H) 9.95 - 10.15 (m, 1 H)
194		420 1.53 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.14 (s, 3 H) 2.96 (dd, J=12.7, 10.0 Hz, 1 H) 3.10 – 3.25 (m, 1 H) 3.37 – 3.56 (m, 3 H) 3.64 – 3.72 (m, 2 H) 3.76 (td, J=11.6, 2.6 Hz, 1 H) 3.92 – 3.98 (m, 1 H) 4.79 (t, J=5.4 Hz, 1 H) 7.10 (br s, 1 H) 7.17 (br s, 1 H) 7.24 (t, J=53.3 Hz, 1 H) 7.78 (s, 1 H) 10.40 – 10.70 (m, 1 H)
195		341 0.84 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.71 - 1.81 (m, 2 H) 2.03 (s, 3 H) 2.04 - 2.21 (m, 1 H) 2.22 (s, 3 H) 2.58 - 2.69 (m, 3 H) 2.91 (t, J=11.8 Hz, 1 H) 3.14 (td, J=11.8, 3.8 Hz, 1 H) 3.61 (td, J=11.8, 3.8 Hz, 1 H) 3.79 - 3.87 (m, 1 H) 3.97 (br d, J=11.8 Hz, 1 H) 4.06 (dd, J=11.8, 3.8 Hz, 1 H) 4.15 - 4.26 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.19 (d, J=9.5 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 9.39 (br s, 1 H)
196		341.3 2.38 E	1H NMR (500 MHz, DMSO-d6) δ (ppm): 9.38 (br. s, 1H), 7.29 (d, J = 6.3 Hz, 2H), 6.57 (br. s, 2H), 3.82 (br. s, 2H), 3.63 (d, J = 8.6 Hz, 1H), 3.57 – 3.44 (m, 5H), 2.85 (d, J = 22.9 Hz, 2H), 2.22 (br. s, 3H), 2.03 (br. s, 3H), 1.86 (br. s, 1H), 1.80 (br. s, 1H). Another proton hidden under DMSO peak.

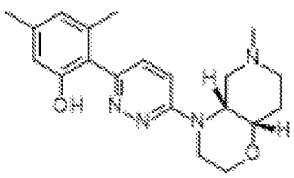
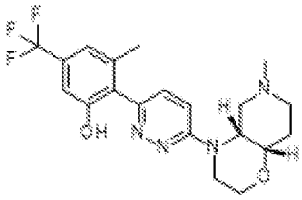
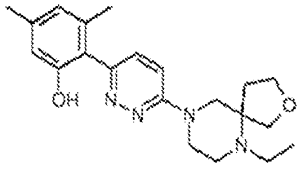
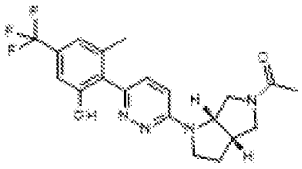
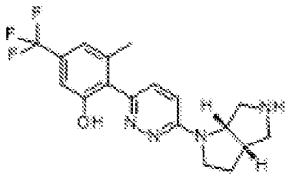
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
197		365 1.01 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.71 - 1.80 (m, 2 H) 2.13 (s, 3 H) 2.58 - 2.66 (m, 3 H) 2.92 (t, J=11.8 Hz, 1 H) 3.16 (td, J=11.8, 3.8 Hz, 1 H) 3.62 (td, J=11.8, 3.8 Hz, 1 H) 3.78 - 3.89 (m, 1 H) 3.99 (br d, J=11.8 Hz, 1 H) 4.06 (dd, J=11.8, 3.8 Hz, 1 H) 4.17 - 4.30 (m, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.39 (d, J=9.5 Hz, 1 H) 9.02 - 11.04 (m, 1 H)
198		346 0.90 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 3.39 - 3.48 (m, 2 H) 3.49 - 3.59 (m, 4 H) 3.77 (dd, J=12.7, 3.7 Hz, 2 H) 3.81 - 3.89 (m, 2 H) 4.76 (t, J=5.7 Hz, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.22 (d, J=9.5 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 9.40 (br s, 1 H)
199		400 1.15 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 3.46 (br dd, J=12.7, 6.5 Hz, 2 H) 3.50 - 3.58 (m, 4 H) 3.75 - 3.90 (m, 4 H) 4.69 - 4.85 (m, 2 H) 7.07 (br s, 1 H) 7.10 (br s, 1 H) 7.26 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.05 - 10.80 (m, 1 H)
200		400 1.15 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 3.46 (dd, J=12.7, 6.5 Hz, 2 H) 3.50 - 3.59 (m, 4 H) 3.80 (dd, J=12.7, 3.5 Hz, 2 H) 3.83 - 3.90 (m, 2 H) 4.65 - 4.90 (m, 2 H) 7.07 (br s, 1 H) 7.11 (br s, 1 H) 7.26 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.05 - 10.65 (m, 1 H)
201		346 0.89 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 3.43 (br dd, J=12.7, 6.5 Hz, 2 H) 3.50 - 3.58 (m, 4 H) 3.77 (dd, J=12.7, 3.5 Hz, 2 H) 3.81 - 3.89 (m, 2 H) 4.65 - 4.87 (m, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.22 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.41 (br s, 1 H)

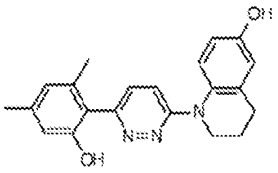
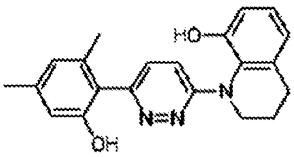
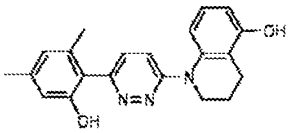
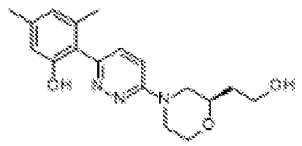
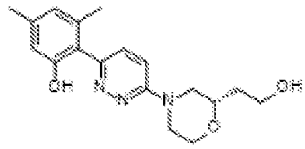
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
203		342 1.60 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.66 - 2.70 (m, 4 H) 4.00 - 4.04 (m, 4 H) 6.96 (d, J=2.0 Hz, 1 H) 7.13 (d, J=2.0 Hz, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 10.40 - 10.70 (m, 1 H)
204		342 1.05 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.58 - 0.68 (m, 2 H) 0.87 - 0.98 (m, 2 H) 1.78 - 1.87 (m, 1 H) 2.03 (s, 3 H) 2.70 (dd, J=12.7, 10.0 Hz, 1 H) 2.96 (td, J=12.7, 2.6 Hz, 1 H) 3.45 - 3.65 (m, 4 H) 3.99 (dd, J=11.6, 2.6 Hz, 1 H) 4.12 (br d, J=12.7 Hz, 1 H) 4.31 (br d, J=12.7 Hz, 1 H) 4.81 (t, J=5.4 Hz, 1 H) 6.46 (br s, 1 H) 6.48 (br s, 1 H) 7.26 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 9.38 (s, 1 H)
206		312 0.92 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 3.03 - 3.10 (m, 2 H) 3.46 (dd, J=10.9, 3.3 Hz, 2 H) 3.60 (dd, J=8.9, 3.7 Hz, 2 H) 3.66 (br dd, J=10.9, 7.7 Hz, 2 H) 3.88 (br dd, J=8.9, 6.9 Hz, 2 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.94 (d, J=9.4 Hz, 1 H) 7.30 (d, J=9.4 Hz, 1 H) 9.37 (s, 1 H)
207		312 0.91 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 2.04 (s, 3 H) 2.22 (s, 3 H) 2.52 - 2.61 (m, 2 H) 3.22 (br dd, J=10.6, 9.4 Hz, 2 H) 3.47 (br dd, J=10.6, 7.2 Hz, 2 H) 3.78 - 3.84 (m, 2 H) 3.91 (br t, J=6.8 Hz, 2 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.86 (d, J=9.4 Hz, 1 H) 7.29 (d, J=9.4 Hz, 1 H) 9.37 (s, 1 H)
208		399.4 2.90 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.33 (s, 1H), 7.27 (d, J = 9.4 Hz, 1H), 7.18 (d, J = 9.4 Hz, 1H), 6.51 (d, J = 4.3 Hz, 2H), 3.67 (q, J = 9.4 Hz, 6H), 3.55 – 3.44 (m, 2H), 3.13 (d, J = 13.0 Hz, 1H), 2.83 (d, J = 13.4 Hz, 1H), 2.56 (s, 2H), 2.50 (s, 1H), 2.15 (s, 3H), 1.95 (s, 3H), 0.86 (t, J = 7.0 Hz, 3H). 3 protons hidden under DMSO and water peaks (confirmed by HSQC).

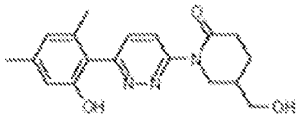
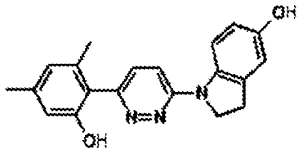
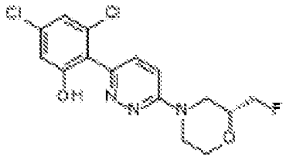
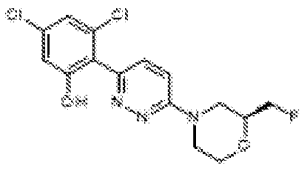
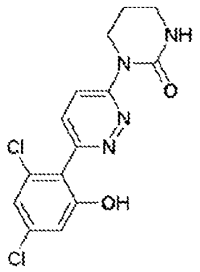
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
209		369 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.04 (s, 3 H) 2.74 (dd, J=12.7, 10.0 Hz, 1 H) 3.00 (td, J=12.7, 2.6 Hz, 1 H) 3.44 - 3.65 (m, 4 H) 3.99 (dd, J=11.6, 2.0 Hz, 1 H) 4.15 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.80 (br s, 1 H) 6.97 (d, J=6.5 Hz, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 9.21 - 10.32 (m, 1 H)
210		423 1.03 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.98 (t, J=7.0 Hz, 3 H) 1.79 - 1.91 (m, 2 H) 2.06 - 2.14 (m, 1 H) 2.13 (s, 3 H) 2.29 - 2.45 (m, 3 H) 2.55 - 2.66 (m, 2 H) 3.18 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.73 - 3.79 (m, 1 H) 3.96 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.37 - 4.47 (m, 1 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.13 (br s, 1 H)
211		375 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.15 - 1.28 (m, 1 H) 1.42 - 1.54 (m, 1 H) 1.62 - 1.85 (m, 3 H) 1.84 (s, 3 H) 2.06 (s, 3 H) 2.69 (dd, J=13.0, 10.5 Hz, 1 H) 2.92 - 3.09 (m, 3 H) 4.21 (br d, J=13.0 Hz, 1 H) 4.32 (br dd, J=13.0, 3.5 Hz, 1 H) 6.81 (d, J=2.0 Hz, 1 H) 6.83 (d, J=2.0 Hz, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 7.90 (t, J=5.9 Hz, 1 H) 9.80 - 10.20 (m, 1 H)
212		375 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.18 - 1.34 (m, 1 H) 1.46 - 1.58 (m, 1 H) 1.68 - 1.85 (m, 3 H) 1.84 (s, 3 H) 2.10 (s, 3 H) 2.84 (dd, J=13.0, 10.5 Hz, 1 H) 2.98 - 3.14 (m, 3 H) 4.19 (br d, J=13.0 Hz, 1 H) 4.25 (br dd, J=13.0, 3.5 Hz, 1 H) 6.85 (d, J=2.0 Hz, 1 H) 6.88 (d, J=2.0 Hz, 1 H) 7.52 - 7.68 (m, 2 H) 7.90 (t, J=5.9 Hz, 1 H) 10.00 - 10;50 (m, 1 H)
213		383 1.09 U	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.81 - 1.89 (m, 2 H) 2.03 (s, 3 H) 2.09 (s, 3 H) 2.25 (s, 3 H) 2.74 - 4.49 (m, 4 H) 3.26 (td, J=12.7, 3.8 Hz, 1 H) 3.72 (td, J=11.8, 3.2 Hz, 1 H) 3.87 - 3.93 (m, 1 H) 4.00 (br d, J=12.8 Hz, 1 H) 4.11 (dd, J=11.8, 3.2 Hz, 1 H) 4.24 - 4.44 (m, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.22 (br d, J=9.5 Hz, 1 H) 7.39 (d, J=9.5 Hz, 1 H) 9.10 - 9.20 (m, 1 H)

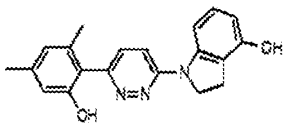
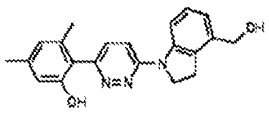
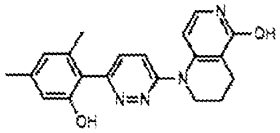
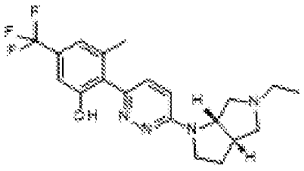
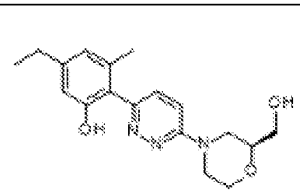
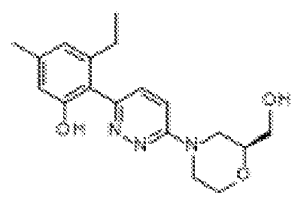
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
214		437 1.38 U	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.81 - 1.91 (m, 2 H) 2.03 (s, 3 H) 2.17 (s, 3 H) 2.72 - 4.48 (m, 4 H) 3.28 (td, J=12.7, 3.8 Hz, 1 H) 3.73 (td, J=11.8, 3.2 Hz, 1 H) 3.88 - 3.94 (m, 1 H) 4.02 (br d, J=11.8 Hz, 1 H) 4.11 (br dd, J=11.8, 3.2 Hz, 1 H) 4.28 - 4.44 (m, 1 H) 7.07 - 7.10 (m, 2 H) 7.26 (br d, J=9.5 Hz, 1 H) 7.43 (d, J=9.5 Hz, 1 H) 9.15 - 10.45 (m, 1 H)
215		335 0.88 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.07 (s, 3 H) 2.25 (s, 3 H) 4.08 - 4.13 (m, 2 H) 4.38 - 4.43 (m, 2 H) 6.62 (br s, 1 H) 6.63 (br s, 1 H) 7.45 (br d, J=5.5 Hz, 1 H) 7.60 (d, J=9.5 Hz, 1 H) 7.71 (d, J=9.5 Hz, 1 H) 7.94 (br d, J=5.5 Hz, 1 H) 8.13 (br s, 1 H) 9.43 (br s, 1 H)
216		411 1.24 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.85 (s, 3 H) 2.13 (s, 3 H) 2.70 (dd, J=12.7, 10.5 Hz, 1 H) 3.01 (td, J=12.7, 3.5 Hz, 1 H) 3.24 (t, J=5.7 Hz, 2 H) 3.52 - 3.65 (m, 2 H) 4.01 (br d, J=11.5 Hz, 1 H) 4.13 (br d, J=12.7 Hz, 1 H) 4.31 (br d, J=12.7 Hz, 1 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.42 (d, J=9.5 Hz, 1 H) 8.01 (t, J=5.7 Hz, 1 H) 10.12 (s, 1 H)
217		348 1.32 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.92 (quin, J=6.3 Hz, 2 H) 2.07 (s, 3 H) 2.24 (s, 3 H) 2.66 (br t, J=6.3 Hz, 2 H) 3.94 (br t, J=6.3 Hz, 2 H) 6.40 (dd, J=8.2, 2.0 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 6.65 (d, J=2.0 Hz, 1 H) 6.98 (d, J=8.2 Hz, 1 H) 7.37 (d, J=9.3 Hz, 1 H) 7.51 (d, J=9.3 Hz, 1 H) 9.17 (br s, 1 H) 9.41 (br s, 1 H)
219		318 1.10 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 2.82 (dd, J=12.7, 10.8 Hz, 1 H) 2.95 - 3.04 (m, 1 H) 3.66 (td, J=11.6, 2.6 Hz, 1 H) 3.75 - 3.88 (m, 1 H) 4.03 (dd, J=11.6, 2.6 Hz, 1 H) 4.13 (br d, J=12.7 Hz, 1 H) 4.31 (br d, J=12.7 Hz, 1 H) 4.44 - 4.66 (m, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 9.36 (br s, 1 H)

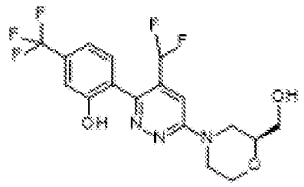
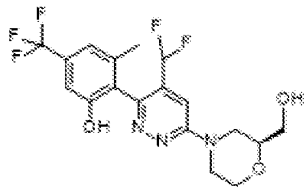
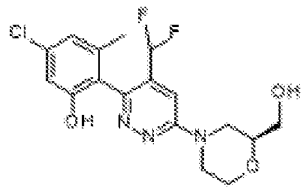
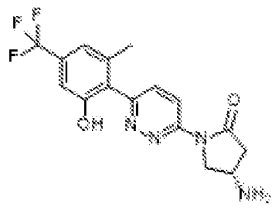
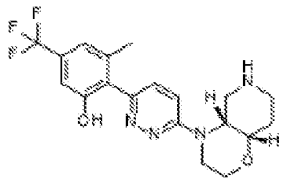
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
220		318 1.10 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 2.82 (dd, J=12.7, 10.8 Hz, 1 H) 2.95 - 3.04 (m, 1 H) 3.66 (td, J=11.6, 2.6 Hz, 1 H) 3.75 - 3.87 (m, 1 H) 4.00 - 4.06 (m, 1 H) 4.13 (br d, J=12.7 Hz, 1 H) 4.31 (br d, J=12.7 Hz, 1 H) 4.44 - 4.67 (m, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 9.36 (br s, 1 H)
221		361 0.91 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.70 – 1.82 (m, 2 H) 2.05 (s, 3 H) 2.59 – 2.70 (m, 3 H) 2.92 (br t, J=11.8 Hz, 1 H) 3.15 (td, J=11.8, 3.8 Hz, 1 H) 3.61 (td, J=11.8, 3.8 Hz, 1 H) 3.77 – 3.89 (m, 1 H) 3.98 (br d, J=11.8 Hz, 1 H) 4.06 (dd, J=11.8, 3.8 Hz, 1 H) 4.14 – 4.28 (m, 1 H) 6.81 (d, J=2.0 Hz, 1 H) 6.84 (d, J=2.0 Hz, 1 H) 7.21 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 8.96 – 10.86 (m, 1 H)
222		403 1.24 U	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.79 - 1.88 (m, 2 H) 2.01 (s, 3 H) 2.08 (s, 3 H) 2.73 - 4.53 (m, 4 H) 3.25 (td, J=12.7, 3.8 Hz, 1 H) 3.70 (td, J=11.8, 3.2 Hz, 1 H) 3.83 - 3.93 (m, 1 H) 3.99 (br d, J=11.8 Hz, 1 H) 4.09 (dd, J=11.8, 3.2 Hz, 1 H) 4.24 - 4.39 (m, 1 H) 6.79 - 6.82 (m, 2 H) 7.21 (br d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 9.35 - 9.95 (m, 1 H)
223		389 0.94 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.97 (t, J=7.1 Hz, 3 H) 1.78 - 1.90 (m, 2 H) 2.05 (s, 3 H) 2.05 - 2.16 (m, 1 H) 2.32 - 2.43 (m, 3 H) 2.56 - 2.65 (m, 2 H) 3.16 (td, J=11.8, 3.8 Hz, 1 H) 3.62 (td, J=11.8, 3.8 Hz, 1 H) 3.71 - 3.79 (m, 1 H) 3.94 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.34 - 4.46 (m, 1 H) 6.81 (d, J=2.0 Hz, 1 H) 6.84 (d, J=2.0 Hz, 1 H) 7.22 (d, J=9.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 9.96 (s, 1 H)
224		375 0.92 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.92 (m, 2 H) 2.05 (s, 3 H) 2.05 - 2.14 (m, 1 H) 2.18 (s, 3 H) 2.29 - 2.36 (m, 1 H) 2.51 - 2.54 (m partially hidden, 2 H) 3.16 (td, J=11.8, 3.8 Hz, 1 H) 3.62 (td, J=11.8, 3.8 Hz, 1 H) 3.71 - 3.76 (m, 1 H) 3.93 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.37 - 4.45 (m, 1 H) 6.81 (d, J=1.8 Hz, 1 H) 6.84 (d, J=1.8 Hz, 1 H) 7.22 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 9.90 - 10.00 (m, 1 H)

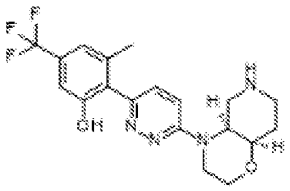
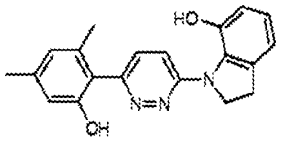
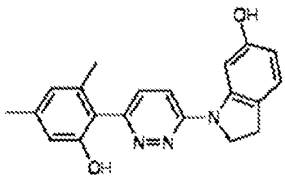
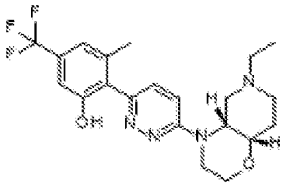
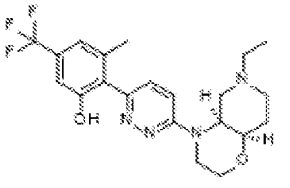
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
225		355 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.93 (m, 2 H) 2.03 (s, 3 H) 2.05 - 2.14 (m, 1 H) 2.18 (s, 3 H) 2.22 (s, 3 H) 2.29 - 2.37 (m, 1 H) 2.51 - 2.57 (m partially hidden, 2 H) 3.16 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.71 - 3.77 (m, 1 H) 3.92 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.36 - 4.44 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.20 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.36 (s, 1 H)
226		409 1.03 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.77 - 1.93 (m, 2 H) 2.04 - 2.12 (m, 1 H) 2.13 (s, 3 H) 2.18 (s, 3 H) 2.30 - 2.38 (m, 1 H) 2.52 - 2.56 (m partially hidden, 2 H) 3.17 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.71 - 3.78 (m, 1 H) 3.95 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.38 - 4.47 (m, 1 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.12 (br s, 1 H)
227		369.3 2.75 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.39 (s, 1H), 7.33 (s, 2H), 6.58 (d, J = 6.3 Hz, 2H), 3.94 – 3.86 (m, 1H), 3.75 (dt, J = 15.4, 9.2 Hz, 4H), 3.43 – 3.36 (m, 2H), 3.29 – 3.26 (m, 1H), 2.74 (d, J = 12.0 Hz, 1H), 2.60 (dd, J = 13.1, 6.9 Hz, 2H), 2.33 (dq, J = 13.5, 7.5 Hz, 1H), 2.23 (s, 3H), 2.04 (s, 3H), 1.96 (dt, J = 16.8, 8.5 Hz, 1H), 1.70 (dq, J = 12.8, 5.5 Hz, 1H), 1.05 (t, J = 7.1 Hz, 3H).
228		407.3 2.73 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) : 10.13 (s, 1H), 7.38 (t, J = 8.7 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 6.99 (dd, J = 9.4, 3.7 Hz, 1H), 4.66 – 4.45 (m, 1H), 4.15 – 3.33 (m, 6H), 3.21 – 2.97 (m, 1H), 2.26 – 2.05 (m, 4H), 2.02 – 1.78 (m, 4H).
229		365.2 2.50 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) : 7.34 (d, J = 9.3 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 6.94 (d, J = 9.4 Hz, 1H), 4.34 (s, 1H), 3.61 (tt, J = 13.9, 7.7 Hz, 2H), 2.96 (dd, J = 11.8, 5.8 Hz, 1H), 2.90 – 2.79 (m, 3H), 2.70 (d, J = 7.6 Hz, 1H), 2.14 (s, 3H), 2.12 – 2.06 (m, 1H), 1.84 (dd, J = 12.3, 6.0 Hz, 1H). (OH and NH not visible)

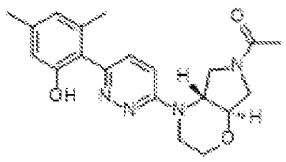
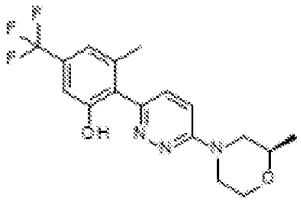
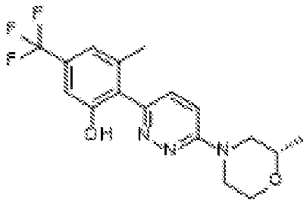
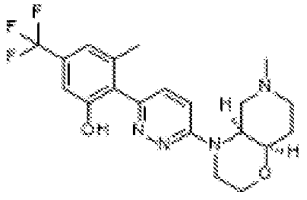
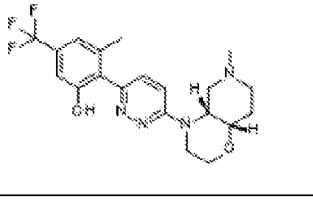
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
230		348 1.20 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.90 (quin, J=6.4 Hz, 2 H) 2.06 (s, 3 H) 2.22 (s, 3 H) 2.66 (t, J=6.4 Hz, 2 H) 3.95 (t, J=6.4 Hz, 2 H) 6.55 - 6.61 (m, 3 H) 6.63 (d, J=2.8 Hz, 1 H) 7.07 (d, J=8.5 Hz, 1 H) 7.27 (d, J=9.5 Hz, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 9.10 - 9.50 (m, 2 H)
231		348 1.23 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.92 (quin, J=6.4 Hz, 2 H) 2.06 (s, 3 H) 2.23 (s, 3 H) 2.69 (t, J=6.4 Hz, 2 H) 4.06 (t, J=6.4 Hz, 2 H) 6.58 (br s, 1 H) 6.59 (br s, 1 H) 6.64 (d, J=9.5 Hz, 1 H) 6.70 - 6.78 (m, 2 H) 6.95 (t, J=7.7 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.45 (br s, 1 H) 9.64 (br s, 1 H)
232		348 1.30 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.87 - 1.96 (m, 2 H) 2.07 (s, 3 H) 2.23 (s, 3 H) 2.65 (t, J=6.4 Hz, 2 H) 3.96 - 4.04 (m, 2 H) 6.52 (d, J=7.7 Hz, 1 H) 6.59 (br s, 1 H) 6.60 (br s, 1 H) 6.65 (d, J=7.7 Hz, 1 H) 6.92 (t, J=7.7 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 7.45 (d, J=9.5 Hz, 1 H) 9.41 (br s, 2 H)
233		330 0.96 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.60 - 1.71 (m, 2 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.68 (dd, J=12.7, 10.0 Hz, 1 H) 2.96 (td, J=12.7, 2.6 Hz, 1 H) 3.50 - 3.66 (m, 4 H) 3.97 (dd, J=11.6, 2.6 Hz, 1 H) 4.13 (br d, J=12.7 Hz, 1 H) 4.24 (br d, J=12.7 Hz, 1 H) 4.47 (t, J=5.4 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.36 (s, 1 H)
234		330 0.96 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.62 - 1.71 (m, 2 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.68 (dd, J=12.7, 10.0 Hz, 1 H) 2.96 (td, J=12.7, 2.6 Hz, 1 H) 3.50 - 3.66 (m, 4 H) 3.97 (dd, J=11.6, 2.6 Hz, 1 H) 4.13 (br d, J=12.7 Hz, 1 H) 4.24 (br d, J=12.7 Hz, 1 H) 4.47 (t, J=5.4 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.36 (br s, 1 H)

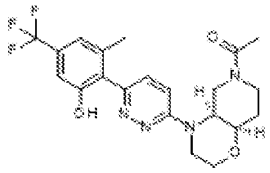
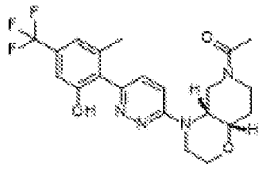
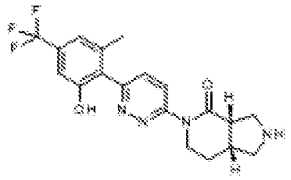
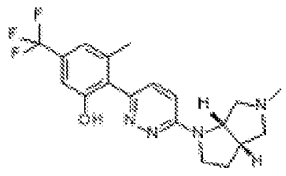
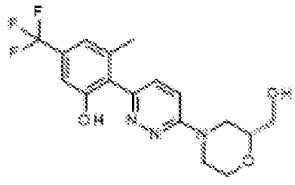
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
235		328 1,16 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.55 - 1.66 (m, 1 H) 1.88 - 1.96 (m, 1 H) 2.02 (s, 3 H) 2.08 - 2.19 (m, 1 H) 2.24 (s, 3 H) 2.54 - 2.61 (m, 2 H) 3.39 - 3.53 (m, 2 H) 3.74 (dd, J=12.7, 10.0 Hz, 1 H) 4.14 - 4.25 (m, 1 H) 4.75 (t, J=5.4 Hz, 1 H) 6.61 (br s, 1 H) 6.62 (br s, 1 H) 7.58 (d, J=9.5 Hz, 1 H) 7.97 (d, J=9.5 Hz, 1 H) 9.43 (s, 1 H)
236		334 1.17 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H) 2.24 (s, 3 H) 3.18 (t, J=8.5 Hz, 2 H) 4.05 (t, J=8.5 Hz, 2 H) 6.57 - 6.61 (m, 3 H) 6.69 - 6.72 (m, 1 H) 7.18 (d, J=9.5 Hz, 1 H) 7.43 (d, J=9.5 Hz, 1 H) 8.17 (d, J=8.5 Hz, 1 H) 8.90 - 9.10 (m, 1 H) 9.30 - 9.50 (m, 1 H)
237		358 1.50 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.85 (dd, J=12.7, 11.0 Hz, 1 H) 2.97 - 3.06 (m, 1 H) 3.66 (td, J=11.6, 2.6 Hz, 1 H) 3.75 - 3.87 (m, 1 H) 4.00 - 4.07 (m, 1 H) 4.17 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 6.96 (d, J=2.0 Hz, 1 H) 7.14 (d, J=2.0 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 7.42 (d, J=9.5 Hz, 1 H) 10.40 - 10.70 (m, 1 H)
238		358 1.50 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.85 (dd, J=12.7, 11.0 Hz, 1 H) 2.98 - 3.06 (m, 1 H) 3.66 (td, J=11.6, 2.6 Hz, 1 H) 3.75 - 3.87 (m, 1 H) 4.04 (dd, J=11.6, 2.6 Hz, 1 H) 4.17 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 6.96 (d, J=2.0 Hz, 1 H) 7.14 (d, J=2.0 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 7.42 (d, J=9.5 Hz, 1 H) 10.40 - 10.70 (m, 1 H)
239		339 1.35 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.98 - 2.04 (m, 2 H) 3.22 - 3.33 (m partially hidden, 2 H) 4.03 - 4.08 (m, 2 H) 6.97 (br s, 1 H) 7.16 (br s, 2 H) 7.52 (d, J=9.5 Hz, 1 H) 8.17 (d, J=9.5 Hz, 1 H) 10.50 - 10.80 (m, 1 H)

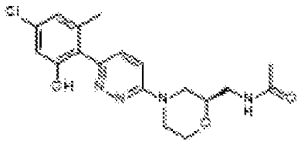
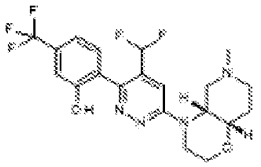
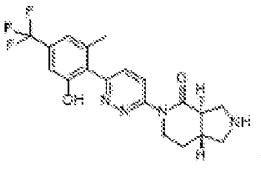
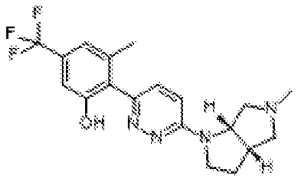
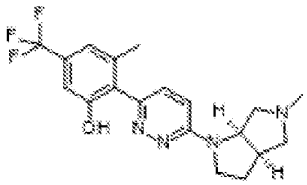
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
240		334 1.27 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H) 2.24 (s, 3 H) 3.09 (t, J=8.5 Hz, 2 H) 4.11 (t, J=8.5 Hz, 2 H) 6.42 (d, J=7.7 Hz, 1 H) 6.60 (br s, 1 H) 6.60 (br s, 1 H) 7.00 (t, J=7.7 Hz, 1 H) 7.27 (d, J=9.5 Hz, 1 H) 7.47 (d, J=9.5 Hz, 1 H) 7.78 (d, J=7.7 Hz, 1 H) 9.37 (br s, 2 H)
241		348 1.37 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.07 (s, 3 H) 2.24 (s, 3 H) 3.21 (t, J=8.5 Hz, 2 H) 4.13 (t, J=8.5 Hz, 2 H) 4.50 (d, J=5.4 Hz, 2 H) 5.08 (br t, J=5.4 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 6.95 (d, J=7.7 Hz, 1 H) 7.18 (t, J=7.7 Hz, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.49 (d, J=9.5 Hz, 1 H) 8.25 (d, J=7.7 Hz, 1 H) 9.38 (br s, 1 H)
242		349 1.28 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.73 - 1.82 (m, 2 H) 2.05 (s, 3 H) 2.25 (s, 3 H) 2.41 (t, J=6.4 Hz, 2 H) 3.18 - 3.25 (m, 2 H) 5.90 (d, J=7.8 Hz, 1 H) 6.63 (br s, 1 H) 6.64 (br s, 1 H) 6.97 (br s, 1 H) 7.69 (d, J=9.5 Hz, 1 H) 7.72 (d, J=7.8 Hz, 1 H) 8.05 (d, J=9.5 Hz, 1 H) 9.53 (br s, 1 H)
243		393.3 2.76 E	1H NMR (400 MHz, DMSO-d6) δ (ppm) : 10.15 (s, 1H), 7.35 (d, J = 9.3 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.11 – 7.04 (m, 1H), 6.97 (d, J = 9.3 Hz, 1H), 4.58 – 4.32 (m, 1H), 3.83 – 3.42 (m, 2H), 3.05 – 2.79 (m, 1H), 2.76 – 2.57 (m, 3H), 2.48 – 2.32 (m, 3H), 2.13 – 2.05 (m, 4H), 1.96 – 1.85 (m, 1H), 1.01 (t, J = 7.2 Hz, 3H).(compound cis confirmed by NMR NOESY)
245		330.2 2.63 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.32 (s, 1H), 7.29 (d, *J* = 9.3 Hz, 1H), 7.20 (d, *J* = 9.4 Hz, 1H), 6.54 (d, *J* = 3.5 Hz, 2H), 4.75 (s, 1H), 4.25 (d, *J* = 12.8 Hz, 1H), 4.05 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 11.3 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.50 – 3.44 (m, 2H), 3.40 (d, *J* = 7.3 Hz, 1H), 2.91 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.69 – 2.60 (m, 1H), 2.47 (d, *J* = 7.7 Hz, 2H), 1.98 (s, 3H), 1.11 (t, *J* = 7.6 Hz, 3H).
246		330.2 2.54 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.24 (s, 1H), 7.31 (d, *J* = 9.3 Hz, 1H), 7.25 (d, *J* = 9.4 Hz, 1H), 6.58 (d, *J* = 3.7 Hz, 2H), 4.82 (s, 1H), 4.31 (d, *J* = 12.8 Hz, 1H), 4.12 (d, *J* = 12.8 Hz, 1H), 3.99 (dd, *J* = 10.7, 3.3 Hz, 1H), 3.61 (td, *J* = 11.5, 2.7 Hz, 1H), 3.57 – 3.51 (m, 2H), 3.49 – 3.43 (m, 1H), 2.96 (td, *J* = 12.3, 3.5 Hz, 1H), 2.70 (dd, *J* = 12.8, 9.8 Hz, 1H), 2.35 (q, *J* = 7.4 Hz, 2H), 2.24 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).

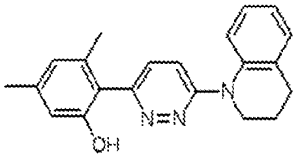
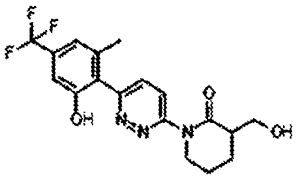
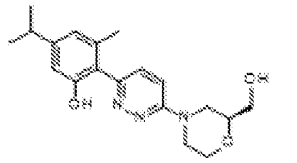
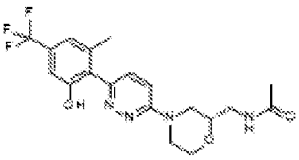
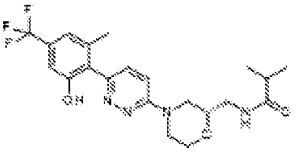
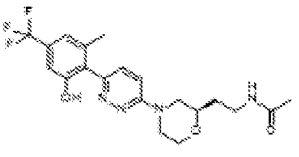
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
247		406 1.40 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.81 (dd, J=12.7, 10.0 Hz, 1 H) 3.02 - 3.11 (m, 1 H) 3.45 - 3.65 (m, 4 H) 4.00 (dd, J=11.6, 2.6 Hz, 1 H) 4.26 (br d, J=12.7 Hz, 1 H) 4.40 (br d, J=12.7 Hz, 1 H) 4.83 (br t, J=5.4 Hz, 1 H) 6.84 (t, J=54.2 Hz, 1 H) 7.23 (s, 1 H) 7.27 (br d, J=7.8 Hz, 1 H) 7.42 (s, 1 H) 7.50 (d, J=7.8 Hz, 1 H) 10.55 - 10.80 (m, 1 H)
248		420 1.43 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.01 (s, 3 H) 2.82 (dd, J=12.7, 10.0 Hz, 1 H) 3.02 - 3.12 (m, 1 H) 3.46 - 3.67 (m, 4 H) 3.96 - 4.06 (m, 1 H) 4.26 (br d, J=12.7 Hz, 1 H) 4.41 (br d, J=12.7 Hz, 1 H) 4.81 (br t, J=5.4 Hz, 1 H) 6.62 (t, J=54.0 Hz, 1 H) 7.07 (br s, 1 H) 7.16 (br s, 1 H) 7.46 (br s, 1 H) 10.20 - 10.40 (m, 1 H)
249		386 1.35 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.92 (s, 3 H) 2.81 (dd, J=12.7, 10.0 Hz, 1 H) 3.06 (td, J=12.7, 2.6 Hz, 1 H) 3.45 - 3.66 (m, 4 H) 4.00 (dd, J=11.6, 2.6 Hz, 1 H) 4.25 (br d, J=12.7 Hz, 1 H) 4.39 (br d, J=12.7 Hz, 1 H) 4.81 (br t, J=5.4 Hz, 1 H) 6.57 (t, J=54.3 Hz, 1 H) 6.82 (d, J=2.0 Hz, 1 H) 6.88 (d, J=2.0 Hz, 1 H) 7.43 (s, 1 H) 10.00 - 10.15 (m, 1 H)
250		353 0.93 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.11 (s, 3 H) 2.31 (dd, J=17.0, 3.5 Hz, 1 H) 2.87 (dd, J=17.0, 6.7 Hz, 1 H) 3.69 - 3.78 (m, 1 H) 3.90 (dd, J=11.0, 3.0 Hz, 1 H) 4.19 (dd, J=11.0, 6.0 Hz, 1 H) 7.09 (br s, 1 H) 7.15 (br s, 1 H) 7.70 (d, J=9.5 Hz, 1 H) 8.62 (d, J=9.5 Hz, 1 H)
251		395 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.70 - 1.83 (m, 2 H) 2.13 (s, 3 H) 2.59 - 2.71 (m, 3 H) 2.93 (br t, J=11.8 Hz, 1 H) 3.16 (td, J=11.8, 3.8 Hz, 2 H) 3.62 (td, J=11.8, 3.8 Hz, 1 H) 3.79 - 3.90 (m, 1 H) 3.99 (br d, J=11.8 Hz, 1 H) 4.06 (dd, J=11.8, 3.8 Hz, 1 H) 4.18 - 4.31 (m, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H)

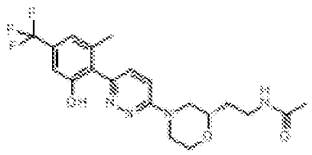
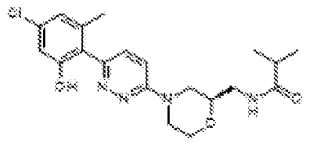
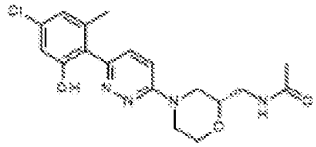
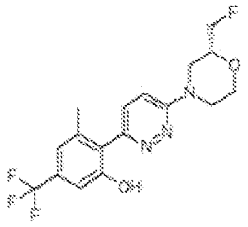
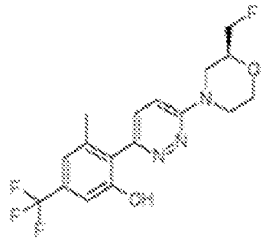
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
252		395 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.80 - 1.87 (m, 2 H) 2.13 (s, 3 H) 2.68 - 2.83 (m, 3 H) 3.01 (br t, J=11.8 Hz, 1 H) 3.15 - 3.21 (m, 1 H) 3.58 - 3.71 (m, 1 H) 3.81 - 3.91 (m, 1 H) 3.98 (br d, J=11.8 Hz, 1 H) 4.07 (dd, J=11.8, 3.8 Hz, 1 H) 4.34 - 4.46 (m, 1 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.26 (d, J=9.5 Hz, 1 H) 7.42 (d, J=9.5 Hz, 1 H) 10.21 (br s, 1 H)
253		334 1.62 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.06 (s, 3 H) 2.24 (s, 3 H) 3.21 (t, J=8.5 Hz, 2 H) 4.09 (t, J=8.5 Hz, 2 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 6.67 (br d, J=7.7 Hz, 1 H) 6.72 (br d, J=7.7 Hz, 1 H) 6.90 (t, J=7.7 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 7.58 (d, J=9.5 Hz, 1 H) 9.40 (s, 1 H) 13.52 (s, 1 H)
254		334 1.28 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.07 (s, 3 H) 2.24 (s, 3 H) 3.12 (t, J=8.5 Hz, 2 H) 4.09 (t, J=8.5 Hz, 2 H) 6.30 (dd, J=8.0, 2.2 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.00 (d, J=8.0 Hz, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.49 (d, J=9.5 Hz, 1 H) 7.96 (d, J=2.2 Hz, 1 H) 9.17 (br s, 1 H) 9.40 (br s, 1 H)
255		423 1.02 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.98 (t, J=7.3 Hz, 3 H) 1.78 - 1.91 (m, 2 H) 2.07 - 2.15 (m, 1 H) 2.13 (s, 3 H) 2.33 - 2.42 (m, 3 H) 2.56 - 2.65 (m, 2 H) 3.18 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.72 - 3.80 (m, 1 H) 3.96 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.37 - 4.47 (m, 1 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.13 (br s, 1 H)
256		423 1.02 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.98 (t, J=7.3 Hz, 3 H) 1.78 - 1.91 (m, 2 H) 2.07 - 2.12 (m, 1 H) 2.13 (s, 3 H) 2.33 - 2.43 (m, 3 H) 2.57 - 2.66 (m, 2 H) 3.18 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.73 - 3.79 (m, 1 H) 3.96 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.38 - 4.46 (m, 1 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.13 (br s, 1 H)

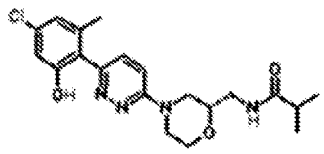
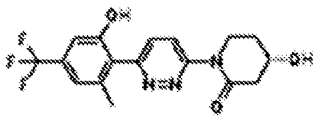
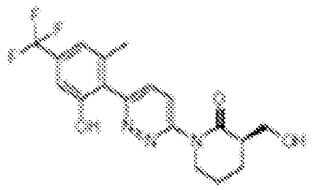
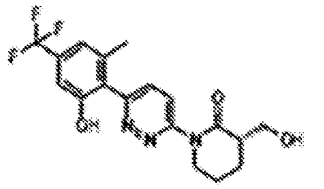
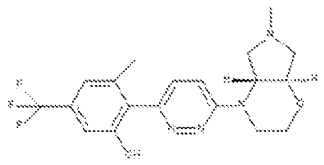
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
257		367.3 2.55 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.40 (s, 1H), 7.47 – 7.42 (m, 2H), 6.60 (s, 1H), 6.59 (s, 1H), 4.73 – 4.58 (m, 1H), 4.19 – 4.09 (m, 1H), 3.91 (m, 2H), 3.85 – 3.71 (m, 2H), 3.48 (t, J = 10.3 Hz, 0.5H), 3.42 – 3.35 (m, 1H), 3.27 – 3.16 (m, 0.5H), 3.14 – 2.94 (m, 2H), 2.23 (s, 3H), 2.02 (d, J = 1.4 Hz, 3H), 1.97 (d, J = 1.5 Hz, 3H).
258		354 1.38 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.19 (d, J=6.0 Hz, 3 H) 2.13 (s, 3 H) 2.64 (dd, J=12.7, 10.5 Hz, 1 H) 2.96 (td, J=12.7, 3.5 Hz, 1 H) 3.57 - 3.67 (m, 2 H) 3.93 - 3.99 (m, 1 H) 4.17 (br d, J=12.7 Hz, 1 H) 4.27 (br d, J=12.7 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.00 - 10.30 (m, 1 H)
259		354 1.38 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.19 (d, J=6.0 Hz, 3 H) 2.13 (s, 3 H) 2.64 (dd, J=12.7, 10.5 Hz, 1 H) 2.96 (td, J=12.7, 3.5 Hz, 1 H) 3.57 - 3.67 (m, 2 H) 3.93 - 4.01 (m, 1 H) 4.17 (br d, J=12.7 Hz, 1 H) 4.27 (br d, J=12.7 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.32 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.00 - 10.25 (m, 1 H)
260		409 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.93 (m, 2 H) 2.05 - 2.15 (m, 1 H) 2.13 (s, 3 H) 2.18 (s, 3 H) 2.29 - 2.38 (m, 1 H) 2.40 - 2.55 (m partially hidden, 2 H) 3.17 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.70 - 3.78 (m, 1 H) 3.95 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.37 - 4.46 (m, 1 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.14 (br s, 1 H)
261		409 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.93 (m, 2 H) 2.04 - 2.15 (m, 1 H) 2.13 (s, 3 H) 2.18 (s, 3 H) 2.29 - 2.37 (m, 1 H) 2.48 - 2.56 (m partially hidden, 2 H) 3.17 (td, J=11.8, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.8 Hz, 1 H) 3.70 - 3.78 (m, 1 H) 3.95 (br d, J=11.8 Hz, 1 H) 4.05 (dd, J=11.8, 3.8 Hz, 1 H) 4.38 - 4.48 (m, 1 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.25 (d, J=9.5 Hz, 1 H) 7.40 (d, J=9.5 Hz, 1 H) 10.15 (br s, 1 H)

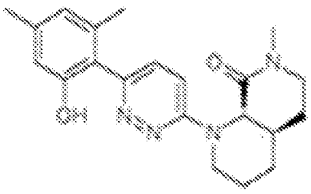
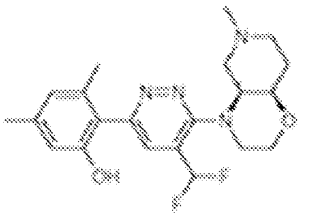
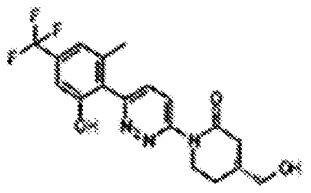
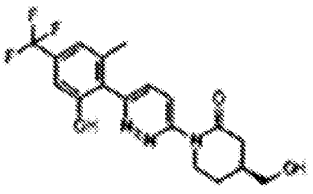
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
262		437 1.36 U	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.79 - 1.89 (m, 2 H) 2.02 (s, 3 H) 2.16 (s, 3 H) 2.72 - 4.57 (m, 4 H) 3.26 (td, J=12.7, 3.8 Hz, 1 H) 3.71 (td, J=11.8, 3.2 Hz, 1 H) 3.83 - 3.94 (m, 1 H) 4.01 (br d, J=11.8 Hz, 1 H) 4.10 (dd, J=11.8, 3.2 Hz, 1 H) 4.26 - 4.42 (m, 1 H) 7.06 - 7.09 (m, 2 H) 7.24 (br d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 9.65 - 9.97 (m, 1 H)
263		437 1.36 U	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.80 - 1.89 (m, 2 H) 2.02 (s, 3 H) 2.16 (s, 3 H) 2.73 - 4.46 (m, 4 H) 3.26 (td, J=12.7, 3.8 Hz, 1 H) 3.71 (td, J=11.8, 3.2 Hz, 1 H) 3.86 - 3.91 (m, 1 H) 4.01 (br d, J=11.8 Hz, 1 H) 4.10 (dd, J=11.8, 3.2 Hz, 1 H) 4.28 - 4.40 (m, 1 H) 7.06 - 7.08 (m, 2 H) 7.24 (br d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 9.70 - 9.90 (m, 1 H)
264	 HCl	393 0.96 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.93 (m, 1 H) 2.11 (s, 3 H) 2.14 - 2.24 (m, 1 H) 2.88 - 2.99 (m, 1 H) 2.99 - 3.10 (m, 1 H) 3.41 - 3.67 (m, 4 H) 3.89 - 3.96 (m partially hidden, 1 H) 4.46 (br dt, J=13.0, 4.0 Hz, 1 H) 7.16 (br s, 1 H) 7.17 (br s, 1 H) 7.74 (d, J=9.0 Hz, 1 H) 8.14 (d, J=9.0 Hz, 1 H) 9.23 - 9.41 (m, 2 H) 10.33 - 10.52 (m, 1 H)
265		379.4 2.68 E	1H NMR (500 MHz, DMSO-d6) δ (ppm) : 10.13 (s, 1H), 7.34 (d, *J* = 9.2 Hz, 1H), 7.11 (s, 1H), 7.06 (d, *J* = 1.9 Hz, 1H), 6.96 (d, *J* = 9.3 Hz, 1H), 4.51 – 4.36 (m, 1H), 3.63 – 3.47 (m, 2H), 2.94 (t, *J* = 4.5 Hz, 1H), 2.75 – 2.61 (m, 1H), 2.61 – 2.51 (m, 2H), 2.44 – 2.36 (m, 1H), 2.20 (s, 3H), 2.16 – 2.09 (m, 4H), 1.98 – 1.80 (m, 1H).
266		370 1.20 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.74 (dd, J=12.7, 10.0 Hz, 1 H) 3.00 (td, J=12.7, 2.6 Hz, 1 H) 3.43 - 3.66 (m, 4 H) 3.96 - 4.03 (m, 1 H) 4.15 (br d, J=12.7 Hz, 1 H) 4.34 (br d, J=12.7 Hz, 1 H) 4.75 - 4.85 (m, 1 H) 7.06 (s, 1 H) 7.12 (s, 1 H) 7.31 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 10.05 - 10.25 (m, 1 H)

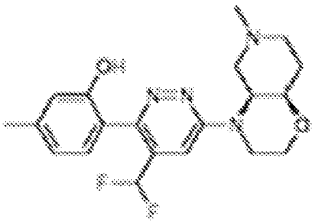
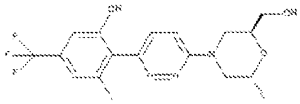
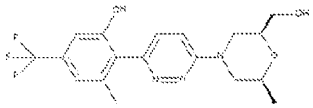
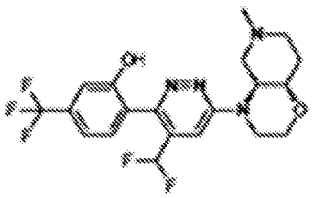
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
267		377 1.08 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.85 (s, 3 H) 2.05 (s, 3 H) 2.69 (dd, J=12.7, 10.5 Hz, 1 H) 2.99 (td, J=12.7, 3.5 Hz, 1 H) 3.23 (t, J=5.7 Hz, 2 H) 3.52 - 3.64 (m, 2 H) 4.00 (br d, J=11.5 Hz, 1 H) 4.11 (br d, J=12.7 Hz, 1 H) 4.29 (br d, J=12.7 Hz, 1 H) 6.81 (d, J=2.0 Hz, 1 H) 6.84 (d, J=2.0 Hz, 1 H) 7.29 (d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 8.00 (t, J=5.7 Hz, 1 H) 9.94 (s, 1 H)
268		445 1.04 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.77 - 1.95 (m, 2 H) 2.07 - 2.16 (m, 1 H) 2.19 (s, 3 H) 2.29 - 2.40 (m, 1 H) 2.45 - 2.58 (m partially hidden, 2 H) 3.19 - 3.28 (m partially hidden, 1 H) 3.64 (td, J=11.8, 3.8 Hz, 1 H) 3.71 - 3.78 (m, 1 H) 3.98 - 4.12 (m, 2 H) 4.41 - 4.66 (m, 1 H) 6.85 (t, J=54.3 Hz, 1 H) 7.23 (br s, 1 H) 7.27 (br d, J=7.8 Hz, 1 H) 7.35 (s, 1 H) 7.51 (d, J=7.8 Hz, 1 H) 10.50 - 10.80 (m, 1 H)
269	 HCl	393 0.95 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.77 - 1.92 (m, 1 H) 2.11 (s, 3 H) 2.14 - 2.24 (m, 1 H) 2.88 - 2.99 (m, 1 H) 2.99 - 3.10 (m, 1 H) 3.41 - 3.67 (m, 4 H) 3.91 - 3.96 (m, 1 H) 4.46 (br dt, J=13.0, 4.0 Hz, 1 H) 7.16 (br s, 1 H) 7.17 (br s, 1 H) 7.73 (d, J=9.0 Hz, 1 H) 8.14 (d, J=9.0 Hz, 1 H) 9.23 - 9.43 (m, 2 H) 10.32 - 10.52 (m, 1 H)
270		379.3 2.67 E	1H NMR (500 MHz, DMSO-d6) δ (ppm) : 10.22 (s, 1H), 7.34 (d, *J* = 9.3 Hz, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 6.96 (d, *J* = 9.3 Hz, 1H), 4.56 – 4.31 (m, 1H), 3.77 – 3.58 (m, 1H), 3.58 – 3.43 (m, 1H), 3.09 – 2.77 (m, 1H), 2.71 – 2.59 (m, 1H), 2.61 – 2.53 (m, 2H), 2.44 – 2.34 (m, 1H), 2.20 (s, 3H), 2.15 – 2.06 (m, 4H), 2.01 – 1.82 (m, 1H).
271		379.4 2.66 E	1H NMR (500 MHz, DMSO-d6) δ (ppm) : 10.14 (s, 1H), 7.34 (d, *J* = 9.3 Hz, 1H), 7.11 (s, 1H), 7.06 (s, 1H), 6.96 (d, *J* = 9.3 Hz, 1H), 4.62 – 4.26 (m, 1H), 3.67 – 3.62 (m, 1H), 3.57 – 3.50 (m, 1H), 3.00 – 2.90 (m, 1H), 2.73 – 2.62 (m, 2H), 2.61 – 2.50 (m, 2H), 2.46 – 2.33 (m, 1H), 2.20 (s, 3H), 2.18 – 2.09 (m, 3H), 2.01 – 1.79 (m, 1H).

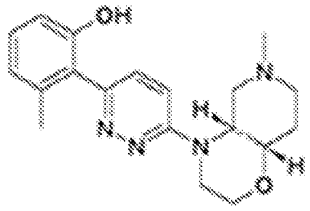
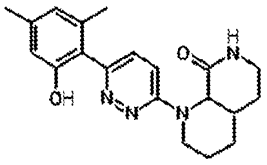
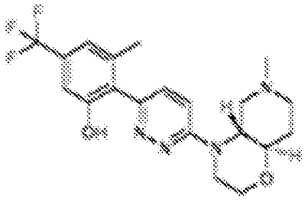
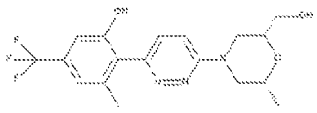
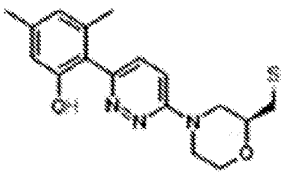
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
272		332 1.50 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.96 (quin, J=6.4 Hz, 2 H) 2.07 (s, 3 H) 2.23 (s, 3 H) 2.77 (t, J=6.4 Hz, 2 H) 3.98 (t, J=6.4 Hz, 2 H) 6.59 (br s, 1 H) 6.60 (br s, 1 H) 6.98 (br t, J=7.5 Hz, 1 H) 7.13 (br t, J=7.5 Hz, 1 H) 7.21 (br d, J=7.5 Hz, 1 H) 7.25 (br d, J=7.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 7.46 (d, J=9.5 Hz, 1 H) 9.41 (s, 1 H)
273		382 1.36 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.84 - 2.09 (m, 4 H) 2.11 (s, 3 H) 2.61 - 2.70 (m, 1 H) 3.66 - 3.84 (m, 2 H) 3.99 - 4.08 (m, 2 H) 4.70 (br t, J=5.3 Hz, 1 H) 7.10 (br s, 1 H) 7.16 (br s, 1 H) 7.67 (d, J=9.0 Hz, 1 H) 8.03 (d, J=9.0 Hz, 1 H) 10.25 - 10.50 (m, 1 H)
274		344 1.12 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.20 (d, J=7.0 Hz, 6 H) 2.05 (s, 3 H) 2.71 (dd, J=12.7, 10.0 Hz, 1 H) 2.75 - 2.83 (m, 1 H) 2.97 (br td, J=11.6, 2.6 Hz, 1 H) 3.43 - 3.65 (m, 4 H) 3.96 - 4.02 (m, 1 H) 4.12 (br d, J=12.7 Hz, 1 H) 4.31 (br d, J=12.7 Hz, 1 H) 4.80 (t, J=5.4 Hz, 1 H) 6.64 (br s, 2 H) 7.26 (d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 9.36 (s, 1 H)
275		411.4 2.46 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H), 8.06 (t, *J* = 5.9 Hz, 1H), 7.43 (d, *J* = 9.4 Hz, 1H), 7.33 (d, *J* = 9.5 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.32 (d, *J* = 12.8 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H), 4.06 – 3.97 (m, 1H), 3.67 – 3.51 (m, 2H), 3.24 (t, *J* = 5.8 Hz, 2H), 3.00 (td, *J* = 12.4, 3.5 Hz, 1H), 2.75 – 2.64 (m, 1H), 2.13 (s, 3H), 1.85 (s, 3H).
276		439.4 2.69 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.27 (s, 1H), 7.94 (t, *J* = 5.8 Hz, 1H), 7.43 (d, *J* = 9.4 Hz, 1H), 7.31 (d, *J* = 9.5 Hz, 1H), 7.11 (s, 1H), 7.08 – 7.03 (m, 1H), 4.32 (d, *J* = 12.8 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.67 – 3.51 (m, 2H), 3.30 – 3.15 (m, 2H), 3.00 (td, *J* = 12.3, 3.5 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.42 (h, *J* = 6.8 Hz, 1H), 2.13 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 6H).
277		425 1.23 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.59 - 1.68 (m, 2 H) 1.80 (s, 3 H) 2.13 (s, 3 H) 2.69 (dd, J=12.7, 10.5 Hz, 1 H) 2.98 (td, J=12.7, 3.5 Hz, 1 H) 3.08 - 3.27 (m, 2 H) 3.50 - 3.56 (m, 1 H) 3.60 (td, J=11.6, 2.5 Hz, 1 H) 3.99 (dd, J=11.6, 2.5 Hz, 1 H) 4.19 (br d, J=12.7 Hz, 1 H) 4.25 (br d, J=12.7 Hz, 1 H) 7.06 (s, 1 H) 7.11 (s, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 7.85 (br t, J=5.5 Hz, 1 H) 10.05 - 10.25 (m, 1 H)

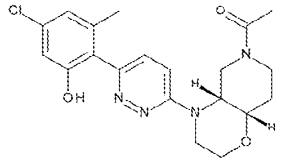
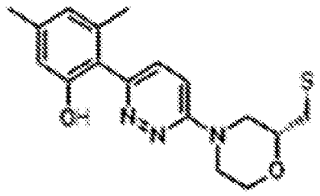
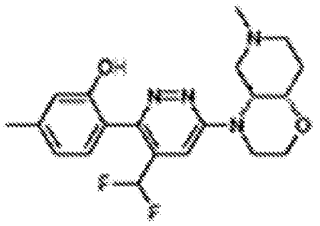
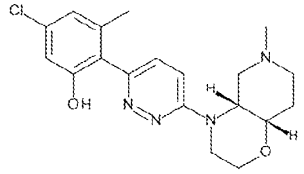
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
278		425 1.23 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.58 - 1.69 (m, 2 H) 1.80 (s, 3 H) 2.13 (s, 3 H) 2.69 (dd, J=12.7, 10.5 Hz, 1 H) 2.98 (td, J=12.7, 3.5 Hz, 1 H) 3.07 - 3.27 (m, 2 H) 3.49 - 3.56 (m, 1 H) 3.60 (td, J=11.6, 2.5 Hz, 1 H) 3.99 (dd, J=11.6, 2.5 Hz, 1 H) 4.19 (br d, J=12.7 Hz, 1 H) 4.25 (br d, J=12.7 Hz, 1 H) 7.06 (s, 1 H) 7.11 (s, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 7.41 (d, J=9.5 Hz, 1 H) 7.85 (t, J=5.5 Hz, 1 H) 10.05 - 10.25 (m, 1 H)
279		405.4 2.60 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.97 (s, 1H), 7.91 (s, 1H), 7.38 (d, J = 9.4 Hz, 1H), 7.27 (d, J = 9.4 Hz, 1H), 7.02 – 6.67 (m, 2H), 4.32 – 4.23 (m, 1H), 4.15 – 4.04 (m, 1H), 4.02 – 3.87 (m, 1H), 3.70 – 3.49 (m, 2H), 3.29 – 3.14 (m, 2H), 3.09 – 2.89 (m, 1H), 2.78 – 2.58 (m, 1H), 2.46 – 2.33 (m, 1H), 2.04 (s, 3H), 1.01 (d, J = 6.8 Hz, 6H).
280		377.3 2.47 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.96 (s, 1H), 8.03 (s, 1H), 7.38 (d, J = 9.3 Hz, 1H), 7.29 (d, J = 9.4 Hz, 1H), 6.83 (dd, J = 15.7, 2.1 Hz, 2H), 4.36 – 4.20 (m, 1H), 4.14 – 4.07 (m, 1H), 4.06 – 3.93 (m, 1H), 3.66 – 3.51 (m, 2H), 3.23 (t, J = 5.9 Hz, 2H), 3.10 – 2.85 (m, 1H), 2.75 – 2.63 (m, 1H), 2.05 (s, 3H), 1.85 (s, 3H).
283		372 1.38 B	^{1}H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.13 (s, 3 H) 2.85 (dd, J=12.6, 10.8 Hz, 1 H) 3.02 (td, J=12.6, 3.0 Hz, 1 H) 3.66 (td, J=11.5, 3.0 Hz, 1 H) 3.76 - 3.87 (m, 1 H) 4.04 (dd, J=11.5, 3.0 Hz, 1 H) 4.16 (br d, J=12.6 Hz, 1 H) 4.35 (br d, J=12.6 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 7.07 (br s, 1 H) 7.12 (br s, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 7.43 (d, J=9.5 Hz, 1 H) 10.05 - 10.24 (m, 1 H)
284		372 1.38 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.13 (s, 3 H) 2.85 (dd, J=12.6, 10.8 Hz, 1 H) 3.02 (td, J=12.6, 3.0 Hz, 1 H) 3.66 (td, J=11.5, 3.0 Hz, 1 H) 3.76 - 3.87 (m, 1 H) 4.04 (dd, J=11.5, 3.0 Hz, 1 H) 4.16 (br d, J=12.6 Hz, 1 H) 4.35 (br d, J=12.6 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 7.43 (d, J=9.5 Hz, 1 H) 10.08 - 10.20 (m, 1 H)

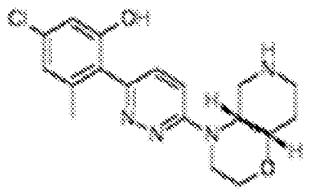
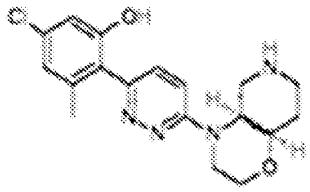
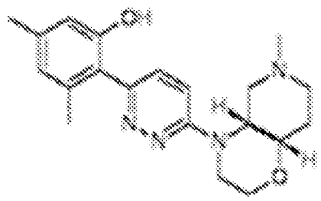
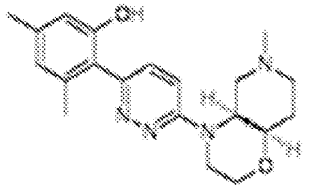
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
285		405.4 2.60 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.02 (s, 1H), 7.92 (t, *J* = 5.8 Hz, 1H), 7.38 (d, *J* = 9.4 Hz, 1H), 7.28 (d, *J* = 9.5 Hz, 1H), 6.86 – 6.79 (m, 2H), 4.29 (d, *J* = 12.7 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.66 – 3.58 (m, 1H), 3.57 – 3.51 (m, 1H), 3.29 – 3.16 (m, 2H), 3.04 – 2.95 (m, 1H), 2.73 – 2.65 (m, 1H), 2.47 – 2.39 (m, 1H), 2.05 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 6H)
286		368 1.26 B	^{1}H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.86 - 1.95 (m, 1 H) 2.08 - 2.16 (m, 1 H) 2.11 (s, 3 H) 2.43 - 2.48 (m partially hidden, 1 H) 2.81 (dd, *J*=17.3, 4.8 Hz, 1 H) 3.91 - 4.00 (m, 1 H) 4.14 - 4.24 (m, 2 H) 5.14 (d, *J*=3.5 Hz, 1 H) 7.10 (br s, 1 H) 7.16 (br s, 1 H) 7.67 (d, *J*=9.0 Hz, 1 H) 8.03 (d, *J*=9.0 Hz, 1 H) 10.18 - 10.40 (m, 1 H)
287		382 1.35 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.82 - 1.97 (m, 2 H), 1.97 - 2.09 (m, 2 H), 2.11 (s, 3 H), 2.60 - 2.77 (m, 1 H), 3.63 - 3.75 (m, 1 H), 3.75 - 3.87 (m, 1 H), 3.95 - 4.15 (m, 2 H), 4.62 - 4.77 (m, 1 H), 7.10 (br s, 1 H), 7.16 (br s, 1 H), 7.67 (d, J=9.1 Hz, 1 H), 8.03 (d, J=9.1 Hz, 1 H), 10.04 - 10.55 (m, 1 H)
288		382 1.35 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.82 - 1.97 (m, 2 H), 1.97 - 2.09 (m, 2 H), 2.11 (s, 3 H), 2.60 - 2.77 (m, 1 H), 3.63 - 3.75 (m, 1 H), 3.75 - 3.87 (m, 1 H), 3.95 - 4.15 (m, 2 H), 4.62 - 4.77 (m, 1 H), 7.10 (br s, 1 H), 7.16 (br s, 1 H), 7.67 (d, J=9.1 Hz, 1 H), 8.03 (d, J=9.1 Hz, 1 H), 10.00 - 10.62 (m, 1 H)
289		394.2 1.09 P	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.26 (s, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 9.4 Hz, 1H), 7.12 (s, 1H), 7.07 (s, 1H), 4.09 (d, *J* = 11.7 Hz, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 3.84 (t, *J* = 11.7 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.68 (t, *J* = 8.3 Hz, 1H), 3.27 – 3.22 (m, 1H), 3.01 (t, *J* = 11.9 Hz, 1H), 2.90 (t, *J* = 7.9 Hz, 1H), 2.82 (t, *J* = 9.9 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.41 (s, 3H), 2.11 (s, 3H)

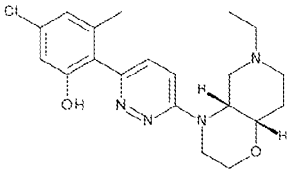
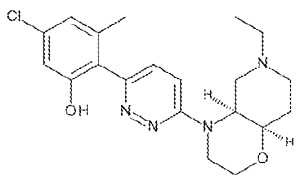
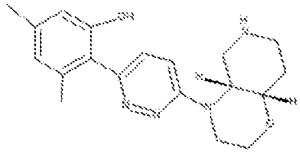
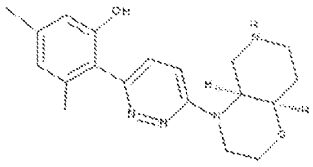
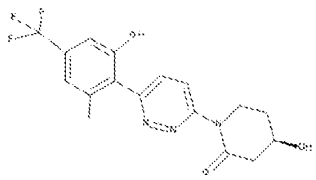
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
290		367 1.04 U	1H NMR (400 MHz, DMSO-d_6, 80°C) δ ppm 1.35 - 1.44 (m, 1 H) 1.49 - 1.61 (m, 1 H) 1.68 - 1.81 (m, 3 H) 2.08 (s, 3 H) 2.17 - 2.27 (m, 2 H) 2.22 (s, 3 H) 2.61 - 2.72 (m, 1 H) 2.82 (s, 3 H) 3.28 - 3.41 (m, 2 H) 4.30 (br d, *J*=11.8 Hz, 1 H) 5.28 (br d, *J*=4.5 Hz, 1 H) 6.56 (br s, 1 H) 6.58 (br s, 1 H) 7.15 (d, *J*=9.5 Hz, 1 H) 7.27 (d, *J*=9.5 Hz, 1 H) 8.94 - 9.81 (m, 1 H)
291		405 1.02 U	1H NMR (500 MHz, DMSO-d6, 27°C) d ppm 1.73 - 1.86 (m, 2 H), 2.05 (s, 3 H), 2.07 - 2.13 (m, 1 H), 2.17 (br s, 3 H), 2.24 (s, 3 H), 2.44 - 2.49 (m partially hidden, 1 H), 2.51 - 2.53 (m partially hidden, 1 H), 2.55 - 2.62 (m, 1 H), 3.27 - 3.31 (m partially hidden, 1 H), 3.60 - 3.78 (m, 2 H), 3.80 - 3.86 (m, 1 H), 3.89 - 3.94 (m, 1 H), 3.96 - 4.01 (m, 1 H), 6.62 (br s, 2 H), 7.20 (t, J=53.4 Hz, 1 H), 7.64 (s, 1 H), 9.46 (s, 1 H)
292		382 1.27 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.59 - 1.71 (m, 1 H) 2.04 - 2.18 (m, 2 H) 2.11 (s, 3 H) 2.30 - 2.39 (m, 1 H) 2.54 - 2.62 (m, 1 H) 3.34 - 3.46 (m, 2 H) 3.95 - 4.05 (m, 1 H) 4.11 - 4.19 (m, 1 H) 4.65 - 4.77 (m, 1 H) 7.10 (br s, 1 H) 7.16 (br s, 1 H) 7.67 (d, *J*=9.2 Hz, 1 H) 8.06 (d, *J*=9.2 Hz, 1 H) 10.17 - 10.42 (m, 1 H)
293		382 1.27 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.59 - 1.71 (m, 1 H) 2.06 - 2.18 (m, 2 H) 2.11 (s, 3 H) 2.30 - 2.40 (m, 1 H) 2.53 - 2.62 (m, 1 H) 3.34 - 3.46 (m, 2 H) 3.95 - 4.05 (m, 1 H) 4.11 - 4.19 (m, 1 H) 4.66 - 4.76 (m, 1 H) 7.10 (br s, 1 H) 7.15 (br s, 1 H) 7.67 (d, *J*=9.2 Hz, 1 H) 8.06 (d, *J*=9.2 Hz, 1 H) 10.09 - 10.40 (m, 1 H)

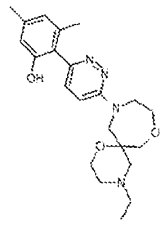
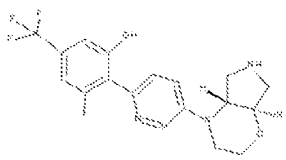
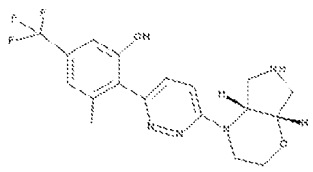
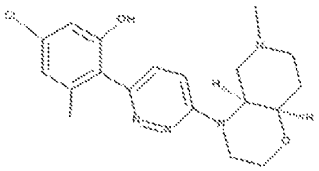
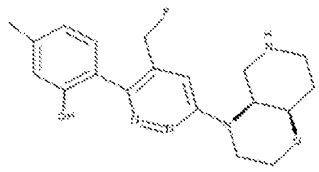
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
295		391 0.93 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.75 - 1.84 (m, 1 H), 1.84 - 1.95 (m, 1 H), 2.08 - 2.16 (m, 1 H), 2.19 (br s, 3 H), 2.30 (s, 3 H), 2.31 - 2.40 (m, 1 H), 2.52 - 2.58 (m partially hidden, 2 H), 3.21 (br td, J=3.8 and 12.7 Hz, 1 H), 3.63 (td, J=3.2 and 11.8 Hz, 1 H), 3.72 - 3.77 (m, 1 H), 3.99 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=3.8 and 11.8 Hz, 1 H), 4.48 - 4.57 (m, 1 H), 6.77 (t, J=54.8 Hz, 1 H), 6.74 - 6.78 (m, 1 H), 6.77 (s, 1 H), 7.15 (d, J=7.5 Hz, 1 H), 7.31 (br s, 1 H), 9.78 (s, 1 H)
296		384 1.20 B	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.20 (d, J=6.4 Hz, 3 H) 2.16 (s, 3 H) 3.28 (dd, J=12.8, 7.3 Hz, 1 H) 3.49 - 3.64 (m, 3 H) 3.74 (dd, J=12.8, 3.6 Hz, 1 H) 3.82 (dd, J=12.8, 3.6 Hz, 1 H) 3.86 - 3.95 (m, 1 H) 4.01 - 4.13 (m, 1 H) 4.16 - 4.48 (m, 1 H) 7.06 (s, 2 H) 7.19 (d, J=9.4 Hz, 1 H) 7.36 (d, J=9.4 Hz, 1 H) 9.66 - 9.90 (m, 1 H)
297		384 1.24 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.20 (d, J=6.1 Hz, 3 H) 2.13 (s, 3 H) 2.53 - 2.69 (m, 2 H) 3.41 - 3.77 (m, 4 H) 4.27 (br d, J=12.4 Hz, 1 H) 4.38 (br d, J=12.6 Hz, 1 H) 4.80 (br t, J=5.3 Hz, 1 H) 7.06 (s, 1 H) 7.12 (s, 1 H) 7.31 (d, J=9.4 Hz, 1 H) 7.40 (d, J=9.4 Hz, 1 H) 10.13 (s, 1 H)
298		445 1.03 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.71 - 1.99 (m, 2 H), 2.05 - 2.15 (m, 1 H), 2.19 (s, 3 H), 2.31 - 2.42 (m, 1 H), 2.43 - 2.62 (m hidden, 2 H), 3.13 - 3.33 (m partially hidden, 1 H), 3.64 (td, J=11.9, 3.3 Hz, 1 H), 3.75 (q, J=2.8 Hz, 1 H), 3.96 - 4.10 (m, 2 H), 4.48 - 4.60 (m, 1 H), 6.85 (t, J=54.3 Hz, 1 H), 7.23 (s, 1 H), 7.27 (br d, J=7.8 Hz, 1 H), 7.35 (s, 1 H), 7.51 (d, J=7.8 Hz, 1 H), 10.34 - 11.03 (m, 1 H)

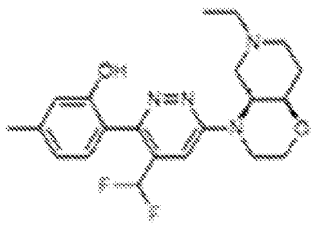
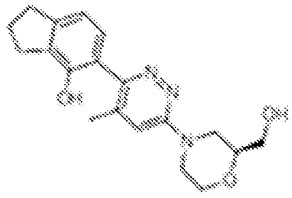
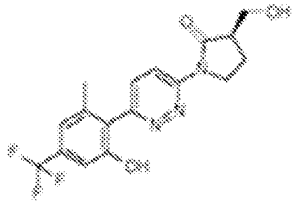
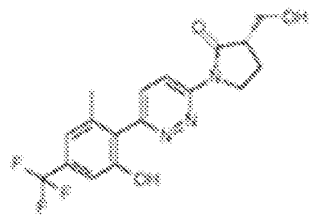
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
299		341 0.73 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.73 - 1.97 (m, 2 H), 2.06 (s, 3 H), 2.04 - 2.15 (m, 1 H), 2.18 (s, 3 H), 2.28 - 2.39 (m, 1 H), 2.44 - 2.58 (m, hidden, 2 H), 3.16 (td, J=12.6, 3.9 Hz, 1 H), 3.63 (td, J=11.8, 3.1 Hz, 1 H), 3.74 (q, J=2.8 Hz, 1 H), 3.90 - 3.96 (m, 1 H), 4.05 (dd, J=11.8, 3.5 Hz, 1 H), 4.35 - 4.48 (m, 1 H), 6.70 - 6.81 (m, 2 H), 7.10 (t, J=7.8 Hz, 1 H), 7.21 (d, J=9.4 Hz, 1 H), 7.36 (d, J=9.4 Hz, 1 H), 9.42 (s, 1 H)
300		353 1.00 U	1H NMR (400 MHz, DMSO-d_6, 80°C) δ ppm 1.37 - 1.50 (m, 1 H) 1.50 - 1.62 (m, 1 H) 1.68 - 1.77 (m, 2 H) 1.77 - 1.85 (m, 1 H) 2.10 (s, 3 H) 2.11 - 2.27 (m, 2 H) 2.24 (s, 3 H) 2.75 (td, *J*=12.6, 2.8 Hz, 1 H) 3.17 - 3.34 (m, 2 H) 4.33 (br d, *J*=12.6 Hz, 1 H) 5.26 (br d, *J*=5.1 Hz, 1 H) 6.58 (br s, 1 H) 6.60 (br s, 1 H) 7.18 (d, *J*=9.5 Hz, 1 H) 7.26 (br s, 1 H) 7.29 (d, *J*=9.5 Hz, 1 H) 9.15 - 9.59 (m, 1 H)
301		409.5 2.61 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) : 10.23 (s, 1H), 7.50 (d, *J* = 9.1 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.13 (s, 1H), 7.08 (s, 1H), 3.93 (dt, *J* = 11.0, 4.4 Hz, 1H), 3.86 (ddd, *J* = 11.1, 8.3, 3.3 Hz, 1H), 3.68 (dt, *J* = 13.3, 4.1 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.48 – 3.39 (m, 3H), 2.83 (d, *J* = 11.4 Hz, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 2.10 – 2.02 (m, 1H), 1.89 – 1.80 (m, 1H), 1.75 (t, *J* = 9.7 Hz, 1H), 1.64 (qd, *J* = 12.1, 4.3 Hz, 1H).
302		384 1.25 B	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.20 (d, J=6.3 Hz, 3 H) 2.13 (s, 3 H) 2.52 - 2.68 (m, 2 H) 3.39 - 3.62 (m, 3 H) 3.63 - 3.74 (m, 1 H) 4.27 (br d, J=12.1 Hz, 1 H) 4.38 (br d, J=12.5 Hz, 1 H) 4.80 (t, J=5.7 Hz, 1 H) 7.06 (s, 1 H) 7.12 (s, 1 H) 7.31 (d, J=9.4 Hz, 1 H) 7.40 (d, J=9.4 Hz, 1 H) 10.13 (s, 1 H)
303		332 1.12 U	1H NMR (400 MHz, DMSO-d_6, 80°C) δ ppm 2.08 (s, 3 H) 2.24 (s, 3 H) 2.31 (br t, *J*=8.1 Hz, 1 H) 2.70 (dd, *J*=8.1, 5.9 Hz, 2 H) 2.94 (dd, *J*=13.1, 10.1 Hz, 1 H) 3.14 (ddd, *J*=13.1, 11.3, 3.6 Hz, 1 H) 3.57 - 3.71 (m, 2 H) 4.02 (ddd, *J*=11.3, 3.6, 2.0 Hz, 1 H) 4.10 (d, *J*=13.1 Hz, 1 H) 4.35 (br d, *J*=13.1 Hz, 1 H) 6.62 (br s, 1 H) 6.63 (br s, 1 H) 7.57 (d, *J*=9.5 Hz, 1 H) 7.64 (d, *J*=9.5 Hz, 1 H)

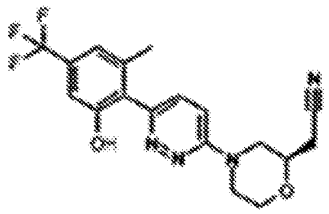
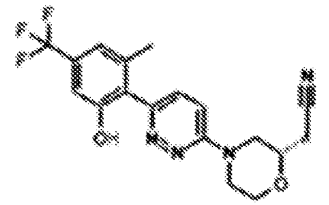
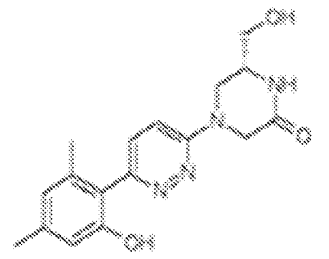
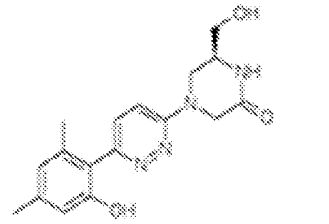
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
304		403 1.19 U	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 1.79 - 1.89 (m, 2 H) 2.01 (s, 3 H) 2.08 (s, 3 H) 2.73 - 3.16 (m, 4 H) 3.25 (br td, *J*=12.6, 3.8 Hz, 1 H) 3.70 (br td, *J*=11.8, 3.2 Hz, 1 H) 3.83 - 3.92 (m, 1 H) 3.99 (br d, *J*=12.6 Hz, 1 H) 4.09 (br dd, *J*=11.8, 3.8 Hz, 1 H) 4.26 - 4.39 (m, 1 H) 6.79 - 6.83 (m, 2 H) 7.21 (br d, *J*=9.5 Hz, 1 H) 7.37 (d, *J*=9.5 Hz, 1 H) 9.36 - 9.72 (m, 1 H)
305		332 1.11 U	1H NMR (400 MHz, DMSO-d_6, 80°C) δ ppm 2.07 (s, 3 H) 2.24 (s, 3 H) 2.31 (br t, *J*=8.1 Hz, 1 H) 2.70 (dd, *J*=8.1, 5.9 Hz, 2 H) 2.89 (dd, *J*=13.1, 10.1 Hz, 1 H) 3.10 (ddd, *J*=13.1, 11.3, 3.6 Hz, 1 H) 3.56 - 3.70 (m, 2 H) 4.01 (ddd, *J*=11.3, 3.6, 2.0 Hz, 1 H) 4.09 (br d, *J*=13.1 Hz, 1 H) 4.35 (br d, *J*=13.1 Hz, 1 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 7.42 (d, *J*=9.5 Hz, 1 H) 7.51 (d, *J*=9.5 Hz, 1 H)
306		391 0.92 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.83 (m, 1 H), 1.85 - 1.96 (m, 1 H), 2.11 (br t, J=11.1 Hz, 1 H), 2.18 (s, 3 H), 2.30 (s, 3 H), 2.31 - 2.41 (m, 1 H), 2.44 - 2.57 (m hidden, 2 H), 3.21 (td, J=12.7, 3.9 Hz, 1 H), 3.63 (td, J=11.8, 3.1 Hz, 1 H), 3.74 (br q, J=2.6 Hz, 1 H), 3.99 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=11.8, 3.5 Hz, 1 H), 4.46 - 4.58 (m, 1 H), 6.59 - 6.99 (m, 3 H), 7.15 (d, J=7.5 Hz, 1 H), 7.31 (s, 1 H), 9.79 (s, 1 H)
307		375 0.89 U	1H NMR (400 MHz, DMSO-d6, 80°C) δ ppm 1.74 - 1.83 (m, 1 H) 1.83 - 1.94 (m, 1 H) 1.95 - 2.06 (m, 1 H) 2.07 (s, 3 H) 2.08 - 2.17 (m, 1 H) 2.19 (s, 3 H) 2.31 - 2.42 (m, 1 H) 2.50 - 2.61 (m partially hidden, 1 H) 3.19 (td, J=12.8, 4.0 Hz, 2 H) 3.64 (td, J=11.6, 3.3 Hz, 1 H) 3.74 (q, J=2.8 Hz, 1 H) 3.93 (dd, J=12.8, 2.6 Hz, 1 H) 4.04 (dd, J=11.6, 3.5 Hz, 1 H) 4.31 - 4.44 (m, 1 H) 6.81 (s, 1 H) 7.17 (d, J=9.4 Hz, 1 H) 7.33 (d, J=9.4 Hz, 1 H) 9.55 - 9.85 (m, 1 H)

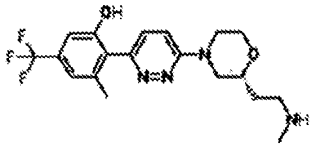
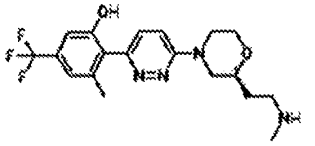
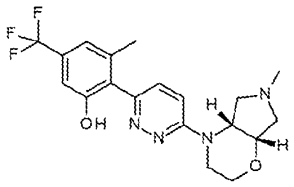
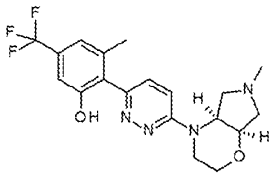
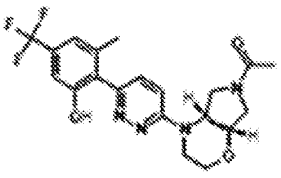
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
308		361 0.88 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.70 - 1.83 (m, 2 H), 2.05 (s, 3 H), 2.57 - 2.70 (m, 3 H), 2.92 (br t, J=11.4 Hz, 1 H), 3.05 - 3.20 (m, 1 H), 3.62 (td, J=11.8, 3.1 Hz, 1 H), 3.83 (br q, J=2.4 Hz, 1 H), 3.98 (br d, J=12.5 Hz, 1 H), 4.06 (dd, J=11.8, 3.4 Hz, 1 H), 4.18 - 4.29 (m, 1 H), 6.80 - 6.82 (m, 1 H), 6.83 - 6.84 (m, 1 H), 7.21 (d, J=9.5 Hz, 1 H), 7.34 (d, J=9.5 Hz, 1 H), 9.03 - 10.74 (m, 1 H)
309		361 0.88 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.72 - 1.84 (m, 2 H), 2.05 (s, 3 H), 2.58 - 2.73 (m, 3 H), 2.92 (br t, J=10.8 Hz, 1 H), 3.07 - 3.22 (m, 1 H), 3.62 (br t, J=10.6 Hz, 1 H), 3.79 - 3.88 (m, 1 H), 3.98 (br d, J=12.8 Hz, 1 H), 4.06 (br dd, J=10.8, 2.6 Hz, 1 H), 4.17 - 4.31 (m, 1 H), 6.80 - 6.82 (m, 1 H), 6.83 - 6.85 (m, 1 H), 7.21 (br d, J=9.1 Hz, 1 H), 7.35 (br d, J=9.1 Hz, 1 H), 9.12 - 10.57 (m, 1 H)
310		355 1.11 Z1	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.72 - 1.83 (m, 1 H), 1.83 - 1.95 (m, 1 H), 2.03 (s, 3 H), 2.05 - 2.14 (m, 1 H), 2.18 (s, 3 H), 2.22 (s, 3 H), 2.28 - 2.38 (m, 1 H), 2.46 - 2.57 (m hidden, 2 H), 3.15 (td, J=12.6, 3.9 Hz, 1 H), 3.63 (td, J=11.4, 3.2 Hz, 1 H), 3.74 (br q, J=2.6 Hz, 1 H), 3.92 (br dd, J=12.8, 2.0 Hz, 1 H), 4.05 (dd, J=11.4, 3.4 Hz, 1 H), 4.36 - 4.43 (m, 1 H), 6.56 - 6.58 (m, 1 H), 6.58 - 6.59 (m, 1 H), 7.20 (d, J=9.5 Hz, 1 H), 7.33 (d, J=9.5 Hz, 1 H), 9.36 (s, 1 H)
311		355 0.81 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.75 - 1.93 (m, 2 H), 2.03 (s, 3 H), 2.04 - 2.14 (m, 1 H), 2.18 (s, 3 H), 2.22 (s, 3 H), 2.28 - 2.37 (m, 1 H), 2.51 - 2.56 (m hidden, 2 H), 3.16 (td, J=3.8 and 12.6 Hz, 1 H), 3.63 (td, J=3.2 and 11.8 Hz, 1 H), 3.74 (q, J=2.8 Hz, 1 H), 3.92 (br d, J=12.6 Hz, 1 H), 4.05 (dd, J=3.6 and 11.8 Hz, 1 H), 4.36 - 4.44 (m, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 7.20 (d, J=9.5 Hz, 1 H), 7.34 (d, J=9.5 Hz, 1 H), 9.36 (s, 1 H)

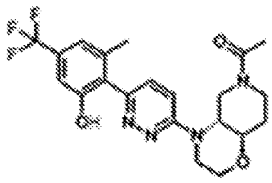
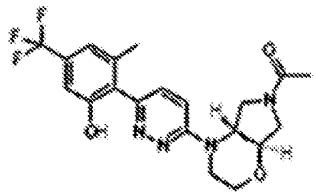
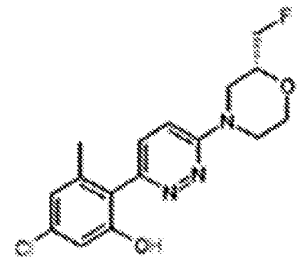
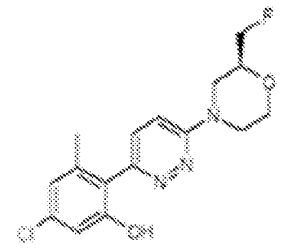
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
312		389 0.92 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.97 (t, *J*=7.3 Hz, 3 H) 1.76 - 1.90 (m, 2 H) 2.02 - 2.13 (m, 1 H) 2.05 (s, 3 H) 2.31 - 2.42 (m, 3 H) 2.55 - 2.65 (m, 2 H) 3.17 (td, *J*=12.7, 3.8 Hz, 1 H) 3.62 (td, *J*=11.8, 3.3 Hz, 1 H) 3.75 (br q, *J*=2.8 Hz, 1 H) 3.94 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.36 - 4.44 (m, 1 H) 6.81 (d, *J*=2.0 Hz, 1 H) 6.84 (d, *J*=2.0 Hz, 1 H) 7.21 (d, *J*=9.5 Hz, 1 H) 7.35 (d, *J*=9.5 Hz, 1 H) 9.89 - 10.03 (m, 1 H)
313		389 0.92 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.97 (t, *J*=7.3 Hz, 3 H) 1.76 - 1.90 (m, 2 H) 2.02 - 2.13 (m, 1 H) 2.05 (s, 3 H) 2.31 - 2.41 (m, 3 H) 2.56 - 2.65 (m, 2 H) 3.17 (td, *J*=12.7, 3.8 Hz, 1 H) 3.62 (td, *J*=11.8, 3.3 Hz, 1 H) 3.75 (br q, *J*=2.8 Hz, 1 H) 3.94 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.36 - 4.44 (m, 1 H) 6.81 (d, *J*=2.0 Hz, 1 H) 6.84 (d, *J*=2.0 Hz, 1 H) 7.21 (d, *J*=9.5 Hz, 1 H) 7.35 (d, *J*=9.5 Hz, 1 H) 9.88 - 10.04 (m, 1 H)
314		341 1.61 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.69 - 1.82 (m, 2 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.60 - 2.69 (m, 3 H) 2.92 (t, *J*=11.8 Hz, 1 H) 3.14 (td, *J*=12.6, 3.8 Hz, 1 H) 3.62 (td, *J*=11.8, 3.2 Hz, 1 H) 3.83 (br q, *J*=2.6 Hz, 1 H) 3.97 (br d, *J*=12.6 Hz, 1 H) 4.06 (dd, *J*=11.8, 3.6 Hz, 1 H) 4.17 - 4.24 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.19 (d, *J*=9.5 Hz, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 9.38 (br s, 1 H)
315		341 1.61 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.69 - 1.82 (m, 2 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.60 - 2.69 (m, 3 H) 2.92 (t, *J*=11.8 Hz, 1 H) 3.14 (td, *J*=12.6, 3.8 Hz, 1 H) 3.62 (td, *J*=11.8, 3.2 Hz, 1 H) 3.83 (br q, *J*=2.6 Hz, 1 H) 3.96 (br d, *J*=12.6 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.6 Hz, 1 H) 4.17 - 4.25 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.19 (d, *J*=9.5 Hz, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 9.38 (br s, 1 H)
316		368 2.05 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.86 - 1.96 (m, 1 H) 2.07 - 2.15 (m, 1 H) 2.11 (s, 3 H) 2.43 - 2.48 (m partially hidden, 1 H) 2.81 (dd, *J*=17.3, 4.8 Hz, 1 H) 3.90 - 4.00 (m, 1 H) 4.13 - 4.24 (m, 2 H) 5.15 (br d, *J*=3.5 Hz, 1 H) 7.10 (br s, 1 H) 7.16 (br s, 1 H) 7.67 (d, *J*=9.0 Hz, 1 H) 8.03 (d, *J*=9.0 Hz, 1 H) 10.17 - 10.42 (m, 1 H)

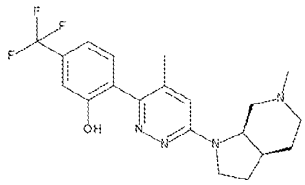
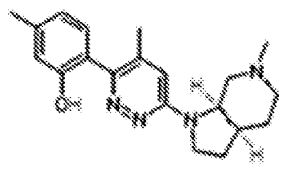
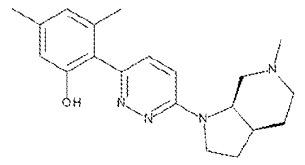
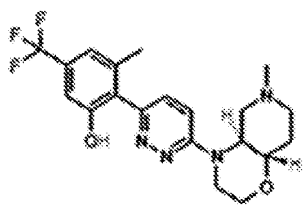
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
317		399.4 3.02 E	1H NMR (500 MHz, DMSO-d6) δ (ppm): 9.44 (s, 1H), 7.30 (d, J = 9.5 Hz, 1H), 7.25 (d, J = 9.5 Hz, 1H), 6.65 – 6.51 (m, 2H), 4.04 (d, J = 15.0 Hz, 1H), 3.96 (s, 2H), 3.85 – 3.67 (m, 5H), 3.68 – 3.55 (m, 2H), 3.46 – 3.39 (m, 2H), 2.41 – 2.25 (m, 4H), 2.23 (s, 3H), 2.04 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H)
318	 HCl	381.3 2.44 E	1H NMR (500 MHz, DMSO-d6) δ (ppm): 10.37 (s, 1H), 9.32 (d, J = 27.9 Hz, 1H), 7.63 (s, 2H), 7.15 (s, 1H), 7.13 (s, 1H), 4.45 – 4.37 (m, 1H), 4.23 – 4.16 (m, 1H), 3.97 (d, J = 12.4 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.85 – 3.76 (m, 1H), 3.36 – 3.28 (m, 1H), 3.27 – 3.19 (m, 1H), 3.12 – 3.01 (m, 2H), 2.13 (s, 3H). (one proton hidden with water pic, confirmed by HSQC)
320	 HCl	381.4 2.37 E	^{1}H NMR (400 MHz, MeOD) δ (ppm): 8.22 – 7.92 (m, 2H), 7.22 (s, 1H), 7.12 (s, 1H), 5.22 – 5.14 (m, 1H), 4.41 – 4.36 (m, 1H), 4.24 – 4.18 (m, 1H), 4.07 (d, *J* = 13.2 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.84 – 3.77 (m, 1H), 3.63 – 3.52 (m, 2H), 3.50 – 3.39 (m, 2H), 2.29 (s, 3H). (OH and NH not visible)
321		375 0.89 U	1H NMR (400 MHz, DMSO-d6, 80°C) δ ppm 1.74 - 1.82 (m, 1 H) 1.83 - 1.94 (m, 1 H) 1.95 - 2.05 (m, 1 H) 2.04 (s, 3 H) 2.08 - 2.17 (m, 1 H) 2.18 (s, 3 H) 2.30 - 2.40 (m, 1 H) 2.48 - 2.57 (mpartially hidden, 1 H) 3.12 - 3.24 (m, 1 H) 3.63 (td, J=11.6, 3.4 Hz, 1 H) 3.74 (q, J=2.9 Hz, 1 H) 3.91 (dd, J=13.1, 2.6 Hz, 1 H) 4.03 (dd, J=11.6, 3.4 Hz, 1 H) 4.33 - 4.43 (m, 1 H) 6.47 (br s, 1 H) 6.58 (br s, 1 H) 7.09 (d, J=9.4 Hz, 1 H) 7.36 (d, J=9.4 Hz, 1 H)
322		377 0.42 and 1.75 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.74 - 1.83 (m, 2 H) 2.29 (s, 3 H) 2.61 - 2.72 (m, 3 H) 2.97 (t, *J*=11.8 Hz, 1 H) 3.20 (td, *J*=12.6, 3.8 Hz, 1 H) 3.63 (td, *J*=11.8, 3.2 Hz, 1 H) 3.85 (br q, *J*=2.6 Hz, 1 H) 4.00 - 4.13 (m, 2 H) 4.26 - 4.42 (m, 1 H) 6.77 (t, *J*=54.8 Hz, 1 H) 6.73 - 6.79 (m, 2 H) 7.15 (d, *J*=7.5 Hz, 1 H) 7.31 (s, 1 H) 9.58 - 10.03 (m, 1 H)

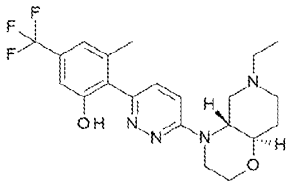
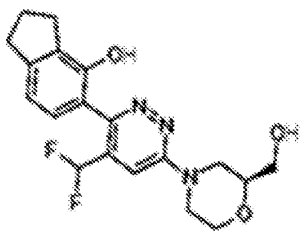
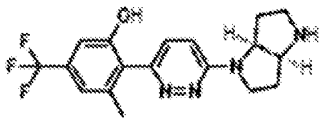
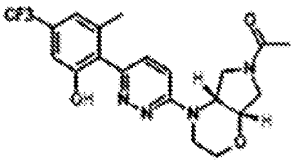
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
323		405 1.80 G	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.97 (t, J=7.1 Hz, 3 H), 1.76 - 1.94 (m, 2 H), 2.10 (td, J=11.7, 3.2 Hz, 1 H), 2.30 (s, 3 H), 2.32 - 2.44 (m, 3 H), 2.57 - 2.66 (m, 2 H), 3.22 (td, J=12.7, 3.8 Hz, 1 H), 3.63 (td, J=11.9, 3.1 Hz, 1 H), 3.76 (q, J=2.8 Hz, 1 H), 3.99 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=11.9, 3.8 Hz, 1 H), 4.51 (br d, J=10.1 Hz, 1 H), 6.59 - 6.92 (m, 3 H), 7.16 (d, J=7.6 Hz, 1 H), 7.30 (s, 1 H), 9.80 (br s, 1 H)
324		342 1.84 G	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.99 - 2.10 (m, 2 H), 2.16 (s, 3 H), 2.70 (dd, J=12.6, 9.8 Hz, 1 H), 2.84 (t, J=7.5 Hz, 2 H), 2.89 (t, J=7.6 Hz, 2 H), 2.96 (td, J=12.3, 3.5 Hz, 1 H), 3.40 - 3.57 (m, 3 H), 3.60 (td, J=11.5, 2.6 Hz, 1 H), 3.98 (br dd, J=11.5, 2.2 Hz, 1 H), 4.13 (br d, J=12.3 Hz, 1 H), 4.29 (br d, J=12.6 Hz, 1 H), 4.80 (t, J=5.5 Hz, 1 H), 6.80 (d, J=7.6 Hz, 1 H), 7.01 (d, J=7.6 Hz, 1 H), 7.17 (s, 1 H), 9.40 (s, 1 H)
325		368 2.17 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.11 (s, 3 H) 2.12 - 2.21 (m, 1 H) 2.21 - 2.32 (m, 1 H) 2.82 - 2.89 (m, 1 H) 3.64 - 3.72 (m, 1 H) 3.75 - 3.82 (m, 1 H) 4.01 - 4.08 (m, 1 H) 4.15 - 4.22 (m, 1 H) 4.87 (br t, *J*=5.0 Hz, 1 H) 7.09 (br s, 1 H) 7.15 (br s, 1 H) 7.72 (d, *J*=9.3 Hz, 1 H) 8.63 (d, *J*=9.3 Hz, 1 H) 9.82 - 10.66 (m, 1 H)
326		368 2.17 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.11 (s, 3 H) 2.12 - 2.21 (m, 1 H) 2.21 - 2.31 (m, 1 H) 2.81 - 2.90 (m, 1 H) 3.62 - 3.73 (m, 1 H) 3.74 - 3.83 (m, 1 H) 4.00 - 4.08 (m, 1 H) 4.15 - 4.22 (m, 1 H) 4.87 (br t, *J*=5.0 Hz, 1 H) 7.09 (br s, 1 H) 7.15 (s, 1 H) 7.72 (d, *J*=9.3 Hz, 1 H) 8.63 (d, *J*=9.3 Hz, 1 H) 9.99 - 10.52 (m, 1 H)

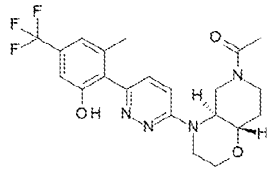
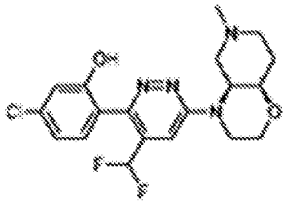
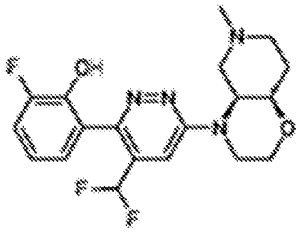
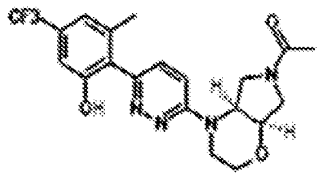
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
327		379 2.14 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.12 (s, 3 H) 2.76 - 2.88 (m, 2 H) 2.91 - 2.98 (m, 1 H) 3.03 (td, *J*=12.6, 2.8 Hz, 1 H) 3.69 (td, *J*=11.5, 2.8 Hz, 1 H) 3.76 - 3.89 (m, 1 H) 4.05 (dd, *J*=11.5, 2.8 Hz, 1 H) 4.13 (br d, *J*=12.6 Hz, 1 H) 4.43 (br d, *J*=12.6 Hz, 1 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.32 (d, *J*=9.5 Hz, 1 H) 7.44 (d, *J*=9.5 Hz, 1 H) 9.82 - 10.58 (m, 1 H)
328		379 2.13 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.12 (s, 3 H) 2.76 - 2.88 (m, 2 H) 2.91 - 2.99 (m, 1 H) 3.03 (td, *J*=12.6, 2.8 Hz, 1 H) 3.69 (td, *J*=11.5, 2.8 Hz, 1 H) 3.76 - 3.89 (m, 1 H) 4.05 (dd, *J*=11.5, 2.8 Hz, 1 H) 4.13 (br d, *J*=12.6 Hz, 1 H) 4.43 (br d, *J*=12.6 Hz, 1 H) 7.06 (br s, 1 H) 7.12 (br s, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 7.45 (d, *J*=9.5 Hz, 1 H) 9.95 - 10.42 (m, 1 H)
329		329 1.7 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 3.35 - 3.53 (m, 3 H) 3.78 (dd, *J*=13.2, 5.5 Hz, 1 H) 3.92 (dd, *J*=13.2, 3.5 Hz, 1 H) 4.03 - 4.18 (m, 2 H) 4.97 (br t, *J*=5.3 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.26 (d, *J*=9.5 Hz, 1 H) 7.35 (d, *J*=9.5 Hz, 1 H) 8.05 (br s, 1 H) 9.35 (br s, 1 H)
330		329 1.7 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.03 (s, 3 H) 2.22 (s, 3 H) 3.35 - 3.52 (m, 3 H) 3.78 (dd, *J*=13.2, 5.5 Hz, 1 H) 3.92 (dd, *J*=13.2, 3.5 Hz, 1 H) 4.04 - 4.17 (m, 2 H) 4.98 (br t, *J*=5.3 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.26 (d, *J*=9.5 Hz, 1 H) 7.35 (d, *J*=9.5 Hz, 1 H) 8.05 (br s, 1 H) 9.36 (br s, 1 H)

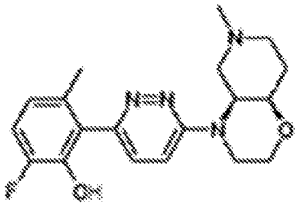
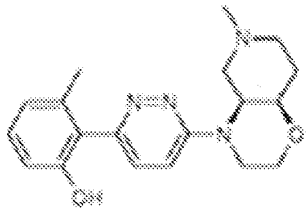
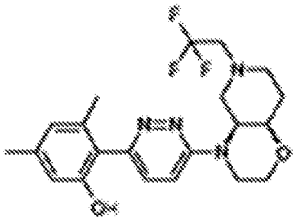
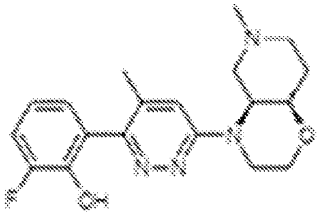
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
331		397 1.75 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.64 (q, *J*=6.9 Hz, 2 H) 2.13 (s, 3 H) 2.29 (s, 3 H) 2.61 (br t, *J*=6.9 Hz, 2 H) 2.65 - 2.72 (m, 1 H) 2.98 (td, *J*=12.3, 3.4 Hz, 1 H) 3.55 - 3.63 (m, 2 H) 3.98 (br dd, *J*=12.3, 2.4 Hz, 1 H) 4.16 (br d, *J*=13.0 Hz, 1 H) 4.26 (br d, *J*=13.0 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.32 (d, *J*=9.5 Hz, 1 H) 7.41 (d, *J*=9.5 Hz, 1 H)
332		397 1.74 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.64 (q, *J*=6.9 Hz, 2 H) 2.13 (s, 3 H) 2.29 (s, 3 H) 2.61 (t, *J*=6.9 Hz, 2 H) 2.65 - 2.73 (m, 1 H) 2.98 (br td, *J*=12.3, 3.4 Hz, 1 H) 3.54 - 3.64 (m, 2 H) 3.98 (br dd, *J*=12.3, 2.4 Hz, 1 H) 4.16 (br d, *J*=13.0 Hz, 1 H) 4.26 (br d, *J*=13.0 Hz, 1 H) 7.06 (br s, 1 H) 7.11 (s, 1 H) 7.32 (d, *J*=9.5 Hz, 1 H) 7.41 (d, *J*=9.5 Hz, 1 H)
333		395.4 2.5 E	1H NMR (500 MHz, DMSO) δ (ppm): 10.16 (s, 1H), 7.42 (d, J = 9.4 Hz, 1H), 7.29 (d, J = 9.5 Hz, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 4.60 (s, 1H), 4.13 (t, J = 4.7 Hz, 1H), 3.99 (dd, J = 11.2, 3.7 Hz, 2H), 3.59 (td, J = 11.8, 2.8 Hz, 1H), 3.23 – 3.10 (m, 2H), 2.97 (t, J = 7.8 Hz, 1H), 2.58 (m, 2H), 2.38 (s, 3H), 2.13 (s, 3H), 1.24 (s, 1H).
334		395.4 2.5 E	1H NMR (500 MHz, DMSO) δ (ppm): 10.25 – 10.03 (m, 1H), 7.41 (d, J = 9.4 Hz, 1H), 7.28 (d, J = 9.4 Hz, 1H), 7.12 (s, 1H), 7.07 (s, 1H), 4.55 (m, 1H), 4.12 (t, J = 4.8 Hz, 1H), 4.03 – 3.95 (m, 2H), 3.58 (td, J = 11.8, 2.9 Hz, 1H), 3.20 – 3.09 (m, 2H), 2.91 (t, J = 7.7 Hz, 1H), 2.58 – 2.53 (m, 2H), 2.33 (s, 3H), 2.13 (s, 3H).
335		423.4 2.53 E	^{1}H NMR (500 MHz, *DMSO-d6)* δ (ppm): 9.80 (s, 1H), 7.48 – 7.39 (m, 1H), 7.38 – 7.26 (m, 1H), 7.18 – 7.07 (m, 2H), 5.06 – 4.73 (m, 1H), 4.31 – 4.10 (m, 1H), 4.11 – 3.95 (m, 2H), 3.91 – 3.80 (m, 1H), 3.70 (t, *J* = 11.7 Hz, 1H), 3.59 – 3.42 (m, 2H), 3.32 – 3.15 (m, 2H), 2.17 (s, 3H), 1.96 (s, 3H).

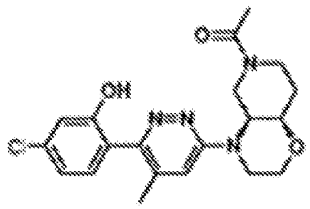
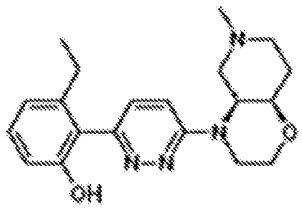
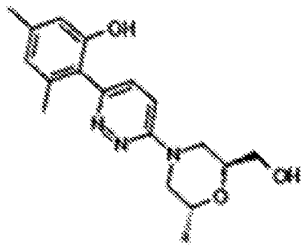
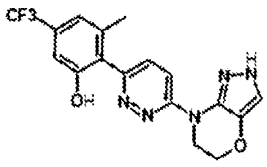
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
336		437.5 2.59 E	^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm): 11.47 (s, 1H), 7.74 (d, *J* = 9.6 Hz, 1H), 7.51 – 7.28 (m, 1H), 7.19 (d, *J* = 5.4 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 5.15 – 4.92 (m, 1H), 4.18 – 4.08 (m, 2H), 4.07 – 4.01 (m, 1H), 3.98 – 3.91 (m, 1H), 3.89 – 3.85 (m, 1H), 3.78 – 3.69 (m, 1H), 3.54 – 3.36 (m, 1H), 3.34 – 3.19 (m, 1H), 2.77 – 2.64 (m, 2H), 2.54 (s, 3H), 2.29 – 2.13 (m, 3H), 2.12 – 1.96 (m, 1H)
337		423.4 2.55 E	^{1}H NMR (500 MHz, CD2Cl2) δ (ppm): 11.36 (s, 1H), 7.66 (t, *J* = 10.0 Hz, 1H), 7.23 (t, *J* = 9.8 Hz, 1H), 7.16 (s, 1H), 7.10 (d, *J* = 4.2 Hz, 1H), 4.83 – 4.74 (m, 1H), 4.24 – 4.16 (m, 1H), 4.06 – 3.97 (m, 1H), 3.96 – 3.68 (m, 3H), 3.53 – 3.15 (m, 4H), 2.48 (m, 3H), 2.04 (m, 3H).
338		338 2.08 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.05 (s, 3 H) 2.83 (dd, *J*=12.6, 10.8 Hz, 1 H) 3.00 (td, *J*=12.6, 3.0 Hz, 1 H) 3.66 (td, *J*=11.5, 3.0 Hz, 1 H) 3.74 - 3.87 (m, 1 H) 4.03 (br dd, *J*=11.5, 3.0 Hz, 1 H) 4.15 (br d, *J*=12.6 Hz, 1 H) 4.33 (br d, *J*=12.6 Hz, 1 H) 4.44 - 4.66 (m, 2 H) 6.81 (d, *J*=2.0 Hz, 1 H) 6.84 (d, *J*=2.0 Hz, 1 H) 7.31 (d, *J*=9.5 Hz, 1 H) 7.39 (d, *J*=9.5 Hz, 1 H) 9.84 - 10.10 (m, 1 H)
339		338 2.08 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.05 (s, 3 H) 2.83 (dd, *J*=12.6, 10.8 Hz, 1 H) 3.00 (td, *J*=12.6, 3.0 Hz, 1 H) 3.66 (td, *J*=11.5, 3.0 Hz, 1 H) 3.75 - 3.87 (m, 1 H) 4.03 (br dd, *J*=11.5, 3.0 Hz, 1 H) 4.15 (br d, *J*=12.6 Hz, 1 H) 4.33 (br d, *J*=12.6 Hz, 1 H) 4.45 - 4.65 (m, 2 H) 6.81 (d, *J*=2.0 Hz, 1 H) 6.84 (d, *J*=2.0 Hz, 1 H) 7.31 (d, *J*=9.5 Hz, 1 H) 7.39 (d, *J*=9.5 Hz, 1 H) 9.69 - 10.16 (m, 1 H)

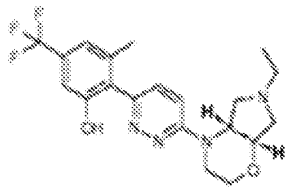
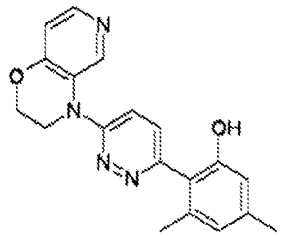
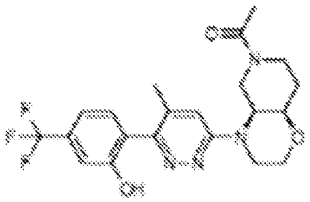
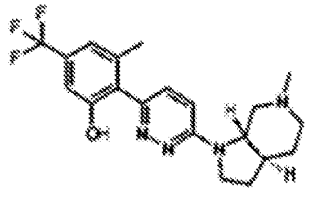
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
340		393 0.47 and 1.80 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.66 - 1.78 (m, 2 H) 1.85 - 2.05 (m, 3 H) 2.08 (s, 3 H) 2.09 - 2.14 (m, 1 H) 2.17 (s, 3 H) 2.31 - 2.40 (m, 1 H) 2.52 - 2.58 (m, 1 H) 3.04 - 3.10 (m, 1 H) 3.34 - 3.43 (m, 1 H) 3.50 - 3.59 (m, 1 H) 4.16 - 4.26 (m, 1 H) 6.77 (s, 1 H) 7.20 (br s, 1 H) 7.22 (br d, *J*=7.8 Hz, 1 H) 7.40 (d, *J*=7.8 Hz, 1 H) 10.32 - 10.54 (m, 1 H)
341		339 1.44 G	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.66 - 1.77 (m, 2 H) 1.85 - 2.07 (m, 3 H) 2.07 - 2.13 (m, 1 H) 2.09 (s, 3 H) 2.17 (s, 3 H) 2.28 (s, 3 H) 2.30 - 2.39 (m, 1 H) 2.52 - 2.56 (m, 1 H) 3.02 - 3.09 (m, 1 H) 3.34 - 3.42 (m, 1 H) 3.49 - 3.57 (m, 1 H) 4.15 - 4.24 (m, 1 H) 6.69 (br d, *J*=7.8 Hz, 1 H) 6.73 (br s, 2 H) 7.05 (d, *J*=7.8 Hz, 1 H) 9.69 (s, 1 H)
342		339 0.46 and 1.58 G	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.81 (m, 2 H), 1.82 - 2.06 (m, 3 H), 2.04 (s, 3 H), 2.06 - 2.15 (m, 1 H), 2.17 (s, 3 H), 2.22 (s, 3 H), 2.31 - 2.40 (m, 1 H), 2.52 - 2.58 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.35 - 3.48 (m, 1 H), 3.50 - 3.60 (m, 1 H), 4.15 - 4.25 (m, 1 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.87 (d, J=9.5 Hz, 1 H), 7.25 (d, J=9.5 Hz, 1 H), 9.39 (s, 1 H)
343		409.4 2.73 E	^{1}H NMR (500 MHz, DMSO) δ (ppm) : 10.21 (br. s, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 3.97 – 3.91 (m, 1H), 3.88 – 3.83 (m, 1H), 3.72 – 3.64 (m, 1H), 3.56 – 3.39 (m, 4H), 2.84 (d, *J* = 11.3 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 4H), 1.94 – 1.73 (m, 2H), 1.73 – 1.54 (m, 1H).

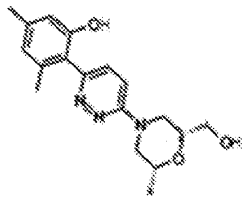
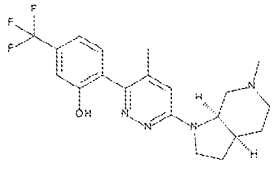
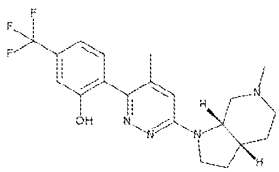
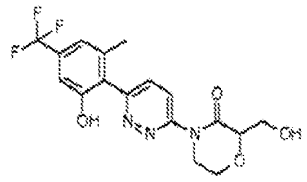
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
344		423.5 2.70 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.22 (s, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.15 (s, 1H), 7.09 (s, 1H), 3.98 – 3.91 (m, 1H), 3.90 – 3.84 (m, 1H), 3.74 – 3.66 (m, 1H), 3.59 – 3.50 (m, 2H), 3.49 – 3.38 (m, 2H), 2.94 (d, *J* = 11.3 Hz, 1H), 2.40 – 2.33 (m, 2H), 2.13 (s, 3H), 2.11 – 2.02 (m, 1H), 1.89 – 1.83 (m, 1H), 1.76 (t, *J* = 10.1 Hz, 1H), 1.67 – 1.57 (m, 1H), 0.97 (t, *J* = 7.1 Hz, 3H).
345		378 2.17 G	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 2.05 (quin, J=7.4 Hz, 2 H), 2.79 (dd, J=12.8, 9.9 Hz, 1 H), 2.83 - 2.94 (m, 4 H), 3.04 (td, J=12.8, 3.5 Hz, 1 H), 3.43 - 3.58 (m, 3 H), 3.62 (td, J=11.6, 2.8 Hz, 1 H), 4.00 (br dd, J=11.6, 2.2 Hz, 1 H), 4.24 (br d, J=12.9 Hz, 1 H), 4.38 (br d, J=12.8 Hz, 1 H), 4.81 (br t, J=5.5 Hz, 1 H), 6.76 (t, J=54.5 Hz, 1 H), 6.84 (d, J=7.6 Hz, 1 H), 7.03 (d, J=7.5 Hz, 1 H), 7.40 (s, 1 H), 9.04 - 9.19 (m, 1 H)
346	 HCl	365 0.47 and 1.81 G	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 2.12 - 2.22 (m, 1 H) 2.20 (s, 3 H) 2.33 - 2.48 (m, 3 H) 3.23 - 3.37 (m, 2 H) 3.77 - 3.90 (m, 2 H) 4.43 - 4.51 (m, 1 H) 4.80 - 4.87 (m, 1 H) 7.12 (br s, 1 H) 7.16 (br s, 1 H) 7.29 (d, *J*=9.5 Hz, 1 H) 7.58 (d, *J*=9.5 Hz, 1 H) 9.40 - 9.89 (m, 2 H)
348		423.3 2.68 E	^{1}H NMR (500 MHz, *DMSO-d_6)* δ (ppm): 10.16 (s, 1H), 7.53 – 7.42 (m, 1H), 7.42 – 7.29 (m, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 5.03 – 4.80 (m, 1H), 4.34 – 4.11 (m, 1H), 4.10 – 3.94 (m, 2H), 3.90 – 3.43 (m, 5H), 3.23 – 3.08 (m, 1H), 2.13 (d, *J* = 3.1 Hz, 3H), 1.95 (d, *J* = 4.9 Hz, 3H).

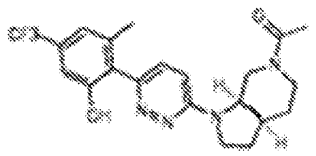
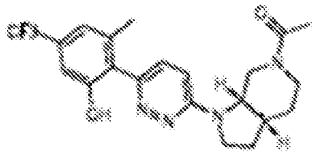
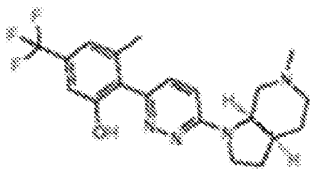
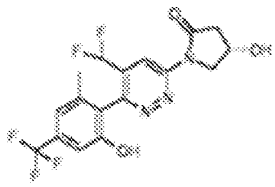
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
349		437.5 2.57 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.23 (s, 1H), 7.65 – 7.38 (m, 2H), 7.14 (s, 1H), 7.09 (s, 1H), 4.71 (d, *J* = 13.2 Hz, 1H), 4.62 – 4.44 (m, 1H), 4.07 – 3.84 (m, 2H), 3.83 – 3.63 (m, 3H), 3.29 – 3.11 (m, 1H), 2.80 – 2.66 (m, 1H), 2.21 – 1.99 (m, 6H), 1.98 – 1.83 (m, 1H), 1.75 – 1.64 (m, 1H), 1.32- 1.25 (m, 1H).
350		411 0.95 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.76 - 1.95 (m, 2 H), 2.06 - 2.14 (m, 1 H), 2.18 (s, 3 H), 2.30 - 2.40 (m, 1 H), 2.51 - 2.57 (m hidden, 2 H), 3.17 - 3.26 (m partially hidden, 1 H), 3.63 (td, J=3.2 and 11.8 Hz, 1 H), 3.74 (br q, J=2.8 Hz, 1 H), 3.96 - 4.10 (m, 2 H), 4.47 - 4.59 (m, 1 H), 6.80 (t, J=54.3 Hz, 1 H), 6.96 - 7.01 (m, 2 H), 7.29 (br d, J=8.1 Hz, 1 H), 7.33 (br s, 1 H), 10.18 - 10.70 (m, 1 H)
351		395 0.85 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.76 - 1.95 (m, 2 H), 2.06 - 2.15 (m, 1 H), 2.18 (s, 3 H), 2.30 - 2.40 (m, 1 H), 2.51 - 2.57 (m hidden, 2 H), 3.12 - 3.26 (m partially hidden, 1 H), 3.63 (td, J=3.2 and 11.8 Hz, 1 H), 3.75 (q, J=2.8 Hz, 1 H), 3.98 - 4.11 (m, 2 H), 4.48 - 4.57 (m, 1 H), 6.79 (br t, J=54.3 Hz, 1 H), 6.90 - 6.96 (m, 1 H), 7.09 (br d, J=7.4 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.35 (br s, 1 H), 9.71 - 10.31 (m, 1 H)
352		423.3 2.68 E	^{1}H NMR (500 MHz, *DMSO-d_6)* δ (ppm): 10.19 (s, 1H), 7.55 – 7.41 (m, 1H), 7.42 – 7.28 (m, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.97 – 4.79 (m, 1H), 4.28 – 4.11 (m, 1H), 4.10 – 3.94 (m, 2H), 3.84 – 3.73 (m, 1H), 3.72 – 3.60 (m, 1H), 3.58 – 3.48 (m, 1H), 3.48 – 3.42 (m, 1H), 3.25 – 3.08 (m, 2H), 2.13 (d, *J* = 3.0 Hz, 3H), 1.95 (d, *J* = 4.8 Hz, 3H). Mixture of rotamers

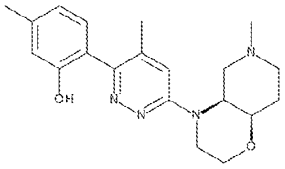
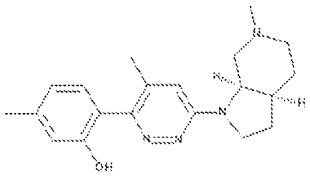
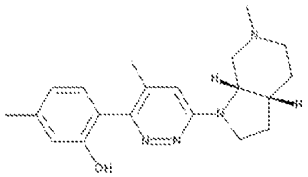
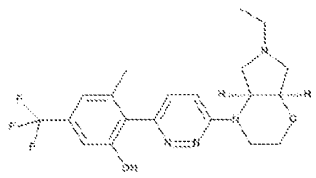
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
353		359 0.98 Z1	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.76 - 1.95 (m, 2 H) 2.04 (s, 3 H) 2.13 - 2.21 (m, 1 H) 2.25 (br s, 3 H) 2.37 - 2.47 (m, 1 H) 2.54 - 2.64 (m, 2 H) 3.17 (td, *J*=12.7, 3.8 Hz, 1 H) 3.64 (td, *J*=11.8, 3.3 Hz, 1 H) 3.73 - 3.79 (m, 1 H) 3.94 (br d, *J*=12.7 Hz, 1 H) 4.06 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.40 - 4.52 (m, 1 H) 6.75 (dd, *J*=8.4, 5.0 Hz, 1 H) 7.11 (dd, *J*=10.8, 8.4 Hz, 1 H) 7.25 (d, *J*=9.5 Hz, 1 H) 7.40 (d, *J*=9.5 Hz, 1 H) 9.58 (br s, 1 H)
354		341 0.69 and 0.72 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.76 - 1.93 (m, 2 H) 2.06 (s, 3 H) 2.07 - 2.13 (m, 1 H) 2.18 (s, 3 H) 2.30 - 2.36 (m, 1 H) 2.51 - 2.56 (m partially hidden, 2 H) 3.16 (td, *J*=12.7, 3.8 Hz, 1 H) 3.63 (td, *J*=11.8, 3.3 Hz, 1 H) 3.72 - 3.77 (m, 1 H) 3.93 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.36 - 4.45 (m, 1 H) 6.73 - 6.79 (m, 2 H) 7.10 (t, *J*=7.6 Hz, 1 H) 7.21 (d, *J*=9.5 Hz, 1 H) 7.36 (d, *J*=9.5 Hz, 1 H) 9.42 (s, 1 H)
355		423 1.32 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.76 - 1.95 (m, 2 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.52 - 2.61 (m, 1 H) 2.64 - 2.74 (m, 2 H) 2.76 - 2.88 (m, 1 H) 3.11 - 3.27 (m, 3 H) 3.64 (td, *J*=11.8, 3.3 Hz, 1 H) 3.73 - 3.79 (m, 1 H) 3.92 (br d, *J*=12.7 Hz, 1 H) 4.06 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.40 - 4.48 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.20 (d, *J*=9.5 Hz, 1 H) 7.35 (d, *J*=9.5 Hz, 1 H) 9.37 (br s, 1 H)
356		359 0.74 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.75 - 1.92 (m, 2 H) 2.06 - 2.13 (m, 1 H) 2.10 (s, 3 H) 2.17 (s, 3 H) 2.26 - 2.36 (m, 1 H) 2.51 - 2.54 (m, partially hidden, 2 H) 3.15 (td, *J*=12.7, 3.8 Hz, 1 H) 3.61 (td, *J*=11.8, 3.3 Hz, 1 H) 3.68 - 3.76 (m, 1 H) 3.93 (br d, *J*=12.7 Hz, 1 H) 4.04 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.37 - 4.45 (m, 1 H) 6.90 (td, *J*=7.8, 5.0 Hz, 1 H) 7.03 (dt, *J*=7.8, 1.3 Hz, 1 H) 7.12 (s, 1 H) 7.20 - 7.27 (m, 1 H) 9.79 - 10.00 (m, 1 H)

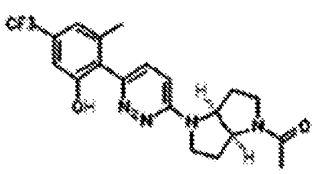
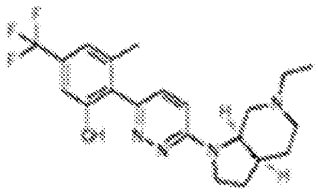
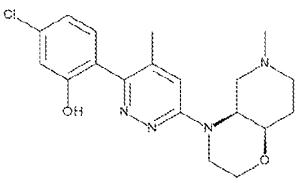
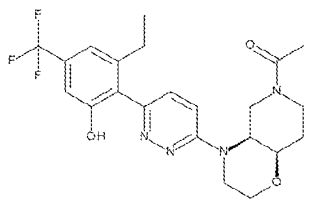
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
357		403 1.11 U	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 1.77 - 1.91 (m, 2 H) 2.02 (s, 3 H) 2.13 (br s, 3 H) 3.19 - 3.27 (m, 1 H) 3.52 - 4.45 (m, 4 H) 3.68 (td, *J*=11.8, 3.3 Hz, 1 H) 3.81 - 3.91 (m, 1 H) 3.96 (br d, *J*=12.7 Hz, 1 H) 4.05 - 4.11 (m, 1 H) 4.24 - 4.39 (m, 1 H) 6.92 (dd, *J*=8.1, 2.1 Hz, 1 H) 6.97 (d, *J*=2.1 Hz, 1 H) 7.07 (s, 1 H) 7.22 (d, *J*=8.1 Hz, 1 H) 8.83 - 10.92 (m, 1 H)
358		355 0.80 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.95 (t, *J*=7.6 Hz, 3 H) 1.76 - 1.93 (m, 2 H) 2.06 - 2.14 (m, 1 H) 2.18 (s, 3 H) 2.30 - 2.42 (m, 3 H) 2.51 - 2.56 (m partially hidden, 2 H) 3.16 (td, *J*=12.7, 3.8 Hz, 1 H) 3.63 (td, *J*=11.8, 3.3 Hz, 1 H) 3.72 - 3.77 (m, 1 H) 3.93 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.36 - 4.45 (m, 1 H) 6.77 (d, *J*=7.8 Hz, 2 H) 7.14 (t, *J*=7.8 Hz, 1 H) 7.20 (d, *J*=9.5 Hz, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 9.32 (s, 1 H)
359		330 0.91 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.19 (d, *J*=6.5 Hz, 3 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 3.21 (dd, *J*=12.7, 7.0 Hz, 1 H) 3.49 - 3.58 (m, 3 H) 3.62 - 3.68 (m, 1 H) 3.81 (dd, *J*=12.7, 3.3 Hz, 1 H) 3.84 - 3.90 (m, 1 H) 3.99 - 4.08 (m, 1 H) 4.72 (t, *J*=5.7 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.23 (d, *J*=9.5 Hz, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 9.36 (s, 1 H)
360		378.4 2.77 E	1H NMR (400 MHz, DMSO) δ (ppm): 11.99 (s, 1H), 10.22 (s, 1H), 8.63 (d, J = 9.4 Hz, 1H), 7.59 (d, J = 9.4 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.15 (s, 1H), 7.09 (s, 1H), 4.38 – 4.20 (m, 4H), 2.14 (s, 3H).

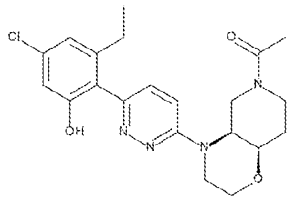
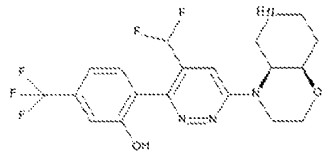
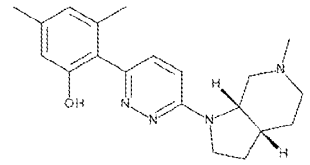
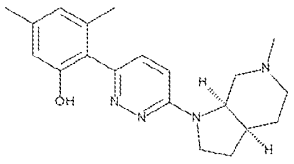
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
361		409.5 2.51 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.16 (s, 1H), 7.41 (d, *J* = 9.4 Hz, 1H), 7.29 (d, *J* = 9.5 Hz, 1H), 7.12 (s, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 4.68 – 4.46 (m, 1H), 4.10 (t, *J* = 4.7 Hz, 1H), 4.03 – 3.96 (m, 2H), 3.58 (td, *J* = 11.8, 2.9 Hz, 1H), 3.19 – 3.10 (m, 2H), 2.96 (t, *J* = 7.7 Hz, 1H), 2.57 – 2.52 (m, 4H), 2.13 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).
362		335 0.82 and 0.83 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.07 (br s, 3 H) 2.24 (s, 3 H) 4.14 - 4.18 (m, 2 H) 4.38 - 4.43 (m, 2 H) 6.60 (br s, 1 H) 6.61 (br s, 1 H) 6.97 (d, *J*=5.4 Hz, 1 H) 7.50 (d, *J*=9.3 Hz, 1 H) 7.61 (d, *J*=9.3 Hz, 1 H) 8.07 (d, *J*=5.4 Hz, 1 H) 8.66 (s, 1 H) 9.40 (br s, 1 H)
363		437 1.21 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.78 - 1.94 (m, 2 H), 2.04 (s, 3 H), 2.15 (br s, 3 H), 2.71 - 3.21 (m partially hidden, 2 H), 3.26 (td, J=3.8 and 12.6 Hz, 1 H), 3.50 - 4.24 (m partially hidden, 2 H), 3.71 (td, J=3.2 and 11.8 Hz, 1 H), 3.89 (br q, J=2.8 Hz, 1 H), 4.00 (br d, J=12.6 Hz, 1 H), 4.11 (dd, J=3.8 and 11.8 Hz, 1 H), 4.27 - 4.44 (m, 1 H), 7.11 (br s, 1 H), 7.21 - 7.25 (m, 2 H), 7.45 (d, J=7.8 Hz, 1 H)
364		393.4 2.69 E	^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.17 (s, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.24 – 7.08 (m, 2H), 7.06 (s, 1H), 4.18 – 3.96 (m, 1H), 3.90 – 3.71 (m, 1H), 3.66 (d, *J* = 13.9 Hz, 1H), 3.24 – 3.11 (m, 1H), 3.08 – 2.85 (m, 1H), 2.41 – 2.31 (m, 2H), 2.29 – 2.22 (m, 3H), 2.18 – 2.08 (m, 4H), 1.98 – 1.79 (m, 2H), 1.70 – 1.56 (m, 1H), 1.53 – 1.38 (m, 1H).

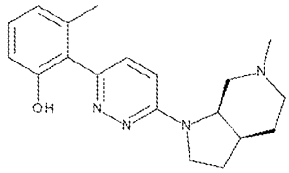
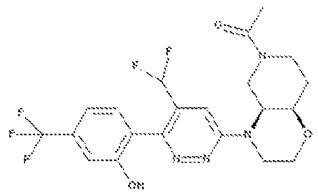
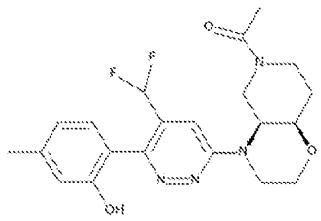
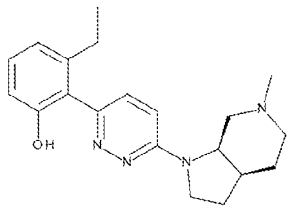
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
365		330 0.93 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.20 (d, *J*=6.0 Hz, 3 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.52 - 2.65 (m, 2 H) 3.43 - 3.50 (m, 1 H) 3.50 - 3.63 (m, 2 H) 3.63 - 3.72 (m, 1 H) 4.24 (br d, *J*=12.5 Hz, 1 H) 4.35 (br d, *J*=12.5 Hz, 1 H) 4.79 (t, *J*=5.5 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.26 (d, *J*=9.5 Hz, 1 H) 7.34 (d, *J*=9.5 Hz, 1 H) 9.34 - 9.40 (m, 1 H)
366		393 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.65 - 1.78 (m, 2 H), 1.86 - 2.05 (m, 3 H), 2.06 - 2.13 (m, 1 H), 2.08 (s, 3 H), 2.17 (s, 3 H), 2.31 - 2.40 (m, 1 H), 2.52 - 2.57 (m partially hidden, 1 H), 3.07 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.36 - 3.42 (m, 1 H), 3.51 - 3.59 (m, 1 H), 4.16 - 4.27 (m, 1 H), 6.77 (s, 1 H), 7.20 (br s, 1 H), 7.22 (br d, J=7.8 Hz, 1 H), 7.40 (d, J=7.8 Hz, 1 H), 10.22 - 10.72 (m, 1 H)
367		393 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.65 - 1.79 (m, 2 H), 1.88 - 2.06 (m, 3 H), 2.06 - 2.14 (m, 1 H), 2.08 (s, 3 H), 2.17 (s, 3 H), 2.29 - 2.38 (m, 1 H), 2.54 - 2.56 (m partially hidden, 1 H), 3.07 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.38 - 3.43 (m, 1 H), 3.51 - 3.59 (m, 1 H), 4.14 - 4.28 (m, 1 H), 6.77 (s, 1 H), 7.20 (br s, 1 H), 7.22 (br d, J=7.8 Hz, 1 H), 7.40 (d, J=7.8 Hz, 1 H), 10.23 - 10.67 (m, 1 H)
368		384 1.22 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.12 (s, 3 H) 3.76 (br d, *J*=12.5 Hz, 1 H) 3.90 (br d, *J*=12.5 Hz, 1 H) 3.94 - 4.04 (m, 1 H) 4.07 - 4.15 (m, 1 H) 4.19 - 4.30 (m, 2 H) 4.37 (dd, *J*=4.0, 2.5 Hz, 1 H) 4.91 - 5.05 (m, 1 H) 7.10 (br s, 1 H) 7.15 (br s, 1 H) 7.74 (d, *J*=9.3 Hz, 1 H) 8.32 (d, *J*=9.3 Hz, 1 H) 9.97 - 10.74 (m, 1 H)

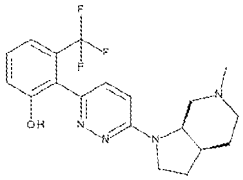
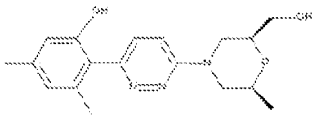
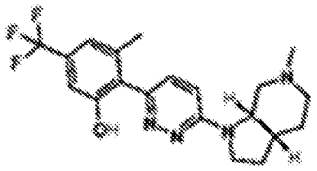
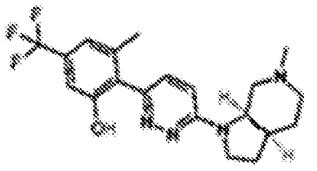
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
369		421.5 2.74 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.40 (s, 1H), 7.37 (d, J = 9.2 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 7.04 – 6.80 (m, 1H), 4.62 (dd, J = 12.9, 5.9 Hz, 1H), 4.34 – 4.06 (m, 1H), 3.79 – 3.54 (m, 2H), 3.51 – 3.36 (m, 2H), 3.23 – 3.07 (m, 1H), 2.69 – 2.60 (m, 1H), 2.27 – 2.04 (m, 4H), 2.06 – 1.89 (m, 4H), 1.85 – 1.71 (m, 1H), 1.68 – 1.55 (m, 1H), mixture of rotamers.
370		421.5 2.74 E	^{1}H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.40 (s, 1H), 7.38 (dd, J = 9.3, 1.0 Hz, 1H), 7.13 (s, 1H), 7.06 (s, 1H), 7.03 – 6.82 (m, 1H), 4.63 (dd, J = 12.8, 5.9 Hz, 1H), 4.30 – 4.10 (m, 1H), 3.81 – 3.54 (m, 2H), 3.53 – 3.39 (m, 2H), 3.29 – 3.11 (m, 1H), 2.62 (dd, J = 12.9, 10.0 Hz, 1H), 2.24 – 2.08 (m, 4H), 2.07 – 1.88 (m, 4H), 1.87 – 1.71 (m, 1H), 1.68 – 1.39 (m, 1H), , mixture of rotamers.
371		393.5 2.66 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.14 (s, 1H), 7.31 (d, J = 9.3 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 9.3 Hz, 1H), 4.33 – 4.15 (m, 1H), 3.67 – 3.53 (m, 1H), 3.48 – 3.37 (m, 1H), 3.12 – 3.03 (m, 1H), 2.61 – 2.53 (m, 1H), 2.43 – 2.35 (m, 1H), 2.18 (s, 3H), 2.14 (s, 3H), 2.12 – 1.87 (m, 4H), 1.83 – 1.66 (m, 2H).
372		404 1.33 and 1.36 B	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 2.01 (br s, 3 H) 2.49 - 2.52 (m hidden, 1 H) 2.96 - 3.02 (m partially hidden, 1 H) 4.11 - 4.19 (m, 1 H) 4.23 - 4.33 (m, 1 H) 4.48 - 4.55 (m, 1 H) 5.12 - 5.16 (m, 1 H) 6.69 (t, J=54.0 Hz, 1 H) 7.07 (br s, 1 H) 7.11 (br s, 1 H) 8.84 (br s, 1 H) 9.23 - 10.80 (m, 1 H)

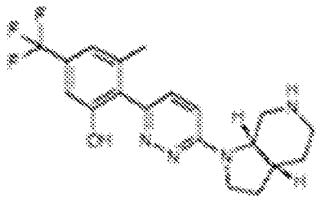
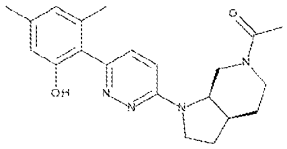
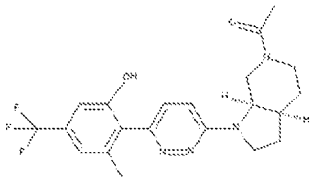
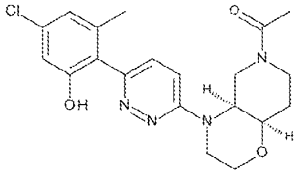
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
373		355 0.77 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.76 - 1.92 (m, 2 H), 2.05 - 2.15 (m, 1 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.28 (s, 3 H), 2.30 - 2.36 (m, 1 H), 2.51 - 2.55 (m partially hidden, 2 H), 3.14 (td, J=3.8 and 12.7 Hz, 1 H), 3.61 (td, J=3.3 and 11.8 Hz, 1 H), 3.72 (br q, J=2.8 Hz, 1 H), 3.90 (br d, J=12.7 Hz, 1 H), 4.04 (dd, J=3.3 and 11.8 Hz, 1 H), 4.36 - 4.44 (m, 1 H), 6.70 (br d, J=7.6 Hz, 1 H), 6.73 (br s, 1 H), 7.04 - 7.08 (m, 2 H), 9.64 (br s, 1 H)
374		339 0.67 Z1	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.77 (m, 2 H), 1.85 - 2.06 (m, 3 H), 2.07 - 2.14 (m, 1 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.28 (s, 3 H), 2.29 - 2.38 (m, 1 H), 2.52 - 2.57 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.41 (m, 1 H), 3.49 - 3.57 (m, 1 H), 4.15 - 4.23 (m, 1 H), 6.69 (dd, J=1.3 and 7.8 Hz, 1 H), 6.73 (br s, 2 H), 7.05 (d, J=7.8 Hz, 1 H), 9.70 (br s, 1 H)
375		339 0.67 Z1	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.78 (m, 2 H), 1.85 - 2.04 (m, 3 H), 2.05 - 2.13 (m, 1 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.28 (s, 3 H), 2.30 - 2.38 (m, 1 H), 2.52 - 2.56 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.42 (m, 1 H), 3.49 - 3.57 (m, 1 H), 4.15 - 4.25 (m, 1 H), 6.69 (br d, J=7.8 Hz, 1 H), 6.73 (br s, 2 H), 7.05 (d, J=7.8 Hz, 1 H), 9.70 (br s, 1 H)
376		409.5 2.58 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H), 7.47 (d, *J* = 9.3 Hz, 1H), 7.41 (d, *J* = 9.3 Hz, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.14 – 4.04 (m, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.79 – 3.68 (m, 2H), 3.26 – 3.12 (m, 1H), 3.06 – 2.90 (m, 2H), 2.80 (t, *J* = 9.9 Hz, 1H), 2.70 – 2.60 (m, 3H), 2.11 (s, 3H), 1.07 – 0.97 (m, 3H)

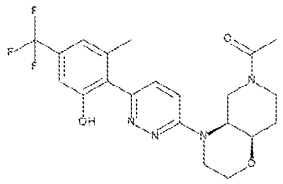
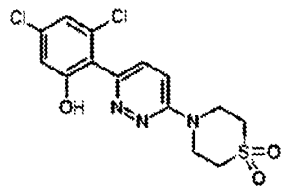
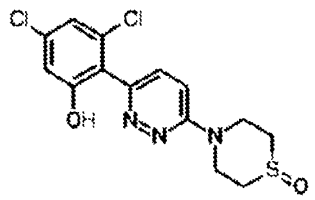
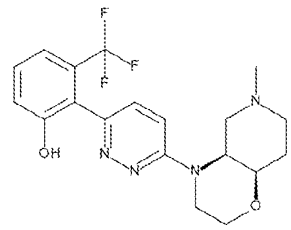
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
377		407 1.09 B	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 1.93 - 2.28 (m, 4 H) 2.00 (br s, 3 H) 2.17 (s, 3 H) 3.19 - 3.59 (m, 2 H) 3.61 - 3.78 (m, 2 H) 4.56 - 4.64 (m, 1 H) 4.64 - 4.79 (m, 1 H) 6.97 (d, *J*=9.3 Hz, 1 H) 7.06 (br s, 2 H) 7.36 (d, *J*=9.3 Hz, 1 H) 9.51 - 10.13 (m, 1 H)
378		407.5 2.71 E	^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.16 (s, 1H), 7.31 (d, *J* = 9.3 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 9.3 Hz, 1H), 4.29 – 4.13 (m, 1H), 3.56 (t, *J* = 9.6 Hz, 1H), 3.49 – 3.37 (m, 1H), 3.22 – 3.07 (m, 1H), 2.76 – 2.65 (m, 1H), 2.45 – 2.27 (m, 3H), 2.20 – 2.00 (m, 5H), 1.97 – 1.84 (m, 2H), 1.80 (t, *J* = 10.6 Hz, 1H), 1.74 – 1.63 (m, 1H), 0.99 (t, *J* = 7.1 Hz, 3H).
379		375 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.75 - 1.93 (m, 2 H), 2.04 - 2.14 (m, 1 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.27 - 2.35 (m, 1 H), 2.51 - 2.55 (m partially hidden, 2 H), 3.14 (td, J=3.8 and 12.7 Hz, 1 H), 3.61 (td, J=3.3 and 11.8 Hz, 1 H), 3.72 (br q, J=2.8 Hz, 1 H), 3.91 (br d, J=12.7 Hz, 1 H), 4.04 (dd, J=3.3 and 11.8 Hz, 1 H), 4.35 - 4.45 (m, 1 H), 6.93 - 6.97 (m, 2 H), 7.09 (br s, 1 H), 7.20 (br d, J=7.8 Hz, 1 H), 10.18 - 10.29 (m, 1 H)
380		451 1.36 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.03 (t, J=7.5 Hz, 3 H), 1.78 - 1.94 (m, 2 H), 2.04 (s, 3 H), 2.51 - 2.54 (m partially hidden, 2 H), 2.72 - 3.17 (m partially hidden, 2 H), 3.28 (br td, J=3.8 and 12.6 Hz, 1 H), 3.50 - 4.31 (m partially hidden, 2 H), 3.73 (td, J=3.2 and 11.8 Hz, 1 H), 3.91 (q, J=2.8 Hz, 1 H), 4.02 (br d, J=12.6 Hz, 1 H), 4.12 (br dd, J=3.8 and 11.8 Hz, 1 H), 4.25 - 4.48 (m, 1 H), 7.08 - 7.11 (m, 2 H), 7.25 (br d, J=9.5 Hz, 1 H), 7.41 (d, J=9.5 Hz, 1 H), 9.07 - 10.18 (m, 1 H)

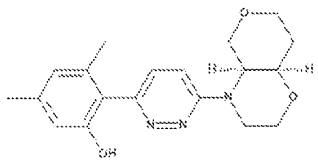
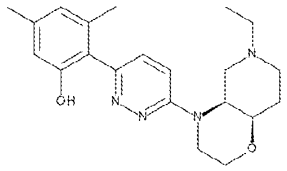
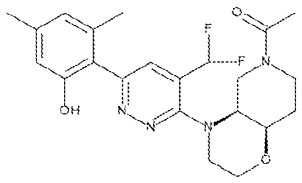
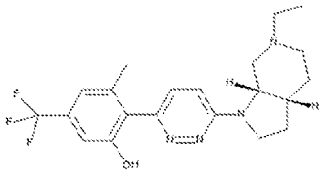
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
381		417 1.23 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.00 (t, J=7.5 Hz, 3 H), 1.78 - 1.94 (m, 2 H), 2.03 (s, 3 H), 2.43 (q, J=7.5 Hz, 2 H), 2.72 - 3.20 (m partially hidden, 2 H), 3.27 (td, J=3.8 and 12.6 Hz, 1 H), 3.48 - 4.25 (m partially hidden, 2 H), 3.73 (td, J=3.2 and 11.8 Hz, 1 H), 3.90 (q, J=2.8 Hz, 1 H), 4.00 (br d, J=12.6 Hz, 1 H), 4.11 (dd, J=3.8 and 11.8 Hz, 1 H), 4.26 - 4.43 (m, 1 H), 6.82 - 6.86 (m, 2 H), 7.22 (br d, J=9.5 Hz, 1 H), 7.36 (d, J=9.5 Hz, 1 H), 8.99 - 9.90 (m, 1 H)
382		431 1.00 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.74 - 1.82 (m, 2 H), 2.63 - 2.69 (m, 3 H), 2.92 - 3.00 (m, 1 H), 3.17 - 3.24 (m partially hidden, 1 H), 3.58 - 3.66 (m, 1 H), 3.84 (br q, J=2.8 Hz, 1 H), 4.03 - 4.13 (m, 2 H), 4.29 - 4.40 (m, 1 H), 6.84 (t, J=54.8 Hz, 1 H), 7.21 (br s, 1 H), 7.24 (br d, J=8.0 Hz, 1 H), 7.34 (s, 1 H), 7.49 (d, J=8.0 Hz, 1 H)
383		339 0.74 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.80 (m, 2 H), 1.85 - 2.02 (m, 3 H), 2.04 (s, 3 H), 2.05 - 2.15 (m, 1 H), 2.16 (s, 3 H), 2.21 (s, 3 H), 2.28 - 2.40 (m, 1 H), 2.53 - 2.54 (m partially hidden, 1 H), 3.05 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.43 (m, 1 H), 3.49 - 3.60 (m, 1 H), 4.15 - 4.25 (m, 1 H), 6.55 (s, 1 H), 6.56 (s, 1 H), 6.86 (d, J=9.5 Hz, 1 H), 7.24 (d, J=9.5 Hz, 1 H), 9.39 (br s, 1 H)
384		339 0.75 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.80 (m, 2 H), 1.85 - 2.02 (m, 3 H), 2.04 (s, 3 H), 2.06 - 2.13 (m, 1 H), 2.17 (s, 3 H), 2.21 (s, 3 H), 2.31 - 2.41 (m, 1 H), 2.53 - 2.56 (m partially hidden, 1 H), 3.05 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.35 - 3.43 (m, 1 H), 3.50 - 3.59 (m, 1 H), 4.15 - 4.26 (m, 1 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.87 (d, J=9.5 Hz, 1 H), 7.24 (d, J=9.5 Hz, 1 H), 9.39 (br s, 1 H)

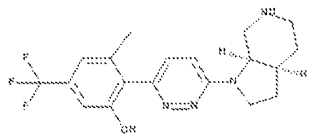
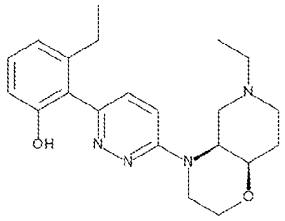
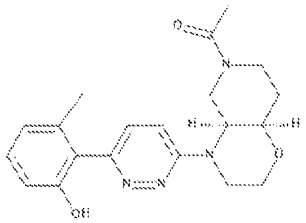
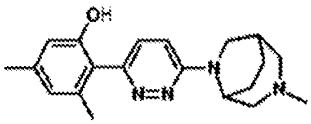
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
385		325 0.66 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.81 (m, 2 H), 1.85 - 2.05 (m, 3 H), 2.04 - 2.14 (m, 1 H), 2.07 (s, 3 H), 2.17 (s, 3 H), 2.34 - 2.41 (m, 1 H), 2.53 - 2.56 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.37 - 3.43 (m, 1 H), 3.52 - 3.60 (m, 1 H), 4.17 - 4.26 (m, 1 H), 6.71 - 6.78 (m, 2 H), 6.88 (d, J=9.5 Hz, 1 H), 7.08 (t, J=8.0 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 9.43 (br s, 1 H)
386		473 1.4 U	1H NMR (400 MHz, DMSO-d6, 101°C) d ppm 1.81 - 1.90 (m, 2 H), 2.02 (s, 3 H), 2.66 - 3.27 (m partially hidden, 2 H), 3.32 (td, J=3.8 and 12.6 Hz, 1 H), 3.51 - 4.34 (m partially hidden, 2 H), 3.72 (td, J=3.2 and 11.8 Hz, 1 H), 3.89 (br q, J=2.8 Hz, 1 H), 4.05 - 4.13 (m, 2 H), 4.37 - 4.50 (m, 1 H), 6.78 (t, J=54.5 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.36 (br s, 1 H), 7.48 (d, J=7.8 Hz, 1 H)
387		419 1.27 U	1H NMR (400 MHz, DMSO-d6, 101°C) d ppm 1.81 - 1.89 (m, 2 H), 2.01 (s, 3 H), 2.30 (s, 3 H), 2.68 - 3.19 (m partially hidden, 2 H), 3.30 (td, J=3.8 and 12.6 Hz, 1 H), 3.53 - 4.28 (m partially hidden, 2 H), 3.71 (td, J=3.2 and 11.8 Hz, 1 H), 3.89 (br q, J=2.8 Hz, 1 H), 4.05 (br d, J=12.6 Hz, 1 H), 4.10 (dd, J=3.8 and 11.8 Hz, 1 H), 4.31 - 4.49 (m, 1 H), 6.66 (br t, J=54.7 Hz, 1 H), 6.73 - 6.80 (m, 2 H), 7.15 (d, J=7.6 Hz, 1 H), 7.32 (br s, 1 H)
388		379 0.84 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.95 (t, J=7.5 Hz, 3 H), 1.67 - 1.82 (m, 2 H), 1.87 - 2.14 (m, 4 H), 2.18 (s, 3 H), 2.34 - 2.44 (m, 3 H), 2.53 - 2.57 (m partially hidden, 1 H), 3.07 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.36 - 3.46 (m, 1 H), 3.52 - 3.61 (m, 1 H), 4.17 - 4.26 (m, 1 H), 6.75 (d, J=7.8 Hz, 2 H), 6.87 (d, J=9.5 Hz, 1 H), 7.12 (t, J=7.8 Hz, 1 H), 7.23 (d, J=9.5 Hz, 1 H), 9.28 (br s, 1 H)

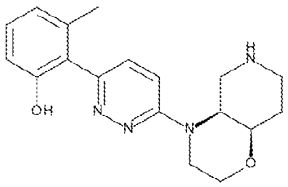
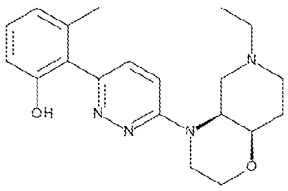
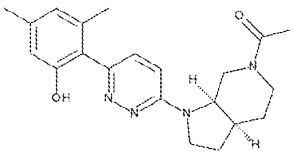
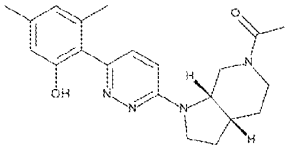
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
389		379 0.84 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.68 - 1.86 (m, 2 H), 1.86 - 2.01 (m, 2 H), 2.04 - 2.16 (m, 2 H), 2.20 (s, 3 H), 2.34 - 2.42 (m, 1 H), 2.54 - 2.60 (m partially hidden, 1 H), 3.04 - 3.13 (m, 1 H), 3.36 - 3.46 (m, 1 H), 3.52 - 3.61 (m, 1 H), 4.16 - 4.29 (m, 1 H), 6.88 (d, J=9.5 Hz, 1 H), 7.20 - 7.27 (m, 3 H), 7.43 (t, J=7.8 Hz, 1 H), 10.02 (br s, 1 H)
390		330 0.95 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.20 (d, *J*=6.0 Hz, 3 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.54 - 2.65 (m, 2 H) 3.40 - 3.50 (m, 1 H) 3.50 - 3.62 (m, 2 H) 3.64 - 3.73 (m, 1 H) 4.24 (br d, *J*=12.5 Hz, 1 H) 4.35 (br d, *J*=12.5 Hz, 1 H) 4.79 (t, *J*=5.6 Hz, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.26 (d, *J*=9.5 Hz, 1 H) 7.34 (d, *J*=9.5 Hz, 1 H) 9.37 (s, 1 H)
391		393.5 2.66 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.06 (s, 1H), 7.24 (d, *J* = 9.3 Hz, 1H), 7.04 (s, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.85 (d, *J* = 9.3 Hz, 1H), 4.16 (s, 1H), 3.54 – 3.46 (m, 1H), 3.43 – 3.30 (m, 1H), 3.04 – 2.98 (m, 1H), 2.52 – 2.45 (m, 1H), 2.37 – 2.30 (m, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 – 2.00 (m, 1H), 2.01 – 1.94 (m, 1H), 1.93 – 1.80 (m, 2H), 1.75 – 1.67 (m, 1H), 1.67 – 1.60 (m, 1H).
392		393.5 2.66 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.15 (s, 1H), 7.31 (d, *J* = 9.3 Hz, 1H), 7.10 (s, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.92 (d, *J* = 9.3 Hz, 1H), 4.23 (s, 1H), 3.62 – 3.52 (m, 1H), 3.43 – 3.40 (m, 1H), 3.12 – 3.03 (m, 1H), 2.59 – 2.52 (m, 1H), 2.43 – 2.34 (m, 1H), 2.18 (s, 3H), 2.14 (s, 3H), 2.12 – 2.06 (m, 1H), 2.05 – 2.00 (m, 1H), 2.00 – 1.85 (m, 2H), 1.82 – 1.66 (m, 2H).

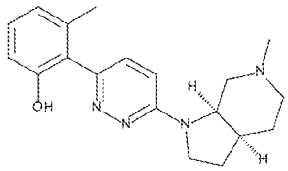
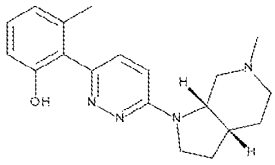
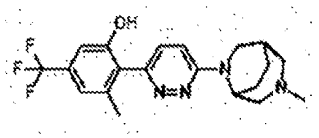
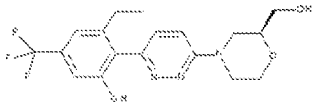
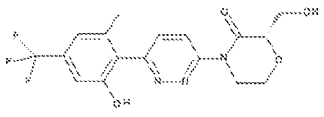
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
393		379.4 2.47 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.80 (s, 1H), 7.24 (d, J = 9.3 Hz, 1H), 7.04 (s, 1H), 6.98 (s, 1H), 6.83 (d, J = 9.3 Hz, 1H), 4.02 (s, 1H), 3.51 (t, J = 9.4 Hz, 1H), 3.38 – 3.31 (m, 2H), 2.70 – 2.65 (m, 1H), 2.60 – 2.51 (m, 1H), 2.39 – 2.26 (m, 2H), 2.18 – 2.09 (m, 1H), 2.07 (s, 3H), 1.90 – 1.73 (m, 2H), 1.63 – 1.56 (m, 1H) (NH not visible)
394		367 0.93 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.63 - 1.78 (m, 1 H), 1.87 - 1.99 (m, 1 H), 1.96 (br s, 3 H), 2.05 - 2.09 (m, 2 H), 2.10 (s, 3 H), 2.25 (s, 3 H), 2.54 - 2.60 (m partially hidden, 1 H), 3.28 - 3.39 (m, 1 H), 3.41 - 3.52 (m, 1 H), 3.59 - 3.69 (m, 2 H), 3.78 - 4.66 (m, 2 H), 4.16 - 4.26 (m, 1 H), 6.59 (br s, 1 H), 6.60 (br s, 1 H), 6.91 (br d, J=9.5 Hz, 1 H), 7.34 (d, J=9.5 Hz, 1 H), 9.13 - 9.25 (m, 1 H)
395		421 1.12 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.65 - 1.79 (m, 1 H), 1.90 - 2.00 (m, 1 H), 1.96 (br s, 3 H), 2.02 - 2.14 (m, 2 H), 2.18 (s, 3 H), 2.54 - 2.61 (m partially hidden, 1 H), 3.27 - 3.38 (m, 1 H), 3.46 - 3.54 (m, 1 H), 3.60 - 3.69 (m, 2 H), 3.82 - 4.69 (m, 2 H), 4.17 - 4.29 (m, 1 H), 6.94 (br d, J=9.3 Hz, 1 H), 7.07 - 7.10 (m, 2 H), 7.37 (d, J=9.3 Hz, 1 H), 9.35 - 10.16 (m, 1 H)
397		403 1.18 U	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 1.73 - 1.91 (m, 2 H) 2.01 (s, 3 H) 2.08 (s, 3 H) 2.73 - 3.16 (m, 4 H) 3.25 (br td, J=12.6, 3.8 Hz, 1 H) 3.70 (br td, J=11.8, 3.2 Hz, 1 H) 3.86 - 3.90 (m, 1 H) 3.99 (br d, J=12.6 Hz, 1 H) 4.09 (br dd, J=11.8, 3.8 Hz, 1 H) 4.28 - 4.39 (m, 1 H) 6.80 - 6.83 (m, 2 H) 7.21 (br d, J=9.5 Hz, 1 H) 7.37 (d, J=9.5 Hz, 1 H) 9.16 - 10.03 (m, 1 H)

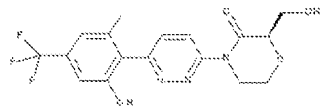
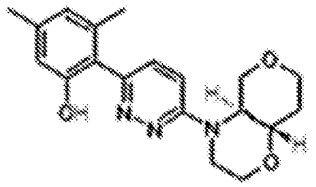
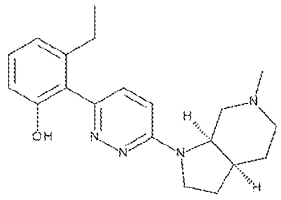
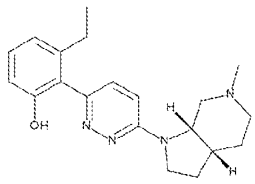
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
398		437 1.36 U	1H NMR (400 MHz, DMSO-d_6, 100°C) δ ppm 1.79 - 1.89 (m, 2 H) 2.02 (s, 3 H) 2.16 (s, 3 H) 2.72 - 4.57 (m, 4 H) 3.26 (td, *J*=12.7, 3.8 Hz, 1 H) 3.71 (td, *J*=11.8, 3.2 Hz, 1 H) 3.83 - 3.94 (m, 1 H) 4.01 (br d, *J*=11.8 Hz, 1 H) 4.10 (dd, *J*=11.8, 3.2 Hz, 1 H) 4.26 - 4.42 (m, 1 H) 7.06 - 7.09 (m, 2 H) 7.24 (br d, *J*=9.5 Hz, 1 H) 7.41 (d, *J*=9.5 Hz, 1 H) 9.65 - 9.97 (m, 1 H)
399		374 1.28 U	1H NMR (500 MHz, DMSO-d_6, 27°C) δ ppm 3.20 - 3.25 (m, 4 H) 4.16 - 4.22 (m, 4 H) 6.97 (d, *J*=2.0 Hz, 1 H) 7.15 (d, *J*=2.0 Hz, 1 H) 7.46 (d, *J*=9.5 Hz, 1 H) 7.50 (d, *J*=9.5 Hz, 1 H) 10.49 - 10.66 (m, 1 H)
400		358 1.16 U	1H NMR (500 MHz, DMSO-d_6, 27°C) δ ppm 2.76 (dt, *J*=13.9, 2.0 Hz, 2 H) 2.97 (ddd, *J*=13.9, 11.2, 3.4 Hz, 2 H) 4.00 (ddd, *J*=14.8, 11.2, 2.0 Hz, 2 H) 4.30 (dt, *J*=14.8, 3.4 Hz, 2 H) 6.97 (d, *J*=2.1 Hz, 1 H) 7.14 (d, *J*=2.1 Hz, 1 H) 7.42 (d, *J*=9.5 Hz, 1 H) 7.45 (d, *J*=9.5 Hz, 1 H) 10.49 - 10.72 (m, 1 H)
402		395 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.76 - 1.94 (m, 2 H), 2.05 - 2.15 (m, 1 H), 2.18 (s, 3 H), 2.30 - 2.39 (m, 1 H), 2.52 - 2.55 (m hidden, 2 H), 3.17 (td, J=3.8 and 12.7 Hz, 1 H), 3.64 (td, J=3.3 and 11.8 Hz, 1 H), 3.75 (br q, J=2.8 Hz, 1 H), 3.94 (br d, J=12.7 Hz, 1 H), 4.05 (br dd, J=3.3 and 11.8 Hz, 1 H), 4.37 - 4.47 (m, 1 H), 7.17 - 7.29 (m, 3 H), 7.35 (d, J=9.5 Hz, 1 H), 7.42 - 7.48 (m, 1 H), 10.01 - 10.13 (m, 1 H)

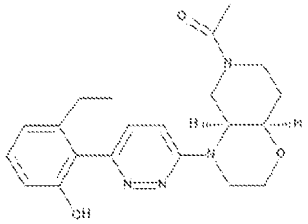
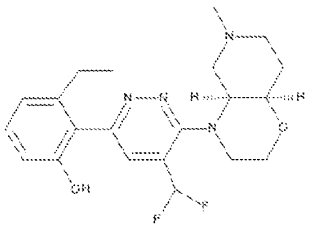
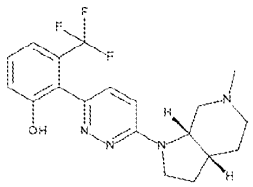
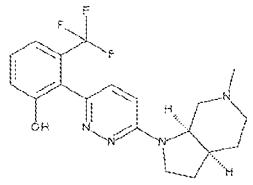
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
403		342 1.03 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.74 - 1.81 (m, 1 H) 1.91 - 2.00 (m, 1 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 3.16 (td, *J*=12.7, 3.8 Hz, 1 H) 3.47 - 3.77 (m, 5 H) 3.86 - 3.97 (m, 2 H) 4.08 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.41 - 4.49 (m, 1 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.23 (d, *J*=9.5 Hz, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 9.35 (br s, 1 H)
404		369 0.82 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.97 (t, *J*=7.0 Hz, 3 H) 1.75 - 1.90 (m, 2 H) 2.03 (s, 3 H) 2.05 - 2.13 (m, 1 H) 2.22 (s, 3 H) 2.30 - 2.41 (m, 3 H) 2.56 - 2.65 (m, 2 H) 3.16 (td, *J*=12.7, 3.8 Hz, 1 H) 3.63 (td, *J*=11.8, 3.3 Hz, 1 H) 3.75 (br q, *J*=2.8 Hz, 1 H) 3.93 (br d, *J*=12.7 Hz, 1 H) 4.04 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.33 - 4.45 (m, 1 H) 6.57 (s, 1 H) 6.58 (s, 1 H) 7.19 (d, *J*=9.5 Hz, 1 H) 7.34 (d, *J*=9.5 Hz, 1 H) 9.36 (s, 1 H)
405		433 1.36 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.70 - 1.82 (m, 1 H), 1.83 - 1.93 (m, 1 H), 1.96 (s, 3 H), 2.08 (s, 3 H), 2.27 (s, 3 H), 2.72 - 3.23 (m partially hidden, 2 H), 3.32 - 3.40 (m, 1 H), 3.46 - 4.27 (m partially hidden, 2 H), 3.63 - 3.71 (m, 1 H), 3.76 - 3.88 (m, 2 H), 4.00 - 4.10 (m, 2 H), 6.64 (br s, 1 H), 6.65 (br s, 1 H), 7.15 (t, J=53.7 Hz, 1 H), 7.64 (s, 1 H), 9.09 (br s, 1 H)
406		407.5 2.71 E	^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.16 (s, 1H), 7.31 (d, *J* = 9.3 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 9.3 Hz, 1H), 4.29 – 4.13 (m, 1H), 3.56 (t, *J* = 9.6 Hz, 1H), 3.49 – 3.37 (m, 1H), 3.22 – 3.07 (m, 1H), 2.76 – 2.65 (m, 1H), 2.45 – 2.27 (m, 3H), 2.20 – 2.00 (m, 5H), 1.97 – 1.84 (m, 2H), 1.80 (t, *J* = 10.6 Hz, 1H), 1.74 – 1.63 (m, 1H), 0.99 (t, *J* = 7.1 Hz, 3H).

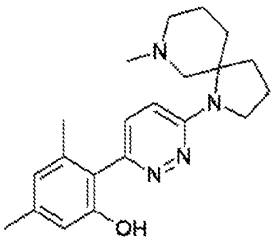
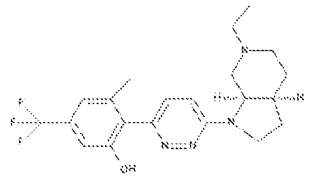
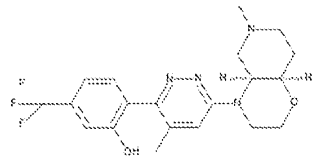
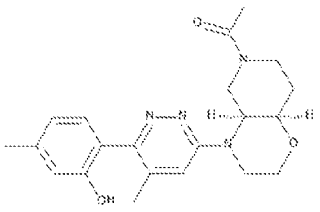
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
407		379.5 2.44 E	^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): δ 7.46 (d, *J* = 9.6 Hz, 1H), 7.17 (d, *J* = 1.7 Hz, 1H), 7.03 (s, 1H), 6.80 (d, *J* = 9.5 Hz, 1H), 4.20 (s, 1H), 3.72 (t, *J* = 9.7 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.44 (s, 1H), 2.89 (d, *J* = 12.6 Hz, 1H), 2.77 (td, *J* = 12.3, 3.2 Hz, 1H), 2.65 – 2.50 (m, 2H), 2.45 (s, 3H), 2.33 – 2.19 (m, 1H), 2.06 – 1.92 (m, 2H), 1.77 (d, *J* = 14.2 Hz, 1H) (NH and OH not visible).
408		368 0.82 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.92 - 1.01 (m, 6 H) 1.75 - 1.91 (m, 2 H) 2.10 (td, *J*=11.4, 3.8 Hz, 1 H) 2.30 - 2.43 (m, 5 H) 2.56 - 2.65 (m, 2 H) 3.17 (td, *J*=12.7, 3.8 Hz, 1 H) 3.63 (td, *J*=11.8, 3.3 Hz, 1 H) 3.76 (br q, *J*=2.8 Hz, 1 H) 3.94 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.35 - 4.44 (m, 1 H) 6.77 (d, *J*=7.8 Hz, 2 H) 7.14 (t, *J*=7.8 Hz, 1 H) 7.20 (d, *J*=9.5 Hz, 1 H) 7.33 (d, *J*=9.5 Hz, 1 H) 9.32 (s, 1 H)
409		369 0.95 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.82 - 1.91 (m, 2 H), 2.04 (s, 3 H), 2.12 (s, 3 H), 2.69 - 3.21 (m partially hidden, 2 H), 3.27 (td, J=3.8 and 12.6 Hz, 1 H), 3.60 - 4.45 (m partially hidden, 2 H), 3.73 (td, J=3.2 and 11.8 Hz, 1 H), 3.91 (br q, J=2.8 Hz, 1 H), 4.01 (br d, J=12.6 Hz, 1 H), 4.11 (dd, J=3.8 and 11.8 Hz, 1 H), 4.29 - 4.43 (m, 1 H), 6.75 - 6.81 (m, 2 H), 7.11 (t, J=7.8 Hz, 1 H), 7.23 (br d, J=9.5 Hz, 1 H), 7.40 (d, J=9.5 Hz, 1 H), 9.11 - 9.21 (m, 1 H)
410		339 0.71 and 0.72 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.56 - 1.66 (m, 1 H) 1.79 - 1.90 (m, 1 H) 1.93 - 2.09 (m, 2 H) 2.05 (s, 3 H) 2.22 (s, 3 H) 2.25 (s, 3 H) 2.26 - 2.34 (m, 3 H) 2.92 - 3.00 (m, 2 H) 3.40 (br dd, *J*=11.5, 3.0 Hz, 1 H) 3.51 (br d, *J*=11.5 Hz, 1 H) 4.73 - 4.87 (m, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.96 (d, *J*=9.5 Hz, 1 H) 7.28 (d, *J*=9.5 Hz, 1 H) 9.42 (br s, 1 H)

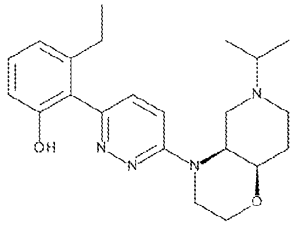
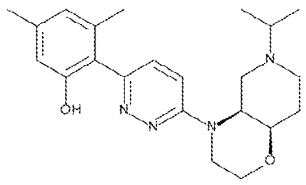
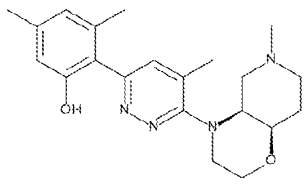
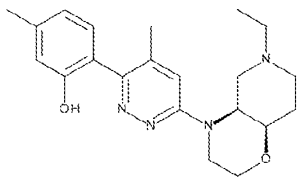
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
411		327 0.69 and 0.70 U	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 1.75 - 1.87 (m, 2 H) 2.06 (s, 3 H) 2.64 - 2.78 (m, 3 H) 2.99 (t, *J*=11.8 Hz, 1 H) 3.16 (td, *J*=12.6, 3.8 Hz, 2 H) 3.63 (td, *J*=11.8, 3.2 Hz, 1 H) 3.85 (br q, *J*=2.6 Hz, 1 H) 3.95 (br d, *J*=12.6 Hz, 1 H) 4.06 (dd, *J*=11.8, 3.8 Hz, 1 H) 4.31 - 4.38 (m, 1 H) 6.72 - 6.78 (m, 2 H) 7.07 - 7.12 (m, 1 H) 7.22 (d, *J*=9.5 Hz, 1 H) 7.36 (d, *J*=9.5 Hz, 1 H) 9.37 - 9.48 (m, 1 H)
412		355 0.73 U	1H NMR (500 MHz, DMSO-d_6, 27°C) δ ppm 0.97 (t, *J*=7.0 Hz, 3 H) 1.76 - 1.91 (m, 2 H) 2.04 - 2.12 (m, 1 H) 2.06 (s, 3 H) 2.31 - 2.41 (m, 3 H) 2.58 - 2.64 (m, 2 H) 3.16 (td, *J*=12.7, 3.8 Hz, 1 H) 3.63 (td, *J*=11.8, 3.3 Hz, 1 H) 3.76 (q, *J*=2.8 Hz, 1 H) 3.94 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.36 - 4.44 (m, 1 H) 6.73 - 6.78 (m, 2 H) 7.10 (t, *J*=7.8 Hz, 1 H) 7.21 (d, *J*=9.5 Hz, 1 H) 7.36 (d, *J*=9.5 Hz, 1 H) 9.44 (br s, 1 H)
413		367 0.92 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.63 - 1.76 (m, 1 H), 1.84 - 1.98 (m, 1 H), 1.94 (br s, 3 H), 2.02 - 2.07 (m, 2 H), 2.08 (s, 3 H), 2.22 (s, 3 H), 2.51 - 2.58 (m partially hidden, 1 H), 3.26 - 3.37 (m, 1 H), 3.40 - 3.49 (m, 1 H), 3.55 - 3.66 (m, 2 H), 3.85 - 4.65 (m, 2 H), 4.13 - 4.29 (m, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 6.89 (br d, J=9.5 Hz, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 9.07 - 9.25 (m, 1 H)
414		367 0.92 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.61 - 1.77 (m, 1 H), 1.85 - 1.98 (m, 1 H), 1.93 (br s, 3 H), 2.01 - 2.07 (m, 2 H), 2.08 (s, 3 H), 2.22 (s, 3 H), 2.51 - 2.59 (m partially hidden, 1 H), 3.26 - 3.37 (m, 1 H), 3.40 - 3.49 (m, 1 H), 3.56 - 3.66 (m, 2 H), 3.84 - 4.66 (m, 2 H), 4.14 - 4.24 (m, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 6.88 (br d, J=9.5 Hz, 1 H), 7.31 (d, J=9.5 Hz, 1 H), 9.10 - 9.24 (m, 1 H)

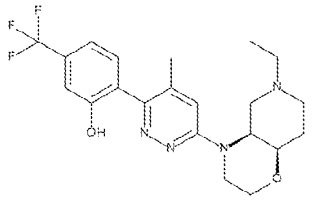
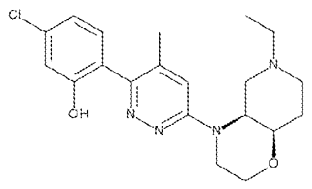
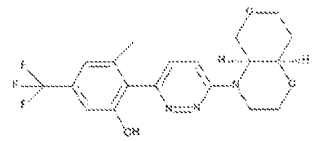
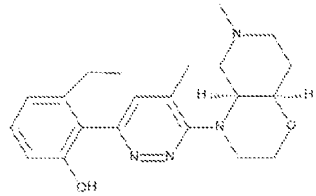
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
415		325 0.60 and 0.63 U	1H NMR (500 MHz, DMSO-d6, 27°C) d ppm 1.66 - 1.81 (m, 2 H), 1.85 - 2.05 (m, 3 H), 2.05 - 2.14 (m, 1 H), 2.06 (s, 3 H), 2.17 (s, 3 H), 2.33 - 2.41 (m, 1 H), 2.51 - 2.55 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.37 - 3.44 (m, 1 H), 3.52 - 3.60 (m, 1 H), 4.17 - 4.26 (m, 1 H), 6.71 - 6.78 (m, 2 H), 6.88 (d, J=9.5 Hz, 1 H), 7.08 (t, J=8.0 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 9.46 (br s, 1 H)
416		325 0.61 and 0.63 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.67 - 1.81 (m, 2 H), 1.87 - 2.05 (m, 3 H), 2.07 (s, 3 H), 2.05 - 2.14 (m, 1 H), 2.17 (s, 3 H), 2.32 - 2.41 (m, 1 H), 2.52 - 2.56 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.36 - 3.44 (m, 1 H), 3.52 - 3.60 (m, 1 H), 4.17 - 4.26 (m, 1 H), 6.71 - 6.78 (m, 2 H), 6.88 (d, J=9.5 Hz, 1 H), 7.08 (t, J=8.0 Hz, 1 H), 7.27 (d, J=9.5 Hz, 1 H), 9.45 (s, 1 H)
417		393 0.91 B	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.58 - 1.69 (m, 1 H), 1.83 - 1.92 (m, 1 H), 1.96 - 2.11 (m, 2 H), 2.18 (s, 3 H), 2.28 (s, 3 H), 2.29 - 2.35 (m, 1 H), 2.35 - 2.43 (m, 2 H), 2.94 - 2.97 (m partially hidden, 2 H), 3.45 (br dd, J=3.5 and 11.5 Hz, 1 H), 3.57 (br d, J=11.5 Hz, 1 H), 4.79 - 4.87 (m, 1 H), 6.96 (d, J=9.4 Hz, 1 H), 7.06 (br s, 2 H), 7.32 (d, J=9.4 Hz, 1 H), 9.58 - 10.10 (m, 1 H)
418		384.3 2.59 E	1H NMR (500 MHz, DMSO) δ (ppm): 10.13 (s, 1H), 7.40 (d, *J* = 9.4 Hz, 1H), 7.31 (d, *J* = 9.4 Hz, 1H), 7.11 (s, 1H), 7.06 (s, 1H), 4.83 (t, *J* = 5.5 Hz, 1H), 4.35 (d, *J* = 12.7 Hz, 1H), 4.15 (d, *J* = 12.8 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.62 (td, *J* = 11.6, 2.8 Hz, 1H), 3.57 – 3.50 (m, 2H), 3.47 (q, *J* = 6.3 Hz, 1H), 2.99 (td, *J* = 12.3, 3.5 Hz, 1H), 2.73 (dd, *J* = 12.9, 9.9 Hz, 1H), 2.45 (q, *J* = 7.7 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).
419		384 1.23 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.12 (s, 3 H) 3.73 - 3.80 (m, 1 H) 3.87 - 3.93 (m, 1 H) 3.95 - 4.03 (m, 1 H) 4.06 - 4.15 (m, 1 H) 4.20 - 4.29 (m, 2 H) 4.37 (dd, *J*=4.0, 2.5 Hz, 1 H) 5.01 (br t, *J*=5.7 Hz, 1 H) 7.10 (br s, 1 H) 7.17 (br s, 1 H) 7.74 (d, *J*=9.3 Hz, 1 H) 8.32 (d, *J*=9.3 Hz, 1 H) 10.20 - 10.47 (m, 1 H)

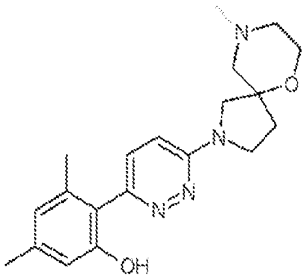
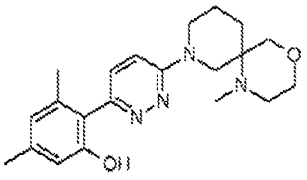
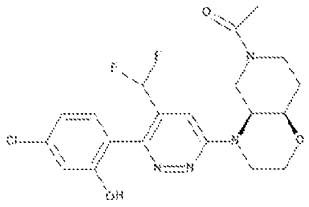
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
420		384 1.23 B	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 2.12 (s, 3 H) 3.73 - 3.80 (m, 1 H) 3.87 - 3.94 (m, 1 H) 3.95 - 4.03 (m, 1 H) 4.06 - 4.14 (m, 1 H) 4.20 - 4.29 (m, 2 H) 4.37 (dd, *J*=4.0, 2.5 Hz, 1 H) 5.01 (br t, *J*=5.7 Hz, 1 H) 7.11 (br s, 1 H) 7.17 (br s, 1 H) 7.74 (d, *J*=9.3 Hz, 1 H) 8.32 (d, *J*=9.3 Hz, 1 H) 10.19 - 10.54 (m, 1 H)
421		342 1.10 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.63 - 1.75 (m, 1 H), 1.83 - 1.90 (m, 1 H), 2.02 (s, 3 H), 2.23 (s, 3 H), 3.04 (dd, J=9.7 and 10.6 Hz, 1 H), 3.20 - 3.27 (m partially hidden, 1 H), 3.35 - 3.40 (m partially hidden, 1 H), 3.47 (br td, J=1.9 and 11.8 Hz, 1 H), 3.63 - 3.76 (m, 2 H), 3.84 - 3.99 (m, 3 H), 4.57 (dd, J=3.7 and 10.6 Hz, 1 H), 6.59 (br s, 1 H), 6.60 (br s, 1 H), 7.36 (d, J=9.3 Hz, 1 H), 7.44 (d, J=9.3 Hz, 1 H), 9.34 - 9.43 (m, 1 H)
422		339 0.74 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.95 (t, J=7.5 Hz, 3 H), 1.67 - 1.81 (m, 2 H), 1.86 - 2.14 (m, 4 H), 2.17 (s, 3 H), 2.32 - 2.43 (m, 3 H), 2.52 - 2.58 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.47 (m, 1 H), 3.51 - 3.60 (m, 1 H), 4.16 - 4.26 (m, 1 H), 6.75 (d, J=7.8 Hz, 2 H), 6.87 (d, J=9.3 Hz, 1 H), 7.12 (t, J=7.8 Hz, 1 H), 7.23 (d, J=9.3 Hz, 1 H), 9.30 (br s, 1 H)
423		339 0.72 and 0.73 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.95 (t, J=7.5 Hz, 3 H), 1.67 - 1.81 (m, 2 H), 1.87 - 2.14 (m, 4 H), 2.17 (s, 3 H), 2.34 - 2.43 (m, 3 H), 2.52 - 2.56 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.46 (m, 1 H), 3.51 - 3.61 (m, 1 H), 4.17 - 4.26 (m, 1 H), 6.75 (d, J=7.8 Hz, 2 H), 6.87 (d, J=9.3 Hz, 1 H), 7.12 (t, J=7.8 Hz, 1 H), 7.23 (d, J=9.3 Hz, 1 H), 9.30 (br s, 1 H)

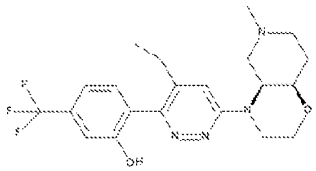
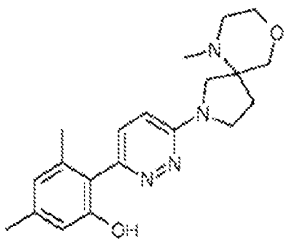
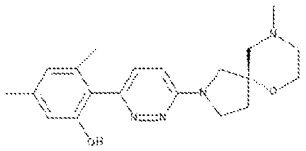
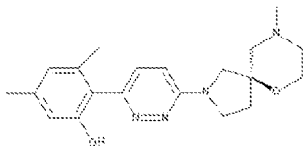
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
424		383 1.04 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 0.98 (t, J=7.5 Hz, 3 H), 1.80 - 1.88 (m, 2 H), 2.01 (s, 3 H), 2.42 (q, J=7.5 Hz, 2 H), 2.68 - 3.38 (m partially hidden, 2 H), 3.25 (td, J=3.8 and 12.7 Hz, 1 H), 3.57 - 4.47 (m partially hidden, 2 H), 3.71 (td, J=3.3 and 11.8 Hz, 1 H), 3.89 (br q, J=2.8 Hz, 1 H), 3.98 (br d, J=12.7 Hz, 1 H), 4.09 (dd, J=3.3 and 11.8 Hz, 1 H), 4.24 - 4.41 (m, 1 H), 6.77 (br d, J=7.9 Hz, 2 H), 7.13 (t, J=7.9 Hz, 1 H), 7.20 (br d, J=9.3 Hz, 1 H), 7.34 (br d, J=9.3 Hz, 1 H), 8.94 (br s, 1 H)
425		405 0.96 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.95 (t, J=7.5 Hz, 3 H), 1.74 - 1.86 (m, 2 H), 2.04 - 2.12 (m, 1 H), 2.16 (s, 3 H), 2.39 (q, J=7.5 Hz, 2 H), 2.43 - 2.48 (m partially hidden, 2 H), 2.54 - 2.64 (m, 1 H), 3.30 - 3.33 (m partially hidden, 1 H), 3.61 - 3.78 (m, 2 H), 3.82 - 3.89 (m, 1 H), 3.92 (br q, J=2.8 Hz, 1 H), 3.96 - 4.02 (m, 1 H), 6.78 - 6.83 (m, 2 H), 7.21 (br t, J=53.5 Hz, 1 H), 7.20 (t, J=7.9 Hz, 1 H), 7.65 (s, 1 H), 9.50 (s, 1 H)
426		379 0.85 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.81 (m, 2 H), 1.85 - 2.16 (m, 4 H), 2.17 (s, 3 H), 2.34 - 2.43 (m, 1 H), 2.53 - 2.57 (m partially hidden, 1 H), 3.06 (dd, J=6.0 and 10.5 Hz, 1 H), 3.36 - 3.44 (m, 1 H), 3.52 - 3.60 (m, 1 H), 4.14 - 4.27 (m, 1 H), 6.88 (d, J=9.3 Hz, 1 H), 7.20 - 7.27 (m, 3 H), 7.43 (t, J=8.0 Hz, 1 H), 9.90 - 10.19 (m, 1 H)
427		379 0.85 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.67 - 1.81 (m, 2 H), 1.85 - 2.16 (m, 4 H), 2.17 (s, 3 H), 2.34 - 2.42 (m, 1 H), 2.53 - 2.57 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.36 - 3.45 (m, 1 H), 3.52 - 3.60 (m, 1 H), 4.14 - 4.27 (m, 1 H), 6.88 (d, J=9.3 Hz, 1 H), 7.20 - 7.27 (m, 3 H), 7.43 (t, J=8.0 Hz, 1 H), 9.97 - 10.13 (m, 1 H)

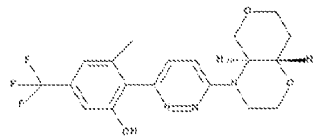
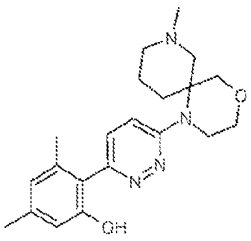
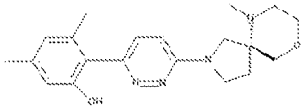
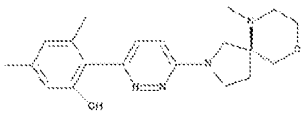
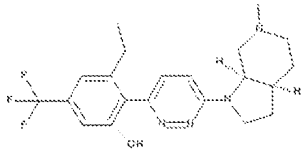
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
428		353 0.80 B	1H NMR (500 MHz, DMSO-d_6, 27°C) δ ppm 1.44 - 1.81 (m, 8 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.35 (br s, 3 H) 2.72 - 2.87 (m, 4 H) 4.02 (br d, *J*=12.6 Hz, 1 H) 4.36 (br d, *J*=12.6 Hz, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 7.25 - 7.26 (m, 2 H) 9.41 (br s, 1 H)
429		407.5 2.73 E	^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.14 (s, 1H), 7.31 (d, *J* = 9.3 Hz, 1H), 7.11 (s, 1H), 7.06 (s, 1H), 6.92 (d, *J* = 9.4 Hz, 1H), 4.31 – 4.13 (m, 1H), 3.68 – 3.51 (m, 1H), 3.49 – 3.37 (m, 1H), 3.20 – 3.08 (m, 1H), 2.68 – 2.59 (m, 1H), 2.45 – 2.29 (m, 3H), 2.20 – 2.02 (m, 5H), 2.01 – 1.87 (m, 2H), 1.81 (t, *J* = 10.6 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H).
430		409 0.93 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.75 - 1.94 (m, 2 H), 2.07 - 2.15 (m, 1 H), 2.10 (s, 3 H), 2.19 (s, 3 H), 2.30 - 2.38 (m, 1 H), 2.52 - 2.58 (m partially hidden, 2 H), 3.15 (td, J=3.8 and 12.7 Hz, 1 H), 3.61 (td, J=3.3 and 11.8 Hz, 1 H), 3.73 (br q, J=2.8 Hz, 1 H), 3.93 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=3.3 and 11.8 Hz, 1 H), 4.37 - 4.49 (m, 1 H), 7.12 (br s, 1 H), 7.22 (br s, 1 H), 7.24 (br d, J=7.8 Hz, 1 H), 7.41 (d, J=7.8 Hz, 1 H), 10.44 (s, 1 H)
431		383 0.95 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.80 - 1.92 (m, 2 H), 2.04 (s, 3 H), 2.17 (br s, 3 H), 2.31 (s, 3 H), 2.73 - 3.38 (m partially hidden, 2 H), 3.25 (td, J=3.8 and 12.7 Hz, 1 H), 3.54 - 4.26 (m partially hidden, 2 H), 3.71 (td, J=3.3 and 11.8 Hz, 1 H), 3.88 (br q, J=2.8 Hz, 1 H), 3.97 (br d, J=12.7 Hz, 1 H), 4.10 (dd, J=3.3 and 11.8 Hz, 1 H), 4.28 - 4.40 (m, 1 H), 6.73 (br d, J=7.8 Hz, 1 H), 6.77 (br s, 1 H), 7.08 (br s, 1 H), 7.12 (d, J=7.8 Hz, 1 H), 9.39 - 9.53 (m, 1 H)

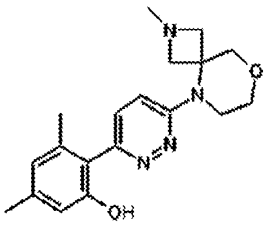
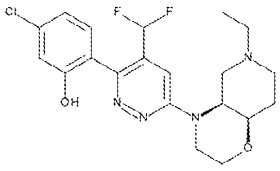
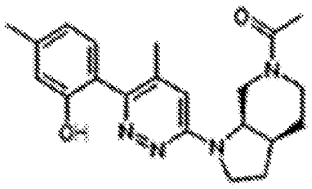
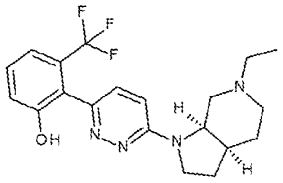
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
432		383 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.92 - 1.07 (m, 9 H), 1.81 - 1.93 (m, 2 H), 2.26 - 3.00 (m partially hidden, 5 H), 2.38 (q, J=7.3 Hz, 2 H), 3.20 (br td, J=3.8 and 12.7 Hz, 1 H), 3.64 (br td, J=3.3 and 11.8 Hz, 1 H), 3.75 - 3.81 (m, 1 H), 3.94 (br d, J=12.7 Hz, 1 H), 4.06 (dd, J=3.3 and 11.8 Hz, 1 H), 4.25 - 4.63 (m, 1 H), 6.77 (d, J=7.9 Hz, 2 H), 7.14 (t, J=7.9 Hz, 1 H), 7.20 (d, J=9.5 Hz, 1 H), 7.35 (d, J=9.5 Hz, 1 H), 9.36 (s, 1 H)
433		383 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.96 (br dd, J=6.8 and 10.1 Hz, 6 H), 1.77 - 1.86 (m, 2 H), 2.03 (s, 3 H), 2.22 (s, 3 H), 2.28 - 2.40 (m, 1 H), 2.52 - 2.58 (m partially hidden, 2 H), 2.58 - 2.65 (m, 1 H), 2.69 - 2.80 (m, 1 H), 3.18 (td, J=3.8 and 12.7 Hz, 1 H), 3.62 (td, J=3.3 and 11.8 Hz, 1 H), 3.76 (br q, J=2.8 Hz, 1 H), 3.93 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=3.3 and 11.8 Hz, 1 H), 4.24 - 4.46 (m, 1 H), 6.57 (br s, 1 H), 6.58 (br s, 1 H), 7.18 (d, J=9.5 Hz, 1 H), 7.34 (d, J=9.5 Hz, 1 H), 9.38 (s, 1 H)
434		369 0.85 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.70 - 1.87 (m, 2 H), 2.01 (s, 3 H), 2.03 - 2.12 (m, 1 H), 2.15 (s, 3 H), 2.23 (s, 3 H), 2.28 (s, 3 H), 2.38 - 2.48 (m partially hidden, 2 H), 2.59 (t, J=10.9 Hz, 1 H), 3.24 - 3.29 (m partially hidden, 1 H), 3.56 - 3.69 (m, 2 H), 3.74 (td, J=2.6 and 11.6 Hz, 1 H), 3.85 (q, J=2.8 Hz, 1 H), 3.97 (br dd, J=2.6 and 11.0 Hz, 1 H), 6.58 (br s, 1 H), 6.59 (br s, 1 H), 7.30 (br s, 1 H), 9.38 (s, 1 H)
435		369 1.71 Z2	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.98 (t, *J*=7.3 Hz, 3 H) 1.75 - 1.94 (m, 2 H) 2.03 - 2.16 (m, 1 H) 2.10 (s, 3 H) 2.28 (s, 3 H) 2.30 - 2.44 (m, 3 H) 2.56 - 2.65 (m, 2 H) 3.14 (td, *J*=12.7, 3.8 Hz, 1 H) 3.60 (td, *J*=11.8, 3.3 Hz, 1 H) 3.73 (br q, *J*=2.8 Hz, 1 H) 3.90 (br d, *J*=12.7 Hz, 1 H) 4.04 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.33 - 4.47 (m, 1 H) 6.70 (br d, *J*=7.8 Hz, 1 H) 6.73 (br s, 1 H) 7.05 - 7.08 (m, 2 H) 9.65 (s, 1 H)

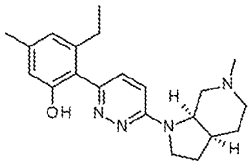
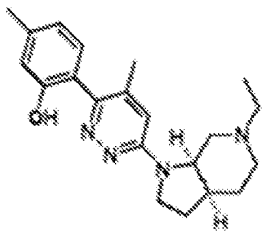
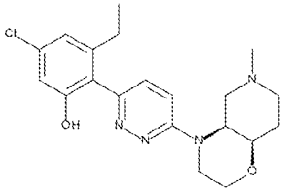
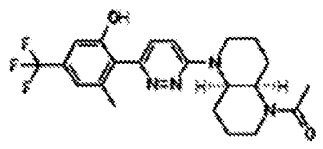
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
436		423 2.54 Z2	1H NMR (400 MHz, DMSO-d_6, 30°C) δ ppm 0.98 (t, *J*=7.3 Hz, 3 H) 1.75 - 1.92 (m, 2 H) 2.04 - 2.13 (m, 1 H) 2.10 (br s, 3 H) 2.26 - 2.45 (m, 3 H) 2.56 - 2.65 (m, 2 H) 3.16 (td, *J*=12.7, 3.8 Hz, 1 H) 3.61 (td, *J*=11.8, 3.3 Hz, 1 H) 3.74 (q, *J*=2.8 Hz, 1 H) 3.93 (br d, *J*=12.7 Hz, 1 H) 4.05 (dd, *J*=11.8, 3.3 Hz, 1 H) 4.38 - 4.47 (m, 1 H) 7.12 (br s, 1 H) 7.22 (d, *J*=1.6 Hz, 1 H) 7.24 (dd, *J*=7.8, 1.6 Hz, 1 H) 7.41 (d, *J*=7.8 Hz, 1 H) 10.38 - 10.51 (m, 1 H)
437		389 2.14 Z2	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.97 (br t, J=7.3 Hz, 3 H), 1.76 - 1.92 (m, 2 H), 2.03 - 2.15 (m, 1 H), 2.09 (br s, 3 H), 2.31 - 2.42 (m, 3 H), 2.57 - 2.67 (m partially hidden, 2 H), 3.15 (br t, J=12.7 Hz, 1 H), 3.60 (br t, J=11.8 Hz, 1 H), 3.69 - 3.76 (m, 1 H), 3.91 (br d, J=12.7 Hz, 1 H), 4.04 (br d, J=11.8 Hz, 1 H), 4.34 - 4.46 (m, 1 H), 6.90 - 7.01 (m, 2 H), 7.09 (br s, 1 H), 7.20 (br d, J=7.8 Hz, 1 H), 10.25 (br s, 1 H)
438		396 1.41 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.75 - 1.82 (m, 1 H), 1.92 - 2.04 (m, 1 H), 2.13 (s, 3 H), 3.18 (td, J=3.8 and 12.7 Hz, 1 H), 3.44 - 3.78 (m, 5 H), 3.91 (br q, J=2.8 Hz, 1 H), 3.93 - 3.99 (m, 1 H), 4.09 (dd, J=3.3 and 11.8 Hz, 1 H), 4.42 - 4.54 (m, 1 H), 7.06 (br s, 1 H), 7.11 (br s, 1 H), 7.29 (d, J=9.5 Hz, 1 H), 7.40 (d, J=9.5 Hz, 1 H), 10.06 - 10.23 (m, 1 H)
439		369 0.89 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.94 (t, J=7.6 Hz, 3 H), 1.71 - 1.88 (m, 2 H), 2.04 - 2.13 (m, 1 H), 2.15 (s, 3 H), 2.28 (br s, 3 H), 2.35 (q, J=7.6 Hz, 2 H), 2.38 - 2.48 (m partially hidden, 2 H), 2.60 (br t, J=11.0 Hz, 1 H), 3.25 - 3.31 (m partially hidden, 1 H), 3.57 - 3.69 (m, 2 H), 3.74 (td, J=2.5 and 11.8 Hz, 1 H), 3.85 (br q, J=2.8 Hz, 1 H), 3.97 (dd, J=2.5 and 11.0 Hz, 1 H), 6.78 (d, J=7.8 Hz, 2 H), 7.16 (t, J=7.8 Hz, 1 H), 7.31 (br s, 1 H), 9.33 (s, 1 H)

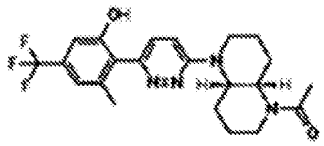
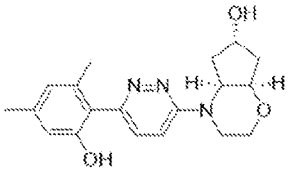
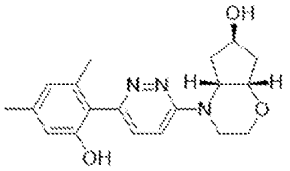
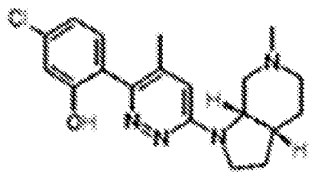
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
440		355 0.69 and 0.7 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.98 - 2.07 (m, 1 H), 2.03 (s, 3 H), 2.11 - 2.18 (m, 1 H), 2.19 (s, 3 H), 2.22 (s, 3 H), 2.24 - 2.29 (m, 1 H), 2.29 - 2.33 (m, 1 H), 2.34 - 2.41 (m, 1 H), 2.47 - 2.53 (m hidden, 1 H), 3.43 - 3.63 (m, 3 H), 3.64 - 3.74 (m, 3 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.89 (d, J=9.3 Hz, 1 H), 7.27 (d, J=9.3 Hz, 1 H), 9.38 (s, 1 H)
441		369 0.79 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.55 - 1.76 (m, 3 H), 1.78 - 1.89 (m, 1 H), 2.03 (s, 3 H), 2.22 (s, 3 H), 2.33 (s, 3 H), 2.53 - 2.56 (m partially hidden, 1 H), 2.69 - 2.78 (m, 1 H), 2.84 - 2.93 (m, 1 H), 3.21 (d, J=12.9 Hz, 1 H), 3.28 - 3.30 (m partially hidden, 1 H), 3.53 (d, J=11.3 Hz, 1 H), 3.56 - 3.61 (m, 1 H), 3.61 - 3.69 (m, 1 H), 4.22 (br d, J=12.9 Hz, 1 H), 4.24 - 4.31 (m, 1 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 7.20 (d, J=9.5 Hz, 1 H), 7.28 (d, J=9.5 Hz, 1 H), 9.36 - 9.47 (m, 1 H)
442		439 1.41 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.83 - 1.92 (m, 2 H), 2.04 (s, 3 H), 2.73 - 3.24 (m partially hidden, 2 H), 3.32 (td, J=3.8 and 12.7 Hz, 1 H), 3.53 - 4.31 (m partially hidden, 2 H), 3.73 (td, J=3.3 and 11.8 Hz, 1 H), 3.91 (br q, J=2.8 Hz, 1 H), 4.05 - 4.15 (m, 2 H), 4.36 - 4.51 (m, 1 H), 6.76 (t, J=54.5 Hz, 1 H), 6.98 (dd, J=2.0 and 8.1 Hz, 1 H), 7.01 (d, J=2.0 Hz, 1 H), 7.30 (d, J=8.1 Hz, 1 H), 7.36 (br s, 1 H), 9.45 - 10.55 (m, 1 H)

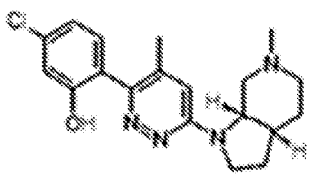
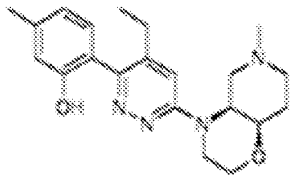
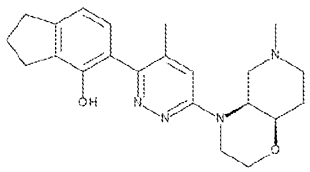
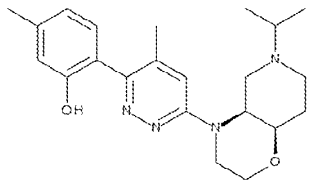
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
443		423 1.04 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.00 (t, J=7.6 Hz, 3 H), 1.76 - 1.93 (m, 2 H), 2.04 - 2.13 (m, 1 H), 2.18 (s, 3 H), 2.29 - 2.36 (m, 1 H), 2.40 (q, J=7.6 Hz, 2 H), 2.52 - 2.57 (m partially hidden, 2 H), 3.16 (td, J=3.8 and 12.7 Hz, 1 H), 3.62 (td, J=3.3 and 11.8 Hz, 1 H), 3.73 (br q, J=2.8 Hz, 1 H), 3.94 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=3.3 and 11.8 Hz, 1 H), 4.42 - 4.51 (m, 1 H), 7.06 (s, 1 H), 7.21 (br s, 1 H), 7.24 (br d, J=7.8 Hz, 1 H), 7.39 (d, J=7.8 Hz, 1 H), 10.25 - 10.46 (m, 1 H)
444		355 0.66 K	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.79 - 1.87 (m, 1 H), 2.04 (s, 3 H), 2.20 - 2.26 (m, 1 H), 2.22 (s, 3 H), 2.24 (s, 3 H), 2.52 - 2.53 (m hidden, 2 H), 3.32 - 3.36 (m partially hidden, 1 H), 3.42 - 3.55 (m, 3 H), 3.59 - 3.69 (m, 4 H), 6.57 (br s, 1 H), 6.57 (br s, 1 H), 6.93 (d, J=9.3 Hz, 1 H), 7.29 (d, J=9.3 Hz, 1 H), 9.37 (s, 1 H)
445		355 0.67 K	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.98 - 2.06 (m, 1 H), 2.03 (s, 3 H), 2.12 - 2.17 (m, 1 H), 2.19 (s, 3 H), 2.22 (s, 3 H), 2.23 - 2.29 (m, 1 H), 2.29 - 2.34 (m, 1 H), 2.34 - 2.40 (m, 1 H), 2.46 - 2.50 (m partially hidden, 1 H), 3.47 - 3.63 (m, 3 H), 3.63 - 3.73 (m, 3 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.89 (d, J=9.3 Hz, 1 H), 7.27 (d, J=9.3 Hz, 1 H), 9.39 (br s, 1 H)
446		355 0.66 K	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.98 - 2.06 (m, 1 H), 2.03 (s, 3 H), 2.13 - 2.17 (m, 1 H), 2.19 (s, 3 H), 2.22 (s, 3 H), 2.24 - 2.29 (m, 1 H), 2.29 - 2.34 (m, 1 H), 2.34 - 2.41 (m, 1 H), 2.46 - 2.49 (m partially hidden, 1 H), 3.48 - 3.63 (m, 3 H), 3.63 - 3.73 (m, 3 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.89 (d, J=9.3 Hz, 1 H), 7.27 (d, J=9.3 Hz, 1 H), 9.39 (br s, 1 H)

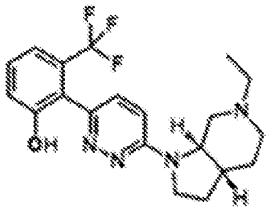
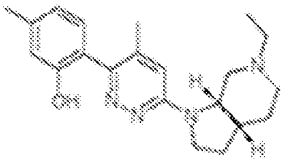
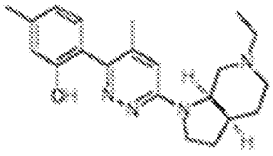
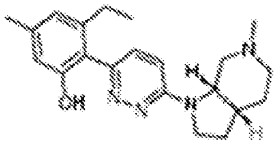
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
448		396 1.46 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.64 - 1.75 (m, 1 H), 1.85 - 1.91 (m, 1 H), 2.12 (s, 3 H), 3.07 (dd, J=9.7 and 10.6 Hz, 1 H), 3.33 - 3.44 (m partially hidden, 2 H), 3.48 (td, J=1.9 and 11.8 Hz, 1 H), 3.70 - 3.78 (m, 2 H), 3.85 - 4.00 (m, 3 H), 4.59 (dd, J=3.7 and 10.6 Hz, 1 H), 7.08 (br s, 1 H), 7.13 (br s, 1 H), 7.42 (d, J=9.3 Hz, 1 H), 7.51 (d, J=9.3 Hz, 1 H), 10.09 - 10.29 (m, 1 H)
449		369 0.79 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.54 - 1.74 (m, 3 H), 1.77 - 1.89 (m, 1 H), 2.03 (s, 3 H), 2.22 (s, 3 H), 2.33 (br s, 3 H), 2.54 - 2.56 (m, 1 H), 2.69 - 2.80 (m, 1 H), 2.84 - 2.94 (m, 1 H), 3.21 (br d, J=12.0 Hz, 1 H), 3.27 - 3.30 (m hidden, 1 H), 3.54 (br d, J=11.8 Hz, 1 H), 3.56 - 3.69 (m, 2 H), 4.22 (d, J=12.0 Hz, 1 H), 4.24 - 4.31 (m, 1 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 7.21 (d, J=9.5 Hz, 1 H), 7.28 (d, J=9.5 Hz, 1 H), 9.41 (br s, 1 H)
450		355 0.74 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.76 - 1.88 (m, 1 H), 2.03 (s, 3 H), 2.19 - 2.26 (m, 1 H), 2.22 (s, 3 H), 2.24 (s, 3 H), 2.52 - 2.53 (m partially hidden, 2 H), 3.33 - 3.36 (m partially hidden, 1 H), 3.44 - 3.54 (m, 3 H), 3.61 - 3.67 (m, 4 H), 6.57 (br s, 1 H), 6.57 (s, 1 H), 6.93 (d, J=9.3 Hz, 1 H), 7.29 (d, J=9.3 Hz, 1 H), 9.39 (br s, 1 H)
451		355 0.73 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.77 - 1.89 (m, 1 H), 2.03 (s, 3 H), 2.17 - 2.26 (m, 1 H), 2.22 (s, 3 H), 2.24 (s, 3 H), 2.51 - 2.53 (m partially hidden, 2 H), 3.31 - 3.36 (m partially hidden, 1 H), 3.42 - 3.55 (m, 3 H), 3.60 - 3.68 (m, 4 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.93 (d, J=9.3 Hz, 1 H), 7.29 (d, J=9.3 Hz, 1 H), 9.38 (br s, 1 H)
452		407.4 2.81 E	^{1}H NMR (400 MHz, DMSO) δ *(ppm)*: 10.13 (s, 1H), 7.29 (d, *J* = 9.3 Hz, 1H), 7.07 (s, 1H), 7.03 (s, 1H), 6.91 (d, *J* = 9.4 Hz, 1H), 4.21 (s, 1H), 3.60 – 3.55 (m, 1H), 3.45 – 3.38 (m, 1H), 3.06 (dd, *J* = 11.3, 5.8 Hz, 1H), 2.58 – 2.53 (m, 1H), 2.47 – 2.34 (m, 3H), 2.17 (s, 3H), 2.14 – 1.86 (m, 4H), 1.80 – 1.66 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

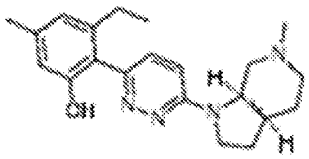
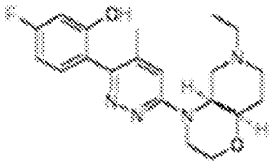
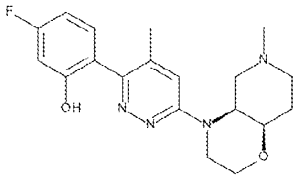
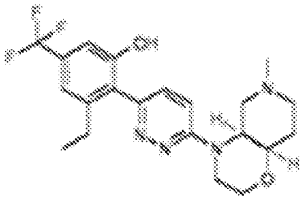
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
455		341 0.84 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 2.01 (s, 3 H), 2.22 (s, 3 H), 2.38 (s, 3 H), 2.45 - 2.48 (m, 2 H), 3.61 - 3.65 (m, 2 H), 3.69 (br s, 2 H), 3.70 (d, J=9.1 Hz, 2 H), 4.20 (d, J=9.1 Hz, 2 H), 6.56 (br s, 1 H), 6.57 (br s, 1 H), 6.84 (d, J=9.1 Hz, 1 H), 7.30 (d, J=9.1 Hz, 1 H), 9.35 (s, 1 H)
456		373 0.78 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.97 (t, J=7.3 Hz, 3 H), 1.77 - 1.92 (m, 2 H), 2.04 - 2.14 (m, 1 H), 2.33 - 2.43 (m, 3 H), 2.57 - 2.66 (m, 2 H), 3.22 (td, J=3.8 and 12.7 Hz, 1 H), 3.63 (td, J=3.3 and 11.8 Hz, 1 H), 3.75 (br q, J=2.8 Hz, 1 H), 3.96 - 4.09 (m, 2 H), 4.46 - 4.59 (m, 1 H), 6.80 (t, J=54.3 Hz, 1 H), 6.96 - 7.01 (m, 2 H), 7.30 (br d, J=7.8 Hz, 1 H), 7.32 (br s, 1 H), 10.06 - 10.79 (m, 1 H)
457		367.5 0.93 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.62 - 1.76 (m, 1 H), 1.83 - 1.97 (m, 1 H), 1.94 (br s, 3 H), 2.00 - 2.09 (m, 2 H), 2.14 (s, 3 H), 2.28 (s, 3 H), 2.50 - 2.58 (m partially hidden, 1 H), 3.24 - 3.34 (m, 1 H), 3.37 - 3.48 (m, 1 H), 3.56 - 3.66 (m, 2 H), 3.80 - 4.67 (m, 2 H), 4.14 - 4.26 (m, 1 H), 6.70 (br d, J=7.8 Hz, 1 H), 6.72 (br s, 1 H), 6.74 (br s, 1 H), 7.09 (d, J=7.8 Hz, 1 H), 9.46 - 9.59 (m, 1 H)
458		393.4 2.4 E	^{1}H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.37 – 7.16 (m, 3H), 6.88 (d, *J* = 9.2 Hz, 1H), 4.22 (s, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 3.16 (m, 1H), 2.80 – 2.60 (m, 1H), 2.36 (m, 3H), 2.27 – 2.02 (m, 2H), 1.92 (m, 2H), 1.81 (m, 1H), 1.72 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H).

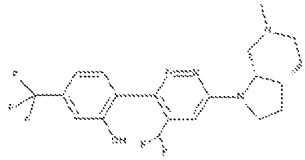
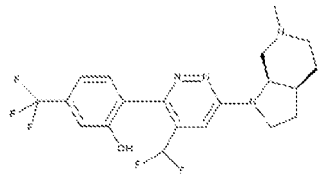
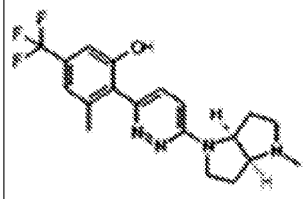
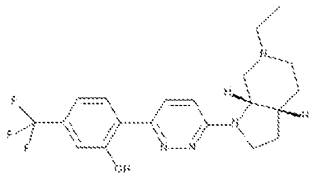
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
459		353.4 2.52 E	1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.23 (s, 1H), 7.21 (d, J = 9.2 Hz, 1H), 6.87 (d, J = 9.3 Hz, 1H), 6.57 (d, J = 3.2 Hz, 2H), 4.20 (s, 1H), 3.56 (t, J = 9.5 Hz, 1H), 3.49 – 3.36 (m, 1H), 3.06 (dd, J = 11.2, 5.8 Hz, 1H), 2.54 (s, 1H), 2.36 (qd, J = 6.8, 2.9 Hz, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.14 – 1.84 (m, 4H), 1.81 – 1.66 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H)
460		353.3 2.43 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.63 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.68 – 6.59 (m, 3H), 4.13 (s, 1H), 3.46 (t, *J* = 9.5 Hz, 1H), 3.34 (s, 1H), 3.11 – 3.03 (m, 1H), 2.59 – 2.53 (m, 1H), 2.32 – 2.24 (m, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 2.08 – 1.91 (m, 2H), 1.91 – 1.77 (m, 2H), 1.74 – 1.60 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 3H).
461		389 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.95 (t, J=7.5 Hz, 3 H), 1.76 - 1.94 (m, 2 H), 2.05 - 2.15 (m, 1 H), 2.19 (s, 3 H), 2.33 - 2.41 (m, 3 H), 2.51 - 2.56 (m partially hidden, 2 H), 3.16 (td, J=3.8 and 12.7 Hz, 1 H), 3.63 (td, J=3.3 and 11.8 Hz, 1 H), 3.74 (br q, J=2.8 Hz, 1 H), 3.93 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=3.3 and 11.8 Hz, 1 H), 4.38 - 4.45 (m, 1 H), 6.81 (d, J=2.0 Hz, 1 H), 6.84 (d, J=2.0 Hz, 1 H), 7.21 (d, J=9.5 Hz, 1 H), 7.34 (d, J=9.5 Hz, 1 H), 9.87 (br s, 1 H)
462		435 1.34 U	1H NMR (400 MHz, DMSO-d6, 30°C, mixture rotamers + atropoisomers) d ppm 1.35 - 1.67 (m, 4 H), 1.69 - 1.80 (m, 1 H), 1.80 - 1.92 (m, 1 H), 1.92 - 2.24 (m, 2 H), 2.03 (s, 1.7 H), 2.06 (s, 1.3 H), 2.13 (s, 3 H), 2.54 - 2.64 (m, 0.45 H), 2.88 - 3.02 (m, 1 H), 3.05 - 3.16 (m, 0.55 H), 3.60 - 3.70 (m, 0.55 H), 3.93 - 4.03 (m, 0.45 H), 4.24 (br d, J=12.7 Hz, 0.55 H), 4.33 (br d, J=12.7 Hz, 0.9 H), 4.44 - 4.53 (m, 0.55 H), 4.54 - 4.67 (m, 1 H), 7.06 (s, 1 H), 7.11 (s, 1 H), 7.30 - 7.43 (m, 2 H), 10.15 (br s, 1 H)

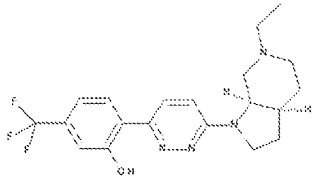
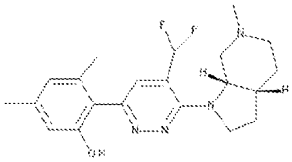
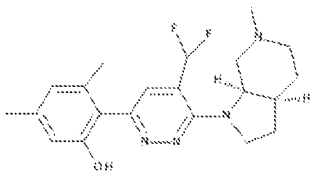
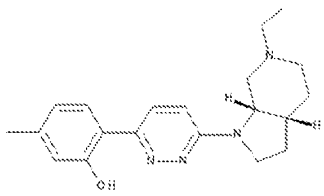
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
463		435 1.34 U	1H NMR (400 MHz, DMSO-d6, 30°C, mixture rotamers + atropoisomers) d ppm 1.35 - 1.67 (m, 4 H), 1.69 - 1.80 (m, 1 H), 1.80 - 1.92 (m, 1 H), 1.92 - 2.24 (m, 2 H), 2.03 (s, 1.7 H), 2.06 (s, 1.3 H), 2.13 (s, 3 H), 2.54 - 2.64 (m, 0.45 H), 2.88 - 3.02 (m, 1 H), 3.05 - 3.16 (m, 0.55 H), 3.60 - 3.70 (m, 0.55 H), 3.93 - 4.03 (m, 0.45 H), 4.24 (br d, J=12.7 Hz, 0.55 H), 4.33 (br d, J=12.7 Hz, 0.9 H), 4.44 - 4.53 (m, 0.55 H), 4.54 - 4.67 (m, 1 H), 7.06 (s, 1 H), 7.11 (s, 1 H), 7.30 - 7.43 (m, 2 H), 10.15 (br s, 1 H)
466		342.3 1.61 Z3	^{1}H NMR (400 MHz, DMSO-*d6*): δ 9.40 (s, 1H), 7.35 (d, *J* = 9.6 Hz, 1H), 7.17 (d, *J* = 9.6 Hz, 1H), 6.58 (d, *J* = 4.0 Hz, 2H), 4.74 (d, *J* = 4.4 Hz, 1H), 4.69-4.64 (m, 1H), 4.34 (s, 1H), 3.99 -3.90 (m, 3H), 3.52 (t, *J* = 12.0 Hz, 1H), 3.08-3.03 (m, 1H), 2.22 (s, 3H), 2.03 (s, 3H), 1.94-1.86 (m, 1H), 1.79-1.72 (m, 2H), 1.24 (s, 1H) ppm
467		342.3 1.61 Z3	1H NMR (400 MHz, DMSO-d6): δ 9.40 (s, 1H), 7.35 (d, J = 9.6 Hz, 1H), 7.17 (d, J = 9.6 Hz, 1H), 6.58 (d, J = 4.6 Hz, 2H), 4.74 (d, J = 4.3 Hz, 1H), 4.67 (t, J = 10.2 Hz, 1H), 4.34 (s, 1H), 3.99-3.91 (m, 3H), 3.52 (t, J = 11.8 Hz, 1H), 3.08-3.03 (m, 1H), 2.22 (s, 3H), 2.03 (s, 3H), 1.94-1.86 (m, 1H), 1.79-1.72 (m, 2H), 1.24 (s, 1H) ppm.
468		359 0.78 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.77 (m, 2 H), 1.84 - 2.05 (m, 3 H), 2.07 (br s, 3 H), 2.06 - 2.13 (m, 1 H), 2.17 (s, 3 H), 2.30 - 2.39 (m, 1 H), 2.52 - 2.57 (m partially hidden, 1 H), 3.06 (br dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.43 (m, 1 H), 3.49 - 3.57 (m, 1 H), 4.15 - 4.25 (m, 1 H), 6.75 (s, 1 H), 6.91 - 6.97 (m, 2 H), 7.19 (br d, J=7.8 Hz, 1 H), 10.27 (br s, 1 H)

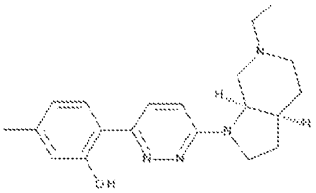
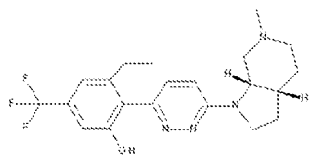
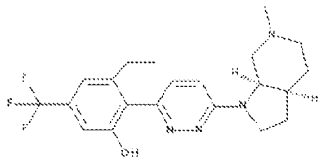
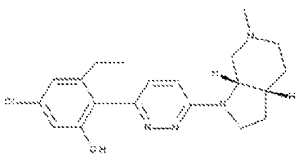
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
469		359 0.78 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.77 (m, 2 H), 1.85 - 2.05 (m, 3 H), 2.07 (s, 3 H), 2.06 - 2.15 (m, 1 H), 2.16 (s, 3 H), 2.29 - 2.39 (m, 1 H), 2.52 - 2.56 (m partially hidden, 1 H), 3.06 (dd, J=6.0 and 10.5 Hz, 1 H), 3.34 - 3.42 (m, 1 H), 3.50 - 3.57 (m, 1 H), 4.15 - 4.24 (m, 1 H), 6.75 (s, 1 H), 6.91 - 6.96 (m, 2 H), 7.18 (br d, J=7.8 Hz, 1 H), 10.29 (br s, 1 H)
470		369 0.84 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.99 (t, J=7.6 Hz, 3 H), 1.74 - 1.95 (m, 2 H), 2.04 - 2.16 (m, 1 H), 2.19 (s, 3 H), 2.28 (s, 3 H), 2.29 - 2.38 (m, 1 H), 2.42 (q, J=7.6 Hz, 2 H), 2.52 - 2.58 (m partially hidden, 2 H), 3.14 (td, J=3.8 and 12.7 Hz, 1 H), 3.62 (td, J=3.3 and 11.8 Hz, 1 H), 3.73 (br q, J=2.8 Hz, 1 H), 3.91 (br d, J=12.7 Hz, 1 H), 4.04 (dd, J=3.3 and 11.8 Hz, 1 H), 4.40 - 4.48 (m, 1 H), 6.70 (br d, J=7.8 Hz, 1 H), 6.73 (br s, 1 H), 7.02 (d, J=7.8 Hz, 1 H), 7.01 (s, 1 H), 9.47 (br s, 1 H)
471		381 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.74 - 1.94 (m, 2 H), 1.99 - 2.13 (m, 3 H), 2.15 (s, 3 H), 2.17 (s, 3 H), 2.27 - 2.35 (m, 1 H), 2.52 - 2.60 (m partially hidden, 2 H), 2.84 (t, J=7.4 Hz, 2 H), 2.89 (t, J=7.4 Hz, 2 H), 3.14 (td, J=3.8 and 12.7 Hz, 1 H), 3.61 (td, J=3.3 and 11.8 Hz, 1 H), 3.72 (br q, J=2.8 Hz, 1 H), 3.91 (br d, J=12.7 Hz, 1 H), 4.04 (dd, J=3.3 and 11.8 Hz, 1 H), 4.36 - 4.43 (m, 1 H), 6.79 (d, J=7.6 Hz, 1 H), 7.01 (d, J=7.6 Hz, 1 H), 7.12 (s, 1 H), 9.39 (s, 1 H)
472		383 0.83 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.94 (br d, J=12.1 Hz, 3 H), 0.95 (br d, J=12.1 Hz, 3 H), 1.76 - 1.85 (m, 2 H), 2.10 (s, 3 H), 2.28 (s, 3 H), 2.30 - 2.37 (m, 1 H), 2.52 - 2.57 (m partially hidden, 2 H), 2.58 - 2.64 (m, 1 H), 2.66 - 2.76 (m, 1 H), 3.16 (td, J=3.8 and 12.7 Hz, 1 H), 3.60 (td, J=3.3 and 11.8 Hz, 1 H), 3.73 (br q, J=2.8 Hz, 1 H), 3.90 (br d, J=12.7 Hz, 1 H), 4.04 (br dd, J=3.3 and 11.8 Hz, 1 H), 4.31 - 4.40 (m, 1 H), 6.71 (br d, J=7.8 Hz, 1 H), 6.73 (s, 1 H), 7.03 - 7.09 (m, 2 H), 9.66 (s, 1 H)

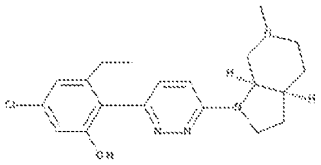
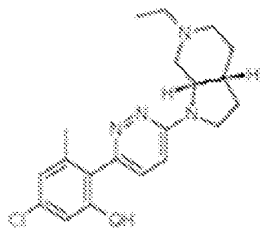
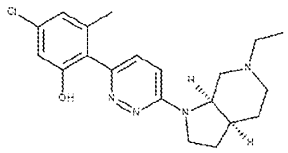
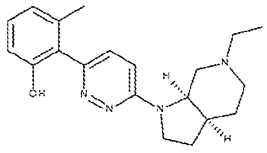
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
473		393.3 2.4 E	^{1}H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.32 – 7.17 (m, 3H), 6.88 (d, *J* = 9.3 Hz, 1H), 4.21 (s, 1H), 3.56 (m, 1H), 3.42 (m, 1H), 3.15 (m, 1H), 2.73 – 2.61 (m, 1H), 2.44 – 2.30 (m, 3H), 2.22 – 2.01 (m, 2H), 1.92 (m, 2H), 1.81 (m, 1H), 1.72 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H).
474		353.4 2.58 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.71 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.84 – 6.56 (m, 3H), 4.21 (s, 1H), 3.53 (t, J = 9.4 Hz, 1H), 3.40 (m, 1H), 3.15 (m, 1H), 2.64 (d, J = 11.3 Hz, 1H), 2.35 (p, J = 6.5 Hz, 3H), 2.28 (s, 3H), 2.09 (m, 4H), 2.06 – 2.00 (m, 1H), 1.92 (m, 2H), 1.82 – 1.67 (m, 2H), 0.99 (t, J = 7.1 Hz, 3H)
475		353.4 2.58 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.71 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.84 – 6.56 (m, 3H), 4.21 (s, 1H), 3.53 (t, J = 9.4 Hz, 1H), 3.40 (m, 1H), 3.15 (m, 1H), 2.64 (m, 1H), 2.35 (m, 3H), 2.28 (s, 3H), 2.17 - 2.06 (m, 4H), 2.06 – 2.00 (m, 1H), 1.92 (m, 2H), 1.82 – 1.67 (m, 2H), 0.99 (t, J = 7.1 Hz, 3H)
476		353.4 2.66 E	1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.24 (s, 1H), 7.21 (d, J = 9.2 Hz, 1H), 6.87 (d, J = 9.3 Hz, 1H), 6.57 (br s, 2H), 4.20 (br, 1H), 3.55 (t, J = 9.4 Hz, 1H), 3.45 – 3.38 (m, 1H), 3.11 – 3.02 (m, 1H), 2.54 – 2.51 (m, 1H), 2.40 – 2.30 (m, 3H), 2.24 (s, 3H), 2.18 (s, 3H), 2.15 – 1.85 (m, 4H), 1.81 – 1.66 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H)

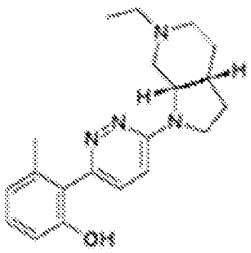
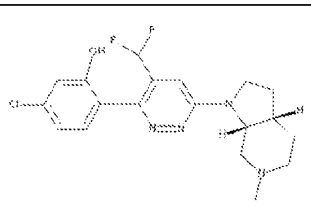
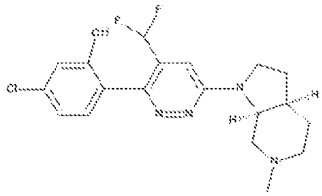
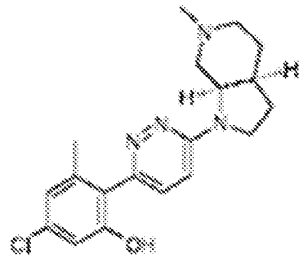
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
477		353.4 2.66 E	1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.25 (s, 1H), 7.21 (d, J = 9.3 Hz, 1H), 6.87 (d, J = 9.3 Hz, 1H), 6.61 – 6.54 (m, 2H), 4.20 (br s, 1H), 3.55 (t, J = 9.5 Hz, 1H), 3.45 – 3.37 (m, 1H), 3.11 – 3.00 (m, 1H), 2.59 – 2.53 (m, 1H), 2.42 – 2.29 (m, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.15 – 1.85 (m, 4H), 1.82 – 1.64 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H)
479		373 0.78 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.97 (t, J=7.3 Hz, 3 H), 1.77 - 1.90 (m, 2 H), 2.04 - 2.13 (m, 1 H), 2.09 (s, 3 H), 2.29 - 2.42 (m, 3 H), 2.55 - 2.65 (m, 2 H), 3.15 (td, J=3.8 and 12.7 Hz, 1 H), 3.60 (td, J=3.3 and 11.8 Hz, 1 H), 3.73 (br q, J=2.8 Hz, 1 H), 3.91 (br d, J=12.7 Hz, 1 H), 4.04 (dd, J=3.3 and 11.8 Hz, 1 H), 4.35 - 4.46 (m, 1 H), 6.69 - 6.76 (m, 2 H), 7.08 (s, 1 H), 7.21 (br t, J=7.8 Hz, 1 H), 10.26 (br s, 1 H)
480		359 0.76 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.75 - 1.93 (m, 2 H), 2.05 - 2.16 (m, 1 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.26 - 2.35 (m, 1 H), 2.45 - 2.59 (m hidden, 2 H), 3.14 (td, J=3.8 and 12.7 Hz, 1 H), 3.60 (td, J=3.3 and 11.8 Hz, 1 H), 3.72 (br q, J=2.8 Hz, 1 H), 3.91 (br d, J=12.7 Hz, 1 H), 4.04 (dd, J=3.3 and 11.8 Hz, 1 H), 4.33 - 4.46 (m, 1 H), 6.69 - 6.76 (m, 2 H), 7.09 (s, 1 H), 7.21 (br t, J=7.8 Hz, 1 H), 10.18 - 10.33 (m, 1 H)
481		423 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.98 (t, J=7.5 Hz, 3 H), 1.77 - 1.93 (m, 2 H), 2.07 - 2.17 (m, 1 H), 2.19 (s, 3 H), 2.33 - 2.40 (m, 1 H), 2.40 - 2.48 (m partially hidden, 2 H), 2.53 - 2.58 (m partially hidden, 2 H), 3.17 (td, J=3.8 and 12.7 Hz, 1 H), 3.64 (td, J=3.3 and 11.8 Hz, 1 H), 3.75 (br q, J=2.8 Hz, 1 H), 3.95 (br d, J=12.7 Hz, 1 H), 4.05 (dd, J=3.3 and 11.8 Hz, 1 H), 4.40 - 4.48 (m, 1 H), 7.06 (d, J=2.0 Hz, 1 H), 7.12 (d, J=2.0 Hz, 1 H), 7.25 (d, J=9.5 Hz, 1 H), 7.39 (d, J=9.5 Hz, 1 H), 10.08 (br s, 1 H)

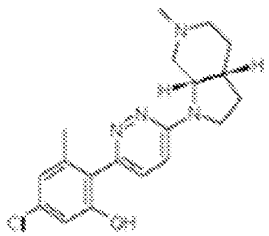
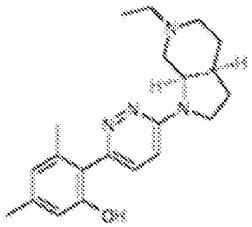
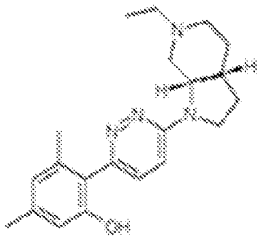
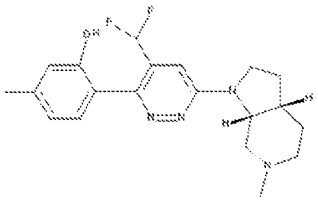
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
482		429 1.05 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.67 - 1.84 (m, 2 H), 1.88 - 2.17 (m, 4 H), 2.18 (s, 3 H), 2.34 - 2.43 (m, 1 H), 2.54 - 2.58 (m partially hidden, 1 H), 3.01 - 3.11 (m, 1 H), 3.41 - 3.50 (m, 1 H), 3.58 - 3.67 (m, 1 H), 4.26 - 4.39 (m, 1 H), 6.83 (t, J=54.3 Hz, 1 H), 6.97 (br s, 1 H), 7.22 (br s, 1 H), 7.26 (br d, J=7.8 Hz, 1 H), 7.48 (d, J=7.8 Hz, 1 H), 10.31 - 10.94 (m, 1 H)
483		429 1.06 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.67 - 1.83 (m, 2 H), 1.89 - 2.16 (m, 4 H), 2.18 (s, 3 H), 2.34 - 2.43 (m, 1 H), 2.53 - 2.58 (m partially hidden, 1 H), 3.01 - 3.10 (m, 1 H), 3.44 - 3.49 (m, 1 H), 3.58 - 3.66 (m, 1 H), 4.26 - 4.39 (m, 1 H), 6.84 (t, J=54.3 Hz, 1 H), 6.97 (br s, 1 H), 7.21 (br s, 1 H), 7.24 (br d, J=7.8 Hz, 1 H), 7.48 (d, J=7.8 Hz, 1 H), 9.82 - 11.36 (m, 1 H)
484		379 0.9 U	1H NMR (400 MHz, DMSO-d6, 100°C) d ppm 1.47 - 1.57 (m, 1 H), 1.79 - 1.89 (m, 1 H), 1.94 - 2.01 (m, 1 H), 2.16 (s, 3 H), 2.23 - 2.38 (m, 2 H), 2.32 (s, 3 H), 2.91 - 2.96 (m partially hidden, 1 H), 3.01 (t, J=6.0 Hz, 1 H), 3.42 - 3.51 (m, 1 H), 3.78 - 3.84 (m, 1 H), 4.44 - 4.50 (m, 1 H), 6.88 (d, J=9.3 Hz, 1 H), 7.04 - 7.07 (m, 2 H), 7.30 (d, J=9.3 Hz, 1 H), 9.70 - 9.94 (m, 1 H)
485		443.3 2.79 E	1H NMR (400 MHz, DMSO) δ (ppm): 10.65 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 6.97 (s, 1H), 6.83 (t, J = 53.9 Hz, 1H), 4.33 (s, 1H), 3.64 – 3.57 (m, 1H), 3.48 – 3.39 (m, 1H), 3.16 (s, 1H), 2.64 (s, 1H), 2.45 – 2.39 (m, 1H), 2.35 (q, J = 7.2 Hz, 2H), 2.20 – 2.03 (m, 2H), 1.99 – 1.88 (m, 2H), 1.82 (t, J = 10.6 Hz, 1H), 1.72 (d, J = 13.5 Hz, 1H), 0.99 (t, J = 7.1 Hz, 3H).

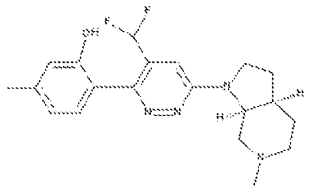
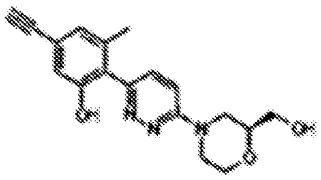
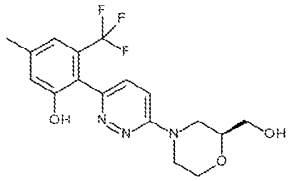
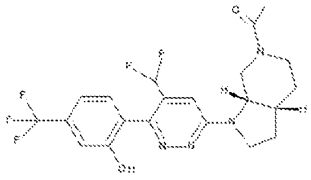
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
486		443.3 2.79 E	1H NMR (400 MHz, DMSO) δ (ppm): 10.58 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 6.98 (d, J = 4.2 Hz, 1H), 6.84 (t, J = 54.1 Hz, 1H), 4.33 (s, 1H), 3.61 (t, J = 9.5 Hz, 1H), 3.44 (d, J = 8.6 Hz, 1H), 3.17 (s, 1H), 2.65 (s, 1H), 2.47 – 2.39 (m, 1H), 2.36 (q, J = 6.3 Hz, 2H), 2.23 – 2.01 (m, 2H), 2.01 – 1.88 (m, 2H), 1.82 (t, J = 10.6 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.00 (t, J = 7.1 Hz, 3H).
487		389.3 2.69 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.43 (s, 1H), 7.47 (s, 1H), 7.35 (t, J = 54.0 Hz, 1H), 6.60 (s, 2H), 4.59 – 4.50 (m, 1H), 3.89 – 3.77 (m, 1H), 3.57 – 3.48 (m, 1H), 2.76 (dd, J = 11.7, 4.9 Hz, 1H), 2.38 – 2.26 (m, 4H), 2.24 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 2.04 – 1.92 (m, 2H), 1.92 – 1.80 (m, 1H), 1.74 – 1.62 (m, 1H).
488		389.3 2.69 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.43 (s, 1H), 7.48 (s, 1H), 7.34 (t, J = 54.4 Hz, 1H), 6.60 (s, 2H), 4.56 (q, J = 6.0 Hz, 1H), 3.90 – 3.78 (m, 1H), 3.58 – 3.47 (m, 1H), 2.91 – 2.71 (m, 1H), 2.43 – 2.27 (m, 4H), 2.24 (s, 3H), 2.18 (bs, 3H), 2.06 (s, 3H), 2.01 – 1.93 (m, 2H), 1.86 (dd, J = 13.3, 6.6 Hz, 1H), 1.74 – 1.65 (m, 1H).
489		389.4 2.56 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.84 (s, 1H), 7.14 (d, J = 7.5 Hz, 1H), 6.92 (s, 1H), 6.76 (m, 2H), 6.74 (t, J = 53.1 Hz, 1H), 4.32 (s, 1H), 3.65 – 3.56 (m, 1H), 3.46 – 3.39 (m, 1H), 3.16 (s, 1H), 2.69 – 2.61 (m, 1H), 2.45 – 2.37 (m, 1H), 2.35 (q, J = 7.0 Hz, 2H), 2.29 (s, 3H), 2.22 – 2.01 (m, 2H), 2.00 – 1.87 (m, 2H), 1.81 (t, J = 10.6 Hz, 1H), 1.72 (d, J = 14.4 Hz, 1H), 0.99 (t, J = 7.1 Hz, 3H).

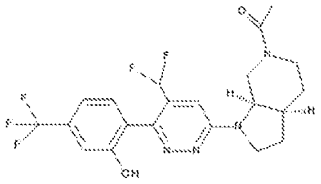
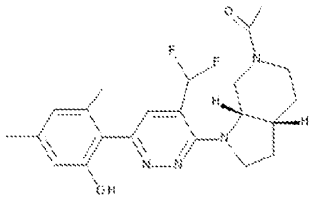
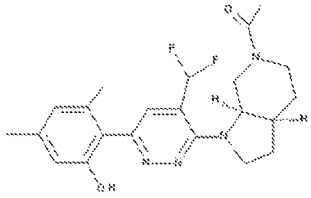
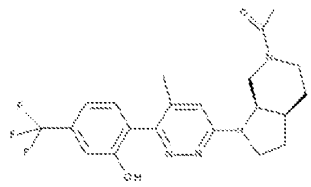
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
490		389.4 2.56 E	1H NMR (400 MHz, DMSO) δ 9.80 (s, 1H), 7.13 (d, J = 7.5 Hz, 1H), 6.92 (s, 1H), 6.75 (m, 2H), 6.73 (t, J = 53.2 Hz, 1H), 4.32 (s, 1H), 3.60 (t, J = 9.5 Hz, 1H), 3.45 – 3.38 (m, 1H), 3.17 (s, 1H), 2.70 – 2.65 (m, 1H), 2.44 – 2.32 (m, 3H), 2.29 (s, 3H), 2.20 – 2.06 (m, 2H), 1.97 – 1.88 (m, 2H), 1.83 (s, 1H), 1.72 (d, J = 13.5 Hz, 1H), 0.99 (t, J = 7.1 Hz, 3H).
491		407.4 2.95 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 10.14 (s, 1H), 7.30 (d, J = 9.3 Hz, 1H), 7.15 – 7.03 (m, 2H), 6.92 (d, J = 9.3 Hz, 1H), 4.22 (s, 1H), 3.57 (t, J = 9.5 Hz, 1H), 3.47 – 3.39 (m, 1H), 3.07 (br. s, 1H), 2.62 – 2.54 (m, 1H), 2.49 – 2.43 (m, 2H), 2.41 – 2.32 (m, 1H), 2.18 (s, 3H), 2.15 – 1.87 (m, 4H), 1.84 – 1.64 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H).
492		407.4 2.95 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.98 (s, 1H), 7.14 (d, J = 9.3 Hz, 1H), 7.00 – 6.88 (m, 2H), 6.76 (d, J = 9.3 Hz, 1H), 4.07 (s, 1H), 3.41 (t, J = 9.5 Hz, 1H), 3.26 (t, J = 9.2 Hz, 1H), 2.97 – 2.88 (m, 1H), 2.42 – 2.37 (3, 1H), 2.30 (td, J = 7.5, 1.7 Hz, 2H), 2.26 – 2.15 (m, 1H), 2.03 (s, 3H), 1.99 – 1.85 (m, 2H), 1.85 – 1.72 (m, 2H), 1.69 – 1.51 (m, 2H), 0.82 (t, J = 7.5 Hz, 3H).
493		374.3 2.81 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.88 (s, 1H), 7.24 (d, J = 9.3 Hz, 1H), 6.89 (d, J = 9.2 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 4.22 (br. s, 1H), 3.56 (t, J = 9.5 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.07 (s, 1H), 2.59 – 2.51 (s, 1H), 2.43 – 2.31 (m, 3H), 2.18 (s, 3H), 2.15 – 1.85 (m, 4H), 1.83 – 1.65 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H).

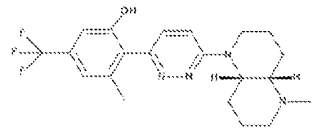
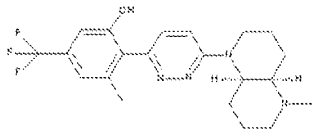
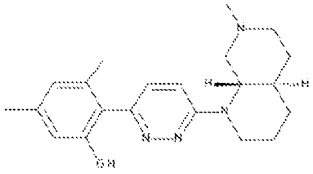
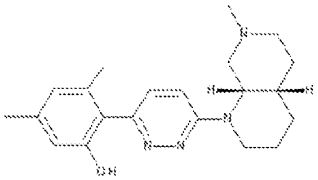
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
494		374.3 2.79 E	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.89 (s, 1H), 7.25 (d, J = 9.2 Hz, 1H), 6.89 (d, J = 9.3 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 4.22 (br. s, 1H), 3.56 (t, J = 9.5 Hz, 1H), 3.44 – 3.36 (m, 1H), 3.08 (s, 1H), 2.57 – 2.53 (m, 1H), 2.42 – 2.31 (m, 3H), 2.19 (s, 3H), 2.15 – 2.03 (m, 2H), 2.01 - 1.85 (m, 2H), 1.83 – 1.65 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H).
496		373 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.00 (t, J=7.1 Hz, 3 H) 1.67 - 1.75 (m, 1 H) 1.76 - 1.86 (m, 1 H) 1.86 - 1.99 (m, 2 H) 2.01 - 2.19 (m, 2 H) 2.06 (s, 3 H) 2.33 - 2.43 (m, 3 H) 2.59 - 2.67 (m, 1 H) 3.10 - 3.21 (m, 1 H) 3.35 - 3.44 (m, 1 H) 3.51 - 3.59 (m, 1 H) 4.15 - 4.28 (m, 1 H) 6.80 (d, J=2.1 Hz, 1 H) 6.83 (br d, J=2.1 Hz, 1 H) 6.88 (br d, J=9.4 Hz, 1 H) 7.27 (d, J=9.4 Hz, 1 H) 9.94 (br s, 1 H)
497		373 0.87 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.99 (t, J=7.1 Hz, 3 H) 1.66 - 1.75 (m, 1 H) 1.77 - 1.85 (m, 1 H) 1.86 - 1.98 (m, 2 H) 2.00 - 2.19 (m, 1 H) 2.06 (s, 3 H) 2.33 - 2.42 (m, 3 H) 2.61 - 2.68 (m, 1 H) 3.11 - 3.19 (m, 1 H) 3.35 - 3.43 (m, 1 H) 3.51 - 3.60 (m, 1 H) 4.15 - 4.27 (m, 1 H) 6.80 (br d, J=2.1 Hz, 1 H) 6.83 (br d, J=2.1 Hz, 1 H) 6.88 (br d, J=9.4 Hz, 1 H) 7.26 (d, J=9.4 Hz, 1 H) 9.94 (br s, 1 H)
498		339 0.72 Z1	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 0.99 (t, J=7.1 Hz, 3 H), 1.68 - 1.74 (m, 1 H), 1.77 - 1.84 (m, 1 H), 1.86 - 1.98 (m, 2 H), 2.01 - 2.19 (m, 2 H), 2.06 (s, 3 H), 2.32 - 2.43 (m, 3 H), 2.61 - 2.69 (m, 1 H), 3.11 - 3.19 (m, 1 H), 3.36 - 3.44 (m, 1 H), 3.52 - 3.59 (m, 1 H), 4.16 - 4.25 (m, 1 H), 6.71 - 6.78 (m, 2 H), 6.88 (br d, J=9.4 Hz, 1 H), 7.08 (t, J=7.8 Hz, 1 H), 7.27 (d, J=9.4 Hz, 1 H), 9.44 (br s, 1 H)

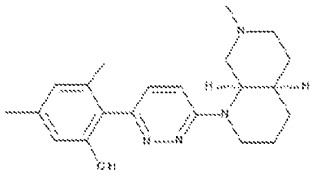
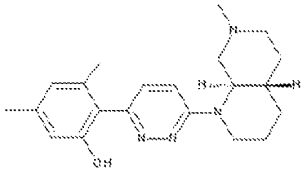
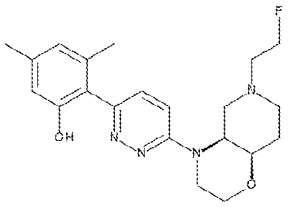
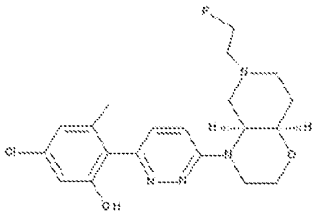
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
499		339 0.71 Z1	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.99 (t, J=7.1 Hz, 3 H) 1.68 - 1.74 (m, 1 H) 1.77 - 1.84 (m, 1 H) 1.86 - 1.98 (m, 2 H) 2.01 - 2.18 (m, 2 H) 2.06 (s, 3 H) 2.32 - 2.43 (m, 3 H) 2.61 - 2.68 (m, 1 H) 3.11 - 3.19 (m, 1 H) 3.35 - 3.44 (m, 1 H) 3.52 - 3.59 (m, 1 H) 4.17 - 4.25 (m, 1 H) 6.71 - 6.78 (m, 2 H) 6.88 (br d, J=9.4 Hz, 1 H) 7.08 (t, J=7.8 Hz, 1 H) 7.27 (d, J=9.4 Hz, 1 H) 9.44 (br s, 1 H)
500		395 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) d ppm 1.66 - 1.83 (m, 2 H), 1.90 - 2.16 (m, 4 H), 2.17 (s, 3 H), 2.34 - 2.43 (m, 1 H), 2.53 - 2.57 (m partially hidden, 1 H), 3.01 - 3.10 (m, 1 H), 3.39 - 3.49 (m, 1 H), 3.57 - 3.66 (m, 1 H), 4.24 - 4.37 (m, 1 H), 6.78 (t, J=54.3 Hz, 1 H), 6.92 - 7.01 (m, 3 H), 7.27 (br d, J=7.8 Hz, 1 H), 10.13 - 10.74 (m, 1 H)
501		395 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.67 - 1.83 (m, 2 H) 1.90 - 2.16 (m, 4 H) 2.17 (s, 3 H) 2.34 - 2.42 (m, 1 H) 2.53 - 2.57 (m partially hidden, 1 H) 3.01 - 3.11 (m, 1 H) 3.39 - 3.49 (m, 1 H) 3.56 - 3.66 (m, 1 H) 4.24 - 4.38 (m, 1 H) 6.78 (t, J=54.3 Hz, 1 H) 6.93 - 7.00 (m, 3 H) 7.27 (br d, J=7.8 Hz, 1 H) 10.25 - 10.65 (m, 1 H)
502		359 0.84 U	1H NMR (500 MHz, DMSO-d6, 27°C) d ppm 1.67 - 1.81 (m, 2 H), 1.86 - 2.13 (m, 4 H), 2.05 (s, 3 H), 2.17 (s, 3 H), 2.33 - 2.40 (m, 1 H), 2.52 - 2.56 (m partially hidden, 1 H), 3.02 - 3.10 (m, 1 H), 3.38 - 3.47 (m, 1 H), 3.52 - 3.59 (m, 1 H), 4.15 - 4.27 (m, 1 H), 6.80 (br d, J=2.1 Hz, 1 H), 6.83 (br d, J=2.1 Hz, 1 H), 6.89 (br d, J=9.4 Hz, 1 H), 7.26 (d, J=9.4 Hz, 1 H), 9.92 - 9.99 (m, 1 H)

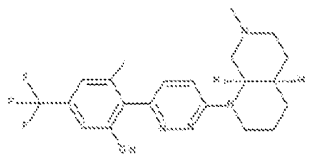
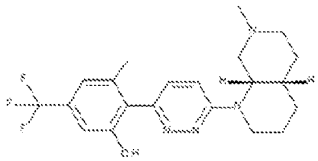
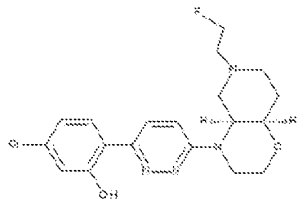
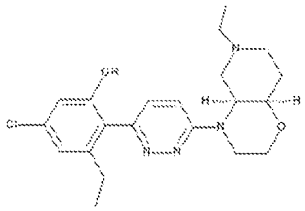
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
503		359 0.84 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.66 - 1.82 (m, 2 H) 1.86 - 2.14 (m, 4 H) 2.05 (s, 3 H) 2.17 (s, 3 H) 2.33 - 2.41 (m, 1 H) 2.53 - 2.57 (m partially hidden, 1 H) 3.01 - 3.10 (m, 1 H) 3.38 - 3.47 (m, 1 H) 3.52 - 3.59 (m, 1 H) 4.15 - 4.27 (m, 1 H) 6.80 (br d, J=2.1 Hz, 1 H) 6.83 (br d, J=2.1 Hz, 1 H) 6.89 (d, J=9.4 Hz, 1 H) 7.26 (d, J=9.4 Hz, 1 H) 9.88 - 10.09 (m, 1 H)
504		353 0.77 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.99 (t, J=7.1 Hz, 3 H) 1.67 - 1.75 (m, 1 H) 1.76 - 1.83 (m, 1 H) 1.85 - 1.98 (m, 2 H) 2.01 - 2.19 (m, 2 H) 2.04 (s, 3 H) 2.22 (s, 3 H) 2.31 - 2.43 (m, 3 H) 2.60 - 2.69 (m, 1 H) 3.10 - 3.19 (m, 1 H) 3.34 - 3.43 (m, 1 H) 3.51 - 3.59 (m, 1 H) 4.16 - 4.24 (m, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.87 (br d, J=9.4 Hz, 1 H) 7.25 (d, J=9.4 Hz, 1 H) 9.39 (br s, 1 H)
505		353 0.77 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.99 (t, J=7.1 Hz, 3 H) 1.67 - 1.74 (m, 1 H) 1.76 - 1.83 (m, 1 H) 1.85 - 1.98 (m, 2 H) 2.01 - 2.18 (m, 2 H) 2.04 (s, 3 H) 2.22 (s, 3 H) 2.31 - 2.42 (m, 3 H) 2.60 - 2.68 (m, 1 H) 3.10 - 3.18 (m, 1 H) 3.34 - 3.43 (m, 1 H) 3.51 - 3.58 (m, 1 H) 4.15 - 4.24 (m, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 6.86 (br d, J=9.4 Hz, 1 H) 7.25 (d, J=9.4 Hz, 1 H) 9.40 (br s, 1 H)
506		375 0.94 U	1H NMR (500 MHz, DMSO-d6, 27°C) d ppm 1.67 - 1.82 (m, 2 H), 1.89 - 2.14 (m, 4 H), 2.17 (s, 3 H), 2.29 (s, 3 H), 2.34 - 2.41 (m, 1 H), 2.53 - 2.56 (m partially hidden, 1 H), 3.01 - 3.10 (m, 1 H), 3.39 - 3.48 (m, 1 H), 3.56 - 3.65 (m, 1 H), 4.25 - 4.37 (m, 1 H), 6.75 (t, J=54.3 Hz, 2 H), 6.73 - 6.76 (m, 1 H), 6.92 (br s, 1 H), 7.13 (d, J=7.8 Hz, 1 H), 9.80 (br s, 1 H)

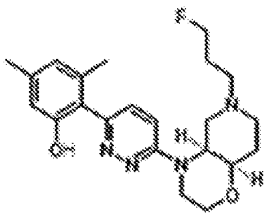
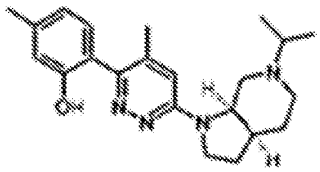
Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
507		375 0.94 U	1H NMR (500 MHz, DMSO-d6, 27°C) d ppm 1.66 - 1.82 (m, 2 H), 1.89 - 2.15 (m, 4 H), 2.17 (s, 3 H), 2.29 (s, 3 H), 2.34 - 2.41 (m, 1 H), 2.52 - 2.56 (m partially hidden, 1 H), 3.01 - 3.10 (m, 1 H), 3.39 - 3.47 (m, 1 H), 3.56 - 3.64 (m, 1 H), 4.24 - 4.38 (m, 1 H), 6.75 (t, J=54.3 Hz, 1 H), 6.72 - 6.77 (m, 2 H), 6.92 (br s, 1 H), 7.13 (d, J=7.8 Hz, 1 H), 9.80 (br s, 1 H)
508		230.1 0.76 S	1H NMR (500 MHz, DMSO) δ 7.56 (d, J = 9.6 Hz, 1H), 7.38 (d, J = 9.6 Hz, 1H), 4.82 (t, J = 5.5 Hz, 1H), 4.24 (dt, J = 13.0, 2.0 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.96 (ddd, J = 11.5, 3.6, 1.5 Hz, 1H), 3.57 (td, J = 11.6, 2.8 Hz, 1H), 3.54 – 3.48 (m, 2H), 3.47 – 3.41 (m, 1H), 2.97 (ddd, J = 12.9, 11.7, 3.6 Hz, 1H), 2.76 – 2.71 (m, 1H)
509		370.3 2.57 E	1H NMR (400 MHz, DMSO-d6) δ (ppm): 10.03 (s, 1H), 7.34 (d, J = 9.4 Hz, 1H), 7.27 (d, J = 9.5 Hz, 1H), 7.08 (d, J = 1.5 Hz, 1H), 7.02 (s, 1H), 4.86 (t, J = 5.5 Hz, 1H), 4.34 (d, J = 12.8 Hz, 1H), 4.14 (d, J = 12.8 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.62 (td, J = 11.6, 2.8 Hz, 1H), 3.50 – 3.50 (m, 2H), 3.49 – 3.43 (m, 1H), 2.98 (td, J = 12.3, 3.5 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.36 (s, 3H).
510		457.3 2.75 E	1H NMR (400 MHz, DMSO) δ (ppm): 10.63 (s, 1H), 7.51 (dd, J = 7.8, 2.8 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 7.10 – 6.69 (m, 1H), 6.86 (t, J = 54.3 Hz, 1H), 4.60 (dd, J = 13.1, 5.9 Hz, 0.5H), 4.37 – 4.27 (m, 0.5H), 4.26 – 4.15 (m, 0.5H), 4.01 (dd, J = 14.0, 5.3 Hz, 0.5H), 3.85 (d, J = 12.7 Hz, 0.5H), 3.68 (t, J = 9.4 Hz, 1H), 3.60 (dt, J = 13.5, 4.4 Hz, 0.5H), 3.46 (q, J = 8.9 Hz, 1H), 3.32 – 3.22 (m, 1H), 3.07 (t, J = 11.7 Hz, 0.5H), 2.70 – 2.63 (m, 0.5H), 2.5 (m, 25H, overintegration due to overlap with DMSO peak, expected 1H), 2.27 – 2.08 (m, 1H), 2.08 – 1.89 (m, 4.5H), 1.88 – 1.61 (m, 1.5H) - mixture of rotamers

Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
511		457.3 2.75 E	1H NMR (400 MHz, DMSO) δ (ppm): 10.62 (s, 1H), 7.51 (dd, J = 8.0, 2.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 7.10 – 6.70 (m, 1H), 6.86 (t, J= 54.4 Hz, 1H), 4.60 (dd, J = 13.1, 5.9 Hz, 0.5H), 4.32 (q, J = 7.1 Hz, 0.5H), 4.21 (s, 0.5H), 4.01 (dd, J = 14.2, 5.3 Hz, 0.5H), 3.85 (d, J = 13.0 Hz, 0.5H), 3.68 (t, J = 9.3 Hz, 1H), 3.60 (d, J = 13.9 Hz, 0.5H), 3.46 (q, J = 9.0 Hz, 1H), 3.28 (d, J = 10.9 Hz, 1H), 3.07 (t, J = 12.0 Hz, 0.5H), 2.70 – 2.63 (m, 0.5H), 2.5 (m, 29H, overintegration due to overlap with DMSO peak, expected 1H), 2.27 – 2.08 (m, 1H), 2.08 – 1.89 (m, 4.5H), 1.89 – 1.61 (m, 1.5H) - mixture of rotamers
512		417.4 2.74 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.46 (s, 1H), 7.55 – 7.48 (m, 1H), 7.29 (td, J = 54.1, 25.8 Hz, 1H), 6.64 – 6.54 (m, 2H), 4.47 – 4.30 (m, 1H), 4.13 – 3.62 (m, 3H), 3.57 – 3.42 (m, 2H), 2.91 – 2.79 (m, 1H), 2.57 – 2.44 (m, 41H; overintegration due to overlap with DMSO peak, expected 1H), 2.23 (s, 3H), 2.09 – 1.93 (m, 5H), 1.88 – 1.75 (m, 1H), 1.73 – 1.61 (m, 1H), 1.49 (s, 2H), 1.47 – 1.36 (m, 1H) - Appears to be a mixture of rotamers
513		417.4 2.74 E	1H NMR (400 MHz, DMSO) δ (ppm): 9.45 (s, 1H), 7.56 – 7.47 (m, 1H), 7.48 – 7.11 (m, 1H), 6.64 – 6.57 (m, 2H), 4.46 – 4.33 (m, 1H), 4.12 – 3.66 (m, 3H), 3.58 – 3.43 (m, 2H), 2.90 – 2.82 (m, 1H), 2.55 – 2.47 (m, 44H; overintegration due to overlap with DMSO peak, expected 1H), 2.24 (s, 3H), 2.09 – 1.99 (m, 4H), 1.97 (s, 1H), 1.86 – 1.77 (m, 1H), 1.72 – 1.63 (m, 1H), 1.50 (s, 2H), 1.49 – 1.36 (m, 1H) - Appears to be a mixture of rotamers.
514		421 1.10 U	1H NMR (400 MHz, DMSO-d6, 100°C) δ ppm 1.63 - 1.76 (m, 1 H) 1.83 - 1.99 (m, 1 H) 1.95 (br s, 3 H) 2.01 - 2.09 (m, 2 H) 2.12 (br s, 3 H) 2.51 - 2.56 (m partially hidden, 1 H) 3.24 - 3.35 (m, 1 H) 3.38 - 3.49 (m, 1 H) 3.57 - 3.67 (m, 2 H) 3.78 - 4.70 (m, 2 H) 4.16 - 4.26 (m, 1 H) 6.75 (br s, 1 H) 7.19 - 7.23 (m, 2 H) 7.42 (d, J=7.8 Hz, 1 H) 9.99 - 10.34 (m, 1 H)

Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
515		407 1.00 U	1H NMR (500 MHz, DMSO-d6, 27°C) d ppm 1.38 - 1.48 (m, 2 H), 1.59 - 1.89 (m, 6 H), 2.13 (s, 3 H), 2.34 (br s, 3 H), 2.38 - 2.48 (m, 2 H), 2.84 - 2.97 (m, 2 H), 4.25 (br d, J=12.7 Hz, 1 H), 4.51 - 4.64 (m, 1 H), 7.06 (br s, 1 H), 7.12 (br s, 1 H), 7.28 (d, J=9.5 Hz, 1 H), 7.33 (d, J=9.5 Hz, 1 H), 10.16 (br s, 1 H)
516		407 1.00 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.37 - 1.49 (m, 2 H) 1.58 - 1.90 (m, 6 H) 2.13 (s, 3 H) 2.33 (br s, 3 H) 2.37 - 2.44 (m, 2 H) 2.83 - 2.97 (m, 2 H) 4.25 (br d, J=12.7 Hz, 1 H) 4.51 - 4.60 (m, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.27 (d, J=9.5 Hz, 1 H) 7.33 (d, J=9.5 Hz, 1 H) 10.15 (br s, 1 H)
517		353 0.87 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.10 - 1.18 (m, 1 H) 1.29 - 1.38 (m, 1 H) 1.63 - 1.81 (m, 6 H) 1.94 - 2.00 (m, 1 H) 2.04 (s, 3 H) 2.18 (s, 3 H) 2.22 (s, 3 H) 2.78 - 2.84 (m, 1 H) 3.13 - 3.19 (m, 1 H) 3.34 - 3.41 (m partially hidden, 2 H) 3.81 - 3.89 (m, 1 H) 6.57 (br s, 1 H) 6.59 (br s, 1 H) 7.13 (d, J=9.4 Hz, 1 H) 7.33 (d, J=9.4 Hz, 1 H) 9.46 (br s, 1 H)
518		353 0.86 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.38 - 1.45 (m, 1 H) 1.47 - 1.57 (m, 2 H) 1.80 - 1.95 (m, 4 H) 1.99 - 2.09 (m, 1 H) 2.04 (s, 3 H) 2.17 (s, 3 H) 2.22 (s, 3 H) 2.24 - 2.30 (m, 1 H) 2.44 - 2.49 (m partially hidden, 2 H) 2.89 (td, J=13.0, 2.7 Hz, 1 H) 4.16 - 4.22 (m, 1 H) 4.60 - 4.66 (m, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 7.19 (d, J=9.5 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.43 (s, 1 H)

Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
519		353 0.86 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.38 - 1.45 (m, 1 H) 1.47 - 1.57 (m, 2 H) 1.80 - 1.96 (m, 4 H) 2.00 - 2.09 (m, 1 H) 2.04 (s, 3 H) 2.17 (s, 3 H) 2.22 (s, 3 H) 2.24 - 2.30 (m, 1 H) 2.45 - 2.49 (m partially hidden, 2 H) 2.88 (td, J=13.0, 2.7 Hz, 1 H) 4.15 - 4.23 (m, 1 H) 4.59 - 4.67 (m, 1 H) 6.56 (br s, 1 H) 6.57 (br s, 1 H) 7.19 (d, J=9.5 Hz, 1 H) 7.28 (d, J=9.5 Hz, 1 H) 9.44 (br s, 1 H)
520		353 0.88 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.10 - 1.18 (m, 1 H) 1.30 - 1.37 (m, 1 H) 1.63 - 1.81 (m, 6 H) 1.94 - 2.00 (m, 1 H) 2.04 (s, 3 H) 2.18 (s, 3 H) 2.22 (s, 3 H) 2.79 - 2.83 (m, 1 H) 3.14 - 3.18 (m, 1 H) 3.34 - 3.40 (m partially hidden, 2 H) 3.83 - 3.88 (m, 1 H) 6.57 (br s, 1 H) 6.59 (br s, 1 H) 7.13 (d, J=9.4 Hz, 1 H) 7.33 (d, J=9.4 Hz, 1 H) 9.49 (br s, 1 H)
521		387 0.83 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.77 - 1.92 (m, 2 H) 2.03 (s, 3 H) 2.22 (s, 3 H) 2.23 - 2.30 (m, 1 H) 2.52 - 2.58 (m partially hidden, 1 H) 2.58 - 2.72 (m, 4 H) 3.16 (td, J=12.7, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.3 Hz, 1 H) 3.75 (q, J=2.8 Hz, 1 H) 3.93 (br d, J=12.7 Hz, 1 H) 4.05 (dd, J=11.8, 3.3 Hz, 1 H) 4.38 - 4.44 (m, 1 H) 4.43 - 4.61 (m, 2 H) 6.57 (br s, 1 H) 6.58 (br s, 1 H) 7.20 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.38 (br s, 1 H)
522		407 0.92 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.92 (m, 2 H) 2.05 (s, 3 H) 2.20 - 2.30 (m, 1 H) 2.52 - 2.59 (m partially hidden , 1 H) 2.59 - 2.72 (m, 4 H) 3.16 (td, J=12.7, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.3 Hz, 1 H) 3.75 (q, J=2.8 Hz, 1 H) 3.94 (br d, J=12.7 Hz, 1 H) 4.05 (dd, J=11.8, 3.3 Hz, 1 H) 4.39 - 4.61 (m, 3 H) 6.81 (br d, J=2.1 Hz, 1 H) 6.84 (br d, J=2.1 Hz, 1 H) 7.22 (d, J=9.5 Hz, 1 H) 7.36 (d, J=9.5 Hz, 1 H) 9.96 (br s, 1 H)

Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	^{1}**H NMR**
523		407 1.05 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.40 - 1.45 (m, 1 H) 1.49 - 1.57 (m, 2 H) 1.82 - 1.96 (m, 4 H) 2.03 - 2.09 (m, 1 H) 2.13 (s, 3 H) 2.18 (s, 3 H) 2.26 - 2.31 (m, 1 H) 2.46 - 2.49 (m partially hidden, 1 H) 2.51 - 2.54 (m partially hidden, 1 H) 2.87 - 2.94 (m, 1 H) 4.19 - 4.25 (m, 1 H) 4.63 - 4.69 (m, 1 H) 7.06 (br s, 1 H) 7.11 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 10.20 (br s, 1 H)
524		407 1.05 U	1H NMR (500 MHz, DMSO-d6, 27°C) δ ppm 1.40 - 1.45 (m, 1 H) 1.49 - 1.58 (m, 2 H) 1.82 - 1.96 (m, 4 H) 2.03 - 2.09 (m, 1 H) 2.13 (s, 3 H) 2.18 (s, 3 H) 2.26 - 2.31 (m, 1 H) 2.46 - 2.49 (m partially hidden, 1 H) 2.51 - 2.54 (m partially hidden, 1 H) 2.87 - 2.94 (m, 1 H) 4.19 - 4.25 (m, 1 H) 4.63 - 4.71 (m, 1 H) 7.05 (br s, 1 H) 7.11 (br s, 1 H) 7.24 (d, J=9.5 Hz, 1 H) 7.35 (d, J=9.5 Hz, 1 H) 10.18 (br s, 1 H)
525		393 1.03 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.76 - 1.92 (m, 2 H) 2.21 - 2.30 (m, 1 H) 2.52 - 2.58 (m partially hidden, 1 H) 2.58 - 2.71 (m, 4 H) 3.19 (td, J=12.7, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.3 Hz, 1 H) 3.76 (q, J=2.8 Hz, 1 H) 3.96 (br d, J=12.7 Hz, 1 H) 4.05 (dd, J=11.8, 3.3 Hz, 1 H) 4.41 - 4.61 (m, 3 H) 6.98 (dd, J=8.4, 2.1 Hz, 1 H) 7.02 (d, J=2.1 Hz, 1 H) 7.51 (d, J=9.8 Hz, 1 H) 7.93 (d, J=8.4 Hz, 1 H) 8.26 (d, J=9.8 Hz, 1 H) 13.84 (br s, 1 H)
526		403 0.99 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 0.91 - 1.01 (m, 6 H) 1.76 - 1.90 (m, 2 H) 2.03 - 2.14 (m, 1 H) 2.32 - 2.41 (m, 5 H) 2.55 - 2.65 (m, 2 H) 3.16 (td, J=12.7, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.3 Hz, 1 H) 3.76 (br q, J=2.8 Hz, 1 H) 3.94 (br d, J=12.7 Hz, 1 H) 4.05 (dd, J=11.8, 3.3 Hz, 1 H) 4.36 - 4.44 (m, 1 H) 6.81 (d, J=2.1 Hz, 1 H) 6.84 (d, J=2.1 Hz, 1 H) 7.21 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.89 (br s, 1 H)

Ex	Compounds of formula (I)	**MS** (m/z, $[M+H]^+$) **Rt** (min) **Analytical method**	**^{1}H NMR**
527		401 0.86 U	1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.72 - 1.92 (m, 4 H) 2.03 (s, 3 H) 2.08 - 2.17 (m, 1 H) 2.22 (s, 3 H) 2.37 - 2.45 (m, 3 H) 2.56 - 2.64 (m, 2 H) 3.16 (td, J=12.7, 3.8 Hz, 1 H) 3.63 (td, J=11.8, 3.3 Hz, 1 H) 3.75 (q, J=2.8 Hz, 1 H) 3.93 (br d, J=12.7 Hz, 1 H) 4.05 (dd, J=11.8, 3.3 Hz, 1 H) 4.36 - 4.44 (m, 1 H) 4.46 (dt, J=47.4, 6.0 Hz, 2 H) 6.57 (s, 1 H) 6.58 (s, 1 H) 7.19 (d, J=9.5 Hz, 1 H) 7.34 (d, J=9.5 Hz, 1 H) 9.38 (s, 1 H)
528		367,4 2.66 E	1H NMR (400 MHz, CDCl3) δ (ppm): 7.29 (d, J = 7.9 Hz, 1H), 6.91 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 4.21 (s, 1H), 3.71 (s, 1H), 3.53 (s, 1H), 3.12 (s, 1H), 2.91 – 2.76 (m, 1H), 2.68 (s, 1H), 2.52 – 2.48 (m, 1H), 2.45 (s, 3H), 2.34 (s, 3H), 2.32 – 2.38 (m, 1H), 2.24 – 1.89 (m, 4H), 1.84 – 1.75 (m, 1H), 1.05 (s, 6H)

EXAMPLES

The examples which follow describe the preparation of certain compounds in accordance with the disclosure. The numbers of the compounds of formula (I) exemplified below match those given above. All reactions are performed under inert atmosphere, unless otherwise stated. These examples are not limitative, and merely illustrate the present disclosure.

Analytical data (LC-MS and ^{1}H RMN) were not repeated in the examples for the final compounds as they are already disclosed in Table 1.

The following abbreviations are used:

ACN or MeCN	Acetonitrile
AcOK	Potassium acetate
Aq.	Aqueous
Ar	Argon
BBr_3	Boron tribromide
BH_3-THF	Borane tetrahydrofuran complex

BippyPhos	5-(di-tert-Butylphosphino)-1',3',5'-triphenyl-1'H-1,4'-bipyrazole
Boc	Tert-butyloxycarbonyl
Boc_2O	Di-tert-butyl Dicarbonate
BrettPhos Pd G3	[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate methanesulfonate
BuOH	Butanol
CO_2	Carbon dioxide
CV	Column Volume
DCM or CH_2Cl_2	Dichloromethane
CbzCl	Benzyl chloroformate
$CDCl_3$	Deuterochloroform
CyJohnPhos	Chloro(2-dicyclohexylphosphino-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
DIAD	Diisopropyl azodicarboxylate
DIPE	Diisopropylether
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylamino Pyridine
DME	Dimethylether
DMF	N,N-dimethylformamide
DMSO-d_6	Hexadeuterodimethyl sulfoxide
EA	Ethyl acetate
Et_3N	Triethylamine
EtOH	Ethanol
EtOAc or AcOEt	Ethylacetate
GPhos Pd G3	Methanesulfonato[Dicyclohexyl[3-(1,1-dimethylethoxy)-6-methoxy-2',6'-bis(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine](2'-amino-1,1'-biphenyl-2-yl)palladium(II)
H_2	Hydrogen
H_2O	Water
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl

	Uronium
HBpin	Pinacolborane
HCl	Hydrogen chloride
HCOOH	Formic acid
HCl	Hydrochloric acid
Hept.	Heptane
HMDS	Bis(trimethylsilyl)amine
I_2	Iodine
IL 1b	Interleukin 1 beta
$iPrNH_2$	Isopropylamine
iPrOH	Isopropanol
K_2CO_3	Potassium carbonate
K_3PO_4	Tripotassium phosphate
LC	Liquid chromatography
LiOH	Lithium hydroxide
$LiOH.H_2O$	Lithium hydroxide monohydrate
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	m-Chloroperbenzoic acid
Me-THF	2-methyl tetrahydrofuran
MeOD	Tetradeuteromethanol
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
N_2	Nitrogen
$NaBD_4$	Sodium borodeuteride
$NaBH_4$	Sodium borohydride
$NaBH_3CN$	Sodium cyanoborohydride
NaCl	Sodium chloride
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium sulfate
$Na_2S_2O_3$	Sodium thiosulfate

NaO^tBu	Sodium tert-butoxide
NaOH	Sodium hydroxide
NaOTMS	Sodium trimethylsiloxide
NBS	N-bromosuccinimide
NEt_3 or TEA	Triethylamine
$NH_3.H_2O$	Ammonia aqueous
NH_4HCO_3	Ammonium hydrogen carbonate
NMP	N-methyl-2-pyrrolidone
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
$Pd(dppf)Cl_2$ or $PdCl_2(dppf)$	[1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride
Pd-118 or $Pd(dtbpf)Cl_2$ or $PdCl_2(dtbpf)$	[1,1'-Bis(di-tert-butylphosphino)ferrocene] dichloropalladium(II)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium (0)
$Pd(OAc)_2$	Palladium (II) acetate
$Pd(OH)_2$	Palladium hydroxide
Pd/C	Palladium on carbon
PPh_3	Triphenyl phosphine
TBAF	Tetra-n-butylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TNF-alpha or TNF-α	Tumor necrosis factor-alpha or Tumor necrosis factor-α
rt	Room temperature
Rt	Retention time
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl;
$RuphosPdG_3$	Methanesulfonato(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl-palladium(II)
SFC	Supercritical fluid chromatography
SiOH	Silicon hydroxide

SiO_2	Silicon dioxide
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
$XPhosPdG_2$	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphényl)[2-(2′-amino-1,1′-biphényl)]palladium(II)
°C	Degree Celsius
ml	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
µmol	Micromole(s)
µl	Microliter(s)
h	Hour(s)

Analytical methods used

NMR:

The proton magnetic resonance spectra (^{1}H NMR), as described below, are recorded at 400 MHz or 500 MHz, mainly in DMSO-d_6, using the DMSO peak as reference. The chemical shifts (δ) are expressed in parts per million (ppm). The signals observed are expressed as follows: s = singlet; d = doublet; t = triplet; m = multiplet or br s = broad singlet; br m = broad multiplet

LCMS:

The LCMS characteristics, as described below, indicates the different high-performance liquid chromatography analytical methods used.

LCMS final compounds:

Method A:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CORTECS C18+ 1.7µm 2.1x50mm; Column temperature: 40°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B

0	98	2
2.00	0	100
2.60	0	100
2.70	98	2
3.00	98	2

Method B:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18+ 1.7µm 2.1x50mm; Column temperature: 60°C
Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)
Gradient:

(min)	%A	%B
0	97	3
2.10	0	100
2.45	0	100
2.50	97	3

Method C:

System SHIMADZU LCMS-2020 Qarray; ionization: electrospray in positive and/or negative mode (ES+/-); Column: HALO C18 2.7µm 3.0x30mm; Column temperature: 50°C
Flow: 1.5 ml/min; Solvents: A = H_2O (0.0375% TFA); B = ACN (0.01875% TFA)
Gradient:

(min)	%A	%B
0	95	5
0.5	5	95
0.8	5	95
0.81	95	5
1.05	95	5

Method D:

System SHIMADZU LCMS-2020 Qarray; ionization: electrospray in positive and/or negative mode (ES+/-); Column: HALO C18 5µm 3.0x30mm; Column temperature: 50°C

Flow: 2 ml/min; Solvents: A = H_2O (0.0375% TFA); B = ACN (0.01875% TFA)

Gradient:

(min)	%A	%B
0	95	5
0.4	5	95
0.75	5	95
0.76	95	5
1.05	95	5

Method E:

System Waters UPLC-DAD and QDa; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY BEH C18 1.7µm 2.1x100mm; Column temperature: 40°C; Flow: 0.343 ml/min; Solvents: A = H_2O 95%, ACN 5% (0.5g/l $AcNH_4$); B = ACN

Gradient:

(min)	%A	%B
0	84.2	15.8
0.49	84.2	15.8
2.67	10.5	89.5
4.61	10.5	89.5
5.34	84.2	15.8
6.07	84.2	15.8

Method F:

System Waters UPLC-DAD and ZQ; ionization: electrospray in positive and/or negative mode (ES+/-); Column: Alliance YMC C18 5µm 4.6x75mm; Column temperature: 30°C

Flow: 1 ml/min; Solvents: A = H_2O (0.2% NH_4HCO_3); B = ACN

Gradient:

(min)	%A	%B
0	90	10
13	0	100
13.5	0	100
13.8	90	10

15	90	10

Method Z1:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x50mm; Column temperature: 60°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	97	3
8.6	1	99
9.6	1	99
9.8	97	3
10	97	3

Method Z2:

System Waters UPLC-XEVO G2S-QTOF ; ionization : electrospray in positive and/or negative mode (ES+/-); Column : ACQUITY BEH C4 - 1.7 µm - 2.1 x 150 mm; Column temperature: 35°C; Flow: 0.5 ml/min; Solvents: A = H2O (0.1 % formic acid + 0.2% TEA); B = CH_3CN (0.1 % formic acid + 0.2% TEA)

Gradient:

(min)	%A	%B
0	90	10
1	80	20
5.5	1	98
8.5	1	98
10	90	10

Method Z3:

System Agilent Technologies 1200 Series; ionization : electrospray in positive and/or negative mode (ES+/-); Column: XBridge C18 3.5µm 4.6x50mm; Column temperature: 45°C; Flow: 1.8 ml/min; Solvents: A = H_2O (10mM NH_4HCO_3); B = ACN

Gradient:

(min)	%A	%B
0	95	5
1.4	5	95
3.0	5	95

LCMS, intermediates

Method G:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x50mm; Column temperature: 50°C
Flow: 0.8 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)
Gradient:

(min)	%A	%B
0	95	5
0.20	95	5
3.60	2	98
3,70	2	98
4,10	95	5
5.00	95	5

Method H:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x30mm; Column temperature: 35°C
Flow: 0.7 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)
Gradient:

(min)	%A	%B
0	95	5
0.18	95	5
3.20	1	99
3,40	1	99
3,55	95	5
4.00	95	5

Method I:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CORTECS C18 1.6µm 2.1x50mm; Column temperature: 55°C; Flow: 0.8 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	98	2
2.50	0	100
2.90	0	100
2.95	98	2
3.00	98	2

Method K:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column : ACQUITY CORTECS C18 1.6µm 2.1x50mm; Column temperature: 50°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% trifluoroacetic acid) ; B = ACN (0.1% trifluoroacetic acid).

Gradient:

(min)	%A	%B
0	97	3
0.1	97	7
2.1	3	97
2.4	3	97
2.5	97	3
3.00	97	3

Method L:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CORTECS C18 1.6µm 2.1x50mm; Column temperature: 50°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	95	5
0.05	94	6
1.50	1	99
1.90	1	99
1.95	95	5
2.00	95	5

Method M:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x30mm; Column temperature: 35°C Flow: 0.7 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	97	3
0.15	97	3
3.30	3	97
3,45	3	97
3,85	97	3
4.00	97	3

Method N:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CORTECS C18 1.6µm 2.1x50mm; Column temperature: 55°C; Flow: 0.8 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	60	40
0.15	60	40
3.30	0	100

3.45	0	100
3.85	98	2
4.00	98	2

Method O:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x30mm; Column temperature: 35°C Flow: 0.7 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	95	5
0.05	94	6
1.50	1	99
1.90	1	99
1.95	98	2
2.00	98	2

Method Q:

System Waters UPLC-DAD and QDa; ionization: electrospray in positive and/or negative mode (ES+/-); Column: HSS-T3 50mm*2,1mm-1,8µm; Column temperature: 40°C; Flow: 0.45 ml/min; Solvents: A = H_2O 95%, ACN 5% (0.5g/l $AcNH_4$); B = CAN; C = Acide formique 0,2%

Gradient:

(min)	%A	%B	%C
0	49	2	49
0.1	49	2	49
0.25	49	2	49
1.8	8	84	8
2.8	8	84	8
3.0	49	2	49
3.8	49	2	49
3.9	49	2	49

Method R:

System Waters UPLC-DAD and QDa; ionization: electrospray in positive and/or negative mode (ES+/-); Column: BEH-C18 50mm*2,1 mm-1,7µm; Column temperature: 40°C; Flow: 0.5 ml/min; Solvents: A = H_2O 95%, ACN 5% (0.5g/l $AcNH_4$); B = ACN

Gradient:

(min)	%A	%B
0	95	5
0.2	95	5
1.2	5	95
2.8	5	95
3.0	95	5
3.4	95	5

Method S:

System Waters UPLC-DAD and QDa; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY BEH C18 1.7µm 2.1x50mm; Column temperature: 40°C Flow: 0.50 ml/min; Solvents: A = H_2O 95%, ACN 5% (0.5g/l $AcNH_4$); B = ACN

Gradient:

(min)	%A	%B
0	95	5
1	5	95
2.6	5	95
2,8	95	5
3,3	95	5
3,5	5	95

Method T:

System Waters UPLC-DAD and ZQ; ionization: electrospray in positive and/or negative mode (ES+/-); Column: Xbridge C18 100mm*4,6 mm 5µm; Column temperature: 30°C; Flow: 0.8 ml/min; Solvents: A = H_2O (0.2% NH_4HCO_3); B = ACN

Gradient:

(min)	%A	%B
0	80	20
0.5	80	20
5.0	10	90
9.0	10	90
10.5	80	20
12	80	20

Method U:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18+ 1.7µm 2.1x50mm; Column temperature: 60°C; Flow: 1.0 ml/min; Solvents: A = H2O (0.1% formic acid) ; B = ACN (0.1% formic acid)
Gradient:

(min)	%A	%B
0	97	3
0,1	97	3
2.10	3	97
2.45	3	97
3,0	97	3

Method V:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CORTECS C18 1.6µm 2.1x50mm; Column temperature: 50°C; Flow: 1 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)
Gradient:

(min)	%A	%B
0	95	5
1.50	1	99
1.90	1	99
1.95	95	5
2.00	95	5

Method W:

System Waters UPLC-SQD2; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CORTECS C18 1.6µm 2.1x50mm; Column temperature: 50°C; Flow: 1 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	100	0
0.20	100	0
1.50	1	99
1.90	1	99
1.95	95	5
2.00	95	5

Method X:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x50mm; Column temperature: 50°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B
0	95	5
0.05	95	5
1.50	2	98
1.90	2	98
1.95	95	5
2.00	95	5

Method Y:

System Waters UPLC/SQD; ionization: electrospray in positive and/or negative mode (ES+/-); Column: ACQUITY CSH C18 1.7µm 2.1x50mm; Column temperature: 50°C; Flow: 1.0 ml/min; Solvents: A = H_2O (0.1% formic acid); B = ACN (0.1% formic acid)

Gradient:

(min)	%A	%B

0	95	5
0.05	94	6
2.50	1	99
3.90	1	99
3.95	95	5
4.00	95	5

Method Z4:

System Agilent Technologies 1200 Series; ionization: electrospray in positive and/or negative mode (ES+/-); Column: XBridge C18 3.5µm 4.6x50mm; Column temperature: 45°C; Flow: 1.8 ml/min Solvents: A = H_2O (10mM NH_4HCO_3); B = ACN

Gradient:

(min)	%A	%B
0	95	5
1.5	5	95

Method Z5:

System Agilent Technologies 1200 Series; ionisation: electrospray in positive and/or negative mode (ES+/-); Column: Poroshell 120 EC C18 4µm 4.6x50mm; Column temperature: 45°C; Flow: 2.0 ml/min; Solvents: A = H_2O (0.01%TFA); B = CAN (0.01%TFA)

Gradient:

(min)	%A	%B
0	95	5
1.5	5	95

Method Z6:

System Agilent Technologies 1200 Series; ionization: electrospray in positive and/or negative mode (ES+/-); Column: Sunfire 3.5µm 4.6x50mm; Column temperature: 45°C; Flow: 2.0 ml/min; Solvents: A = H_2O (0.01%TFA); B = CAN (0.01%TFA)

Gradient:

(min)	%A	%B

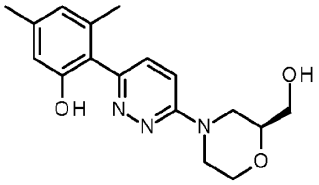
0	95	5
1.3	5	95
3.0	5	95

Mass spectrometry results are reported as the ratio of mass over charge.

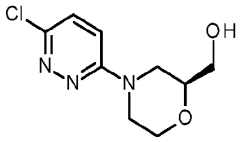
Reactions under microwaves were realized using a Biotage Initiator apparatus.

Synthesis of examples according to reaction scheme 1

Example 8: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 8.1: [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol



In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (2.6 mmol, 400 mg) in 2.5 ml of NMP was added [(2S)-morpholin-2-yl]methanol; hydrochloride (2.6 mmol, 400 mg) and DIPEA (5.2 mmol, 0.9 ml). The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 2.5h. After cooling down the solution, EtOAc was added, and the solution was washed with water (3 times) and brine. The aqueous layer was extracted twice with Me-THF. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a yellow solid (214 mg, 36% yield).

LCMS (**method G**): Rt = 1.19 min; MS m/z $[M+H]^+$ 230

2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 8)

In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.72 mmol, 120 mg) and [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (0.79 mmol, 183 mg) in 4.5 ml of 1,4-dioxane and 1.2 ml of water was added sodium carbonate (1.59 mmol, 132 mg). The solution was purged with Ar for 10 min, then $Pd(PPh_3)_4$ (0.036 mmol, 42 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 2.5h. After concentration under reduced pressure, EtOAc was added, and the resulting mixture was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 98/1/1 to 94/2/2) to give the title compound as a white solid (92 mg, 40% yield).

Compounds Examples 9, 65 and 179 were synthesized analogously to Example 8.

Compounds Examples 14, 15, 16, and 20 were synthesized analogously to Example 8 using Pinacolborane instead of boronic acid for Suzuki coupling.

Compounds Examples 24 and 30 were synthesized analogously to Example 8 using Pinacolborane instead of boronic acid for Suzuki coupling and using K_2CO_3/DMF instead of DIPEA/NMP at 110°C for n-arylation.

Compound Example 79 was synthesized analogously to Example 8 for Suzuki coupling and to Example 85 for n-arylation.

Compound Example 83 was synthesized analogously to Example 8 using BuOH instead of NMP at 130°C for n-arylation.

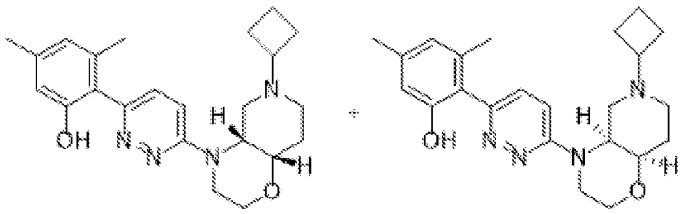
Compounds Examples 84 and 91 were synthesized analogously to Example 8 using DME instead of 1,4-dioxane for Suzuki coupling and using BuOH instead of NMP at 130°C for n-arylation.

Compound Example 113 was synthesized analogously to Example 8 using DMSO instead of NMP at 150°C for n-arylation.

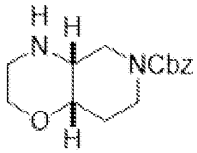
Compound Example 418 was synthesized analogously to Example 8.

Examples 10 and 11: 2-[6-[(4aR,8aS)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(4aS,8aR)-6-

cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

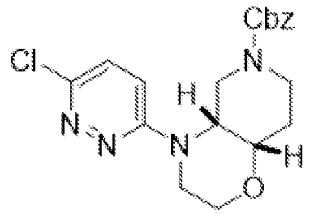


Int 10.7: benzyl rac-(4aR,8aS)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate



Under N_2, at 0 °C, to a solution of benzyl rac-(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (9.47 mmol, 2.75 g) in 25 ml of THF was added a 1.0 M solution of BH_3-THF (8.25 mmol, 8,24 ml). The solution was stirred at 60 °C for 8h. Then at 0 °C, 4 ml of MeOH are added and the mixture was stirred at 60 °C for another 1h. 25 ml of an aqueous solution of 1M HCl was added, and the mixture was stirred at 40 °C for additional 0.5 h. The reaction mixture was concentrated under reduced pressure to give crude benzyl (4a*R*,8a*S*)-hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazine-6(5*H*)-carboxylate (3 g) as a yellow oil. To this oil was added in 30 ml of DCM, then Et_3N (2.3 ml), Boc_2O (16 mmol, 3.55 g) and DMAP (133 mg). The resulting solution was stirred for 6h at 25 °C. The reaction as then poured into 30 ml of water and extracted with DCM (3 times). The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 10/1 to 1/1) to give 4.1 g of 6-benzyl 4-(*tert*-butyl) (4a*R*,8a*S*)-hexahydro-4*H*-pyrido[4,3-*b*][1,4]oxazine-4,6(5*H*)-dicarboxylate as a colourless oil. To 1,25 g of this oil was added 5 ml of 4M HCl/EtOAc. The solution was stirred at 25 °C for 1h, then concentrated under reduced pressure to give 800 mg of crude benzyl (4a*R*,8a*S*)-hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazine-6(5*H*)-carboxylate as a yellow oil, which was used for next step without further purification.

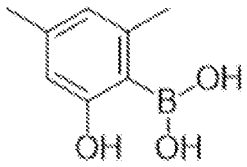
Int 10.8: benzyl rac-(4aR,8aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate



To a solution of crude benzyl rac-(4aR,8aS)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (2.06 mmol, 800 mg, chlorhydrate) in 5 ml of NMP was added 1.5 ml of DIPEA and 3,6-dichloropyridazine (10 mmol, 2.16 g) and the resulting mixture was stirred at 180 °C under microwave irradiation for 1h. After cooling down the solution, the reaction was quenched with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150 * 40 mm* 15 µm; mobile phase: [water (HCOOH)-ACN]; B%: 42%-72%, 10 min) to give the title compound as a yellow solid (450 mg, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (br s, 5H), 7.14 - 6.85 (m, 1H), 6.78 - 6.57 (m, 1H), 5.35 - 4.93 (m, 2H), 4.26 - 3.63 (m, 7H), 3.34 - 2.96 (m, 3H), 2.04 - 1.79 (m, 2H).

Int 10.9: (2-hydroxy-4,6-dimethylphenyl)boronic acid

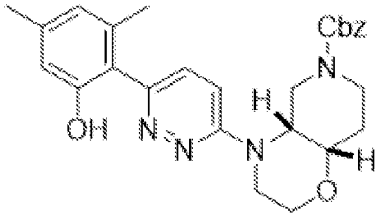


At -78°C, to a solution of (2-methoxy-4,6-dimethyl-phenyl)boronic acid (555 µmol, 100 mg) in 2 ml of DCM was added, BBr_3 (1.1 mmol, 107 µl) and the mixture was stirred at -78 °C for 1h. The reaction was then quenched by addition of 10 ml of ice water at 0 °C, and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by

recrystallization from Petroleum ether to give the title compound as a yellow solid (40 mg, 40% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.12 - 8.86 (m, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 2.46 (s, 3H), 2.25 (s, 3H).

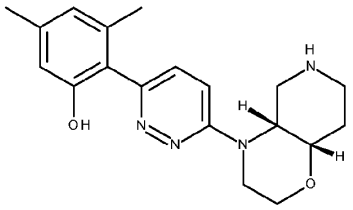
Int 10.10: benzyl rac-(4aR,8aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate



A mixture of benzyl rac-(4aR,8aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (0.85 mmol, 330 mg), (2-methoxy-4,6-dimethyl-phenyl)boronic acid (1.70 mmol, 282 mg), $Pd(PPh_3)_4$ (98 mg), 2 M aqueous solution of Na_2CO_3 (1.27 ml) and 4 ml of 1,4-dioxane was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 140 °C for 2h under microwave irradiation. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 20/1 to 5/1) to give the title compound as a yellow oil (320 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 - 7.46 (m, 1H), 7.38 (br s, 5H), 6.86 - 6.71 (m, 2H), 6.66 (s, 1H), 5.38 - 4.91 (m, 2H), 4.25 - 3.89 (m, 6H), 3.79 (dt, J = 3.2, 11.6 Hz, 1H), 3.48 - 2.99 (m, 3H), 2.45 - 2.25 (m, 6H), 2.02 - 1.85 (m, 2H).

Int 10.11 or Example 195: 3,5-dimethyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol



To a solution of benzyl rac-(4aS,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (2.3 mmol, 1.1 g) in 25 ml of EtOH was added ammonium formate (7 mmol, 440 mg) and 10% Pd/C (440 mg) and the resulting mixture was stirred at 80 °C under microwave irradiation for 1 h 30. After cooling down to RT, the mixture was filtered off over a pad of Decalite® and the cake rinsed with 50 ml of EtOH. The organic layer was concentrated under reduced pressure and the residue was diluted with 200 ml of dichloromethane and washed twice with 200 ml of an aqueous saturated sodium bicarbonate solution, dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a white solid (351 mg, 44% yield).

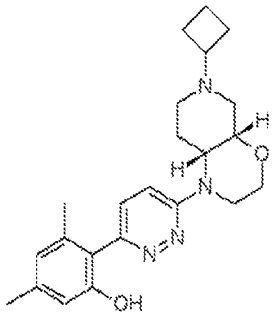
2-[6-[(4aR,8aS)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 10) and 2-[6-[(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 11)

To a solution of 3,5-dimethyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol (0.53 mmol, 180 mg) in 3 ml of DCM was added cyclobutanone (1 mmol, 37 mg), AcOK (1 mmol, 52 mg) and $NaBH_3CN$ (2.6 mmol, 166 mg) and the mixture as stirred at 25 °C for 8 h. The reaction was then concentrated under reduced pressure and the residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 150 * 25 mm * 10 µm; mobile phase: [water (HCOOH)-ACN]; B%: 29%-59%, 10 min) and lyophilized. Then, this racemate was separated by SFC (Column: Daicel Chiralpak® AD, 250×30 mm I.D., 10 µm particle size; Mobile phase: Eluent B: EtOH (0.1%NH_4OH), Isocratic elution: 40% Phase B in Supercritical CO_2; Flow rate: 70 g/min; Cycle time: 3.5 min; Back Pressure: 100 bar) to provide the 2 enantiomers, first one eluting at Rt = 1.99 min

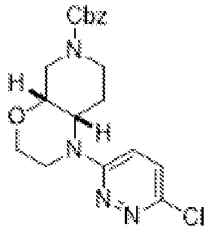
(60.48 mg, **Example 10, Enantiomer 1**) as a white solid, and second one eluting at Rt = 2.26 min (64.8 mg, **Example 11, Enantiomer 2**) as a white solid. (The absolute configurations cannot be assigned).

Compounds Examples 12 and 13 were synthesized analogously to Examples 10 and 11 using Pinacol borolane/Na_2CO_3 instead of boronic acid/$NaHCO_3$ for Suzuki coupling.

Example 4: 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol



Int 4.10: benzyl rac-(4aS,8aR)-1-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate

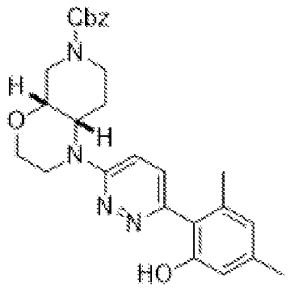


To a solution of 3,6-dichloropyridazine (8.2 mmol, 1.2 g) in 4 ml of NMP was added DIPEA (851 µl, 65 mmol) and benzyl rac-(4aS,8aR)- 1,2,3,4a,5,7,8,8a-octahydropyrido[3,4-b][1,4]oxazine-6-carboxylate (1.63 mmol, 450 mg) and the mixture was stirred at 180 °C for 1h under microwave irradiation. After cooling down the solution, water was added, and the mixture was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150*40 mm* 15 µm; mobile phase:

[water (HCOOH)-ACN]; B%: 36%-66%, 9 min) to give the title compound as a yellow solid (270 mg, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 - 7.28 (m, 5H), 7.24 (d, *J* = 9.6 Hz, 1H), 6.83 (d, *J* = 9.6 Hz, 1H), 5.16 (br d, *J* = 17.2 Hz, 2H), 4.62 - 4.20 (m, 3H), 4.16 - 4.07 (m, 1H), 3.73 (dt, *J* = 3.2, 12.0 Hz, 2H), 3.65 - 3.53 (m, 1H), 3.27 (dt, *J* = 3.6, 12.2 Hz, 1H), 3.15 - 2.75 (m, 2H), 2.19 - 1.97 (m, 1H), 1.63 (br s, 1H).

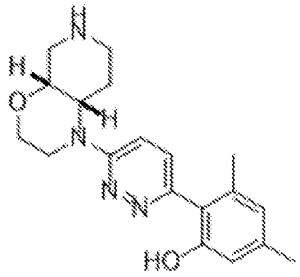
Int 4.11: benzyl rac-(4aS,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate



A mixture of benzyl rac-(4aS,8aR)-1-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (103 µmol, 40 mg), (2-hydroxy-4,6-dimethyl-phenyl) boronic acid (103 µmol, 17 mg), 2M aqueous solution of Na_2CO_3 (155 µl), $Pd(PPh_3)_4$ (12 mg) in 1,5 ml of 1,4-dioxane was degassed and purged with N_2 (3 times), and the mixture was stirred at 140 °C for 2 h under microwave irradiation. Then, the reaction was filtered, and the filtrate concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 150 * 25 mm * 10 µm; mobile phase: [water (HCOOH)-ACN]; B%: 29%-59%, 10 min) to give the title compound as a yellow solid (26 mg, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 9.6 Hz, 1H), 7.43 - 7.30 (m, 5H), 6.98 (d, *J* = 9.6 Hz, 1H), 6.77 (s, 1H), 6.66 (s, 1H), 5.26 - 5.10 (m, 2H), 4.70 - 4.56 (m, 1H), 4.21 - 4.09 (m, 1H), 3.83 - 3.63 (m, 3H), 3.45 - 3.28 (m, 1H), 3.16 - 2.82 (m, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 2.24 - 2.11 (m, 2H), 1.75 - 1.64 (m, 2H).

Int 4.12: 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol

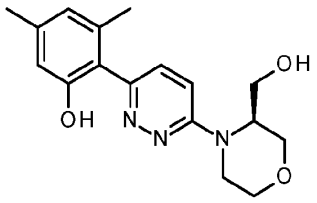


Under N_2, to a solution of benzyl rac-(4aS,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate (0,055 mmol, 26 mg) in 4 ml of EtOAc was added Pd/C (7 mg, 10% purity). The suspension was degassed, purged with H_2 (3 times), and the mixture was stirred under H_2 (15 Psi) at 25 °C for 2h. The reaction was then filtered, and the filtrate was concentrated under reduced pressure to give 18 mg of the crude title compound as a colorless oil, which was used for next step without further purification.

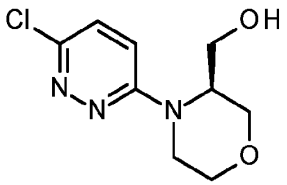
3,5-dimethyl-2-[6-[rac-(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido [3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol (Example 4)

To a solution of 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol (0.053 mmol, 18 mg) in 1 ml of DCM was added cyclobutanone (0.058 mmol, 4.35 µl), AcOK (0.058 mmol) and $NaBH_3CN$ (0.105 mmol, 6.6 mg). The mixture was stirred at rt for 4h. The reaction was then concentrated under reduced pressure, and the residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150 * 25 mm * 10 µm; mobile phase: [water (HCOOH)-ACN]; B%: 1%-30%, 10 min) to give the title compound as a white solid (8 mg, 37% yield).

Example 6: 2-[6-[(3S)-3-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 6.1: [(3S)-4-(6-chloropyridazin-3-yl)morpholin-3-yl]methanol



In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (5.2 mmol, 800 mg) in 3,5 ml of NMP was added [(3S)-morpholin-3-yl]methanol;hydrochloride (5.2 mmol, 800 mg) and DIPEA (10.4 mmol, 1,83 ml). The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 2.5h. After cooling down the solution, EtOAc was added, and the solution was washed with water (3 times) and brine. The aqueous layer was extracted twice with Me-THF. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as an orange oil (460 mg, 38% yield).

LCMS (**Method G**): Rt = 1.17 min; MS m/z $[M+H]^+$ 230

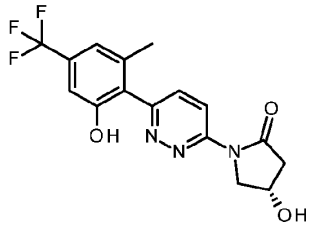
2-[6-[(3S)-3-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 6)

In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.58 mmol, 97 mg) and [(3S)-4-(6-chloropyridazin-3-yl)morpholin-3-yl]methanol (0.96 mmol, 221 mg) in 1,4-dioxane (3.64 ml) was added a solution of sodium carbonate (1.28 mmol, 106.7 mg) in water (0,91 ml). The solution was purged with Ar for 10 min, then $Pd(PPh_3)_4$ (0.029 mmol, 34 mg) was added. The vial was sealed, and the mixture was heated at 75°C under microwave irradiation for 1h, and 110°C for 2h. Then (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0,15 mmol, 25 mg) was added, and the mixture was heated at 100°C under microwave irradiation for 4h. After concentration under reduced pressure,

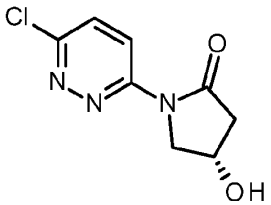
EtOAc was added, and the resulting mixture was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 98/1/1 to 94/3/3) to give the title compound as a yellow solid (52 mg, 28% yield).

Compound Example 5 was synthesized analogously to Example 6.

Example 62: (4S)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]pyrrolidin-2-one



Int 62.1: (4S)-1-(6-chloropyridazin-3-yl)-4-hydroxy-pyrrolidin-2-one



In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (2.25 mmol, 335 mg) and (S)-4-hydroxy-2-pyrrolidinone (2.25 mmol, 227 mg) in 5 ml of 1,4-dioxane was added potassium phosphate tribasic (4.5 mmol, 955 mg), 1-1'-bis(diphenylphosphino)ferrocene (0.27 mmol, 150 mg), palladium acetate (0.090 mmol, 20 mg). The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. After cooling down to rt, the reaction mixture was filtered, the solid part was washed with EtOAc and the combined filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 20/80) to give the title compound as a brown solid (74 mg, 15% yield).

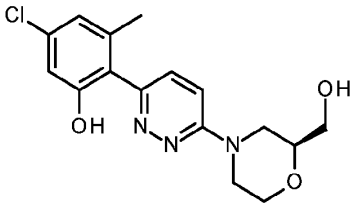
LCMS (**Method M**): Rt = 0.76 min; MS m/z $[M+H]^+$ 214

(4S)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one (Example 62)

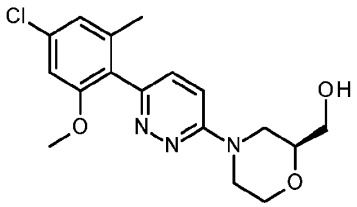
In a microwave vial, under Ar, to a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.34 mmol, 104 mg) and (4S)-1-(6-chloropyridazin-3-yl)-4-hydroxy-pyrrolidin-2-one (0.34 mmol, 74 mg) in 1.8 ml of 1,2-dimethoxyethane are added sodium carbonate (0.86 mmol, 91 mg) and 0.5 ml of water. The solution was purged with Ar for 3 min, then $Pd(PPh_3)_4$ (0.02 mmol, 20 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc and water and then filtered. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 94/3/3) to give the title compound as a white solid (80 mg, 66% yield).

Compounds Examples 61 and 86 were synthesized analogously to Example 62.

Example 63: 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol



Int 63.4: [(2S)-4-[6-(4-chloro-2-methoxy-6-methyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methanol



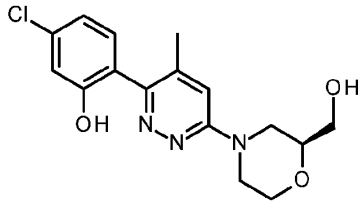
Under Ar, to a solution of 2-(4-chloro-2-methoxy-6-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.708 mmol, 200 mg) and [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (0.708 mmol, 163 mg) in 4 ml of dimethoxyethane and 1 ml of water was added a 2N sodium carbonate aqueous solution (1.77 mmol, 0.88 ml) then tetrakis(triphenylphosphine)palladium(0) (0.035 mmol, 41 mg). The mixture was stirred at 90°C for 3h. After cooling down to rt, DCM was added, and the mixture was washed with water. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give the title compound as a yellow solid (150 mg, 61% yield).
LCMS (**Method I**): Rt = 1.31 min; MS m/z $[M+H]^+$ 350.

5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol (Example 63)

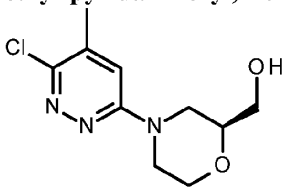
Under Ar, at 0°C, to a solution of [(2S)-4-[6-(4-chloro-2-methoxy-6-methyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methanol (0.391 mmol, 137 mg) in 20 ml of anhydrous DCM was slowly added a 1N solution of boron tribromide in DCM (1.18 mmol, 1.18 ml) and the mixture was stirred at 0°C for 3h. then 3 ml of a 4N aqueous NaOH solution were added under vigorous stirring. After 5 min, ACN and 4N aqueous HCl solution are added, and the mixture was extracted with DCM (twice). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of a 95/5 mixture EtOAc/MeOH in cyclohexane and the pure fractions are pooled and concentrated under reduced pressure, then triturated in diethylether to give the title compound as a light yellow solid (55 mg, 42% yield).

Compounds Example 56 was synthesized analogously to Example 63.
Compounds Examples 44, 45, 48, and 54 were synthesized analogously to Example 63 using OH-phenyl instead of OMe-phenyl and 1,4-dioxane instead of DME for Suzuki coupling.
Compounds Examples 70 and 71 were synthesized analogously to Example 63 using OH-phenyl instead of OMe-phenyl and 1,4-dioxane instead of DME for Suzuki coupling and 1,4-dioxane instead of NMP during 18h for n-arylation.

Example 85: 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]phenol



Int 85.1: [(2S)-4-(6-chloro-5-methyl-pyridazin-3-yl)morpholin-2-yl]methanol



A solution of 3,6-dichloro-4-methyl-pyridazine (24.5 mmol, 4 g), [(2S)-morpholin-2-yl]methanol;hydrochloride (24.5 mmol, 3.77 g) and Et_3N (54 mmol, 7.52 ml) in 50 ml of n-butanol was stirred at 130°C for 11h. The mixture was cooled down, diluted with 100 ml of EtOAc and 50 ml of diethylether and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of a 99/1 mixture EtOAc/MeOH in cyclohexane to give compound **Int 85.1** (2.75g, 46% yield) as a white solid.

LCMS (**Method L**): Rt = 0.40min; MS m/z $[M+H]^+$ 244;

5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl] phenol (Example 85)

Under Ar, to a solution of 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.923 mmol, 235 mg) and [(2S)-4-(6-chloro-5-methyl-pyridazin-3-yl)morpholin-2-yl]methanol (0.615 mmol, 150 mg) in 4 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.66 mmol, 0.83 ml) then tetrakis(triphenylphosphine)palladium(0) (0.03 mmol, 35 mg). The mixture was stirred at 100°C for 3h. After cooling down, EtOAc and diethylether are added and the resulting mixture was washed successively with aqueous saturated $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in DCM to give a yellow solid residue

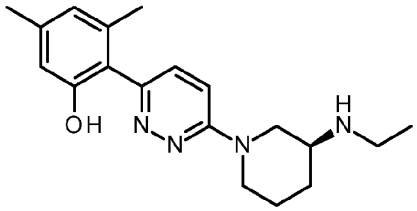
which was purified by prep-HPLC (column: Sunfire prep C18 OBD ; 250 * 50 mm * 10 µm; mobile phase: [water (TFA 10^{-2} N)-ACN]; B%: 10%-100% in 25 min. at 50 ml/min) to give the title compound as a white solid (154 mg, 74% yield).

Compounds Examples 72 to 78, 80, 81, 90, 93, 96, 97, 102, and 103 were synthesized analogously to Example 85.

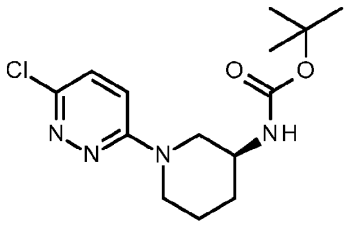
Compounds Examples 109, 110, and 112 were synthesized analogously to Example 85 using OH-phenylboronic acid instead of OH-phenyl borolane for Suzuki coupling.

Compound Example 92 was synthesized analogously to Example 85 using OH-phenylboronic acid instead of OH-phenyl borolane for Suzuki coupling and using NMP instead of BuOH for n-arylation.

Example 68: 2-[6-[(3S)-3-(ethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol



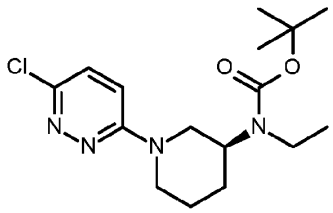
Int 68.1: tert-butyl N-[(3S)-1-(6-chloropyridazin-3-yl)-3-piperidyl]carbamate



A solution of 3,6-dichloropyridazine (6.71 mmol, 1 g), tert-butyl N-[(3S)-3-piperidyl]carbamate (7.38 mmol, 1.48 g) and Et_3N (13.42 mmol, 1.87 ml) in 15 ml of NMP was stirred at 130°C for 4.5 h. The mixture was cooled down, diluted with 50 ml of EtOAc and 50 ml of diethylether and washed with water (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of a 95/5 mixture EtOAc/MeOH in cyclohexane to give the title compound (1.92g, 91% yield) as a white solid.

LCMS (**Method I**): Rt = 1.67 min; MS m/z $[M+H]^+$ 313

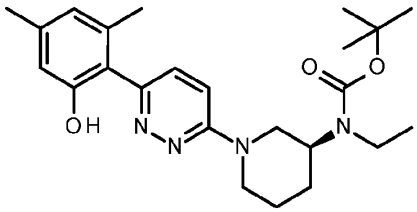
Int 68.2: tert-butyl N-[(3S)-1-(6-chloropyridazin-3-yl)-3-piperidyl]-N-ethyl-carbamate



Under Ar, at -5°C, to a solution of tert-butyl N-[(3S)-1-(6-chloropyridazin-3-yl)-3-piperidyl]carbamate (1.6 mmol, 500 mg) in 10 ml of anhydrous DMF was added NaH (1.92 mmol, 299 mg with 60% purity) and the mixture was stirred at 0°C for 30 min. Then, iodoethane (1.92 mmol, 153 µl) was added and the mixture was stirred at rt for 3h. The mixture was diluted with diethylether and washed successively with an aqueous 2% citric acid solution and water (twice). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in a solution of diethylether and pentane (1/1) to give the title compound (373 mg, 68% yield) as a white solid.

LCMS (**Method I**): Rt = 1.99 min; MS m/z $[M+H]^+$ 341

Int 68.3: tert-butyl N-ethyl-N-[(3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-piperidyl]carbamate



Under Ar, to a solution of tert-butyl N-[(3S)-1-(6-chloropyridazin-3-yl)-3-piperidyl]-N-ethyl-carbamate (1.09 mmol, 373 mg) and (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.42 mmol, 236 mg) in 8 ml of 1,4-dioxane and 3 ml of water was added 2N sodium carbonate aqueous solution (3.28 mmol, 1.64 ml) then tetrakis(triphenylphosphine)palladium(0) (0.08 mmol, 89 mg). The mixture was stirred at 100°C for 13h. After cooling down to rt, the mixture was diluted with EtOAc and

diethylether, then washed successively with an aqueous 2% citric acid solution and water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give the title compound (350 mg, 75% yield) as a white solid.

LCMS (**Method I**): Rt = 1.73 min; MS m/z $[M+H]^+$ 427

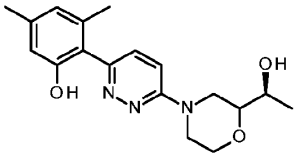
2-[6-[(3S)-3-(ethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 68)

A solution of tert-butyl N-ethyl-N-[(3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-piperidyl]carbamate (0.82 mmol, 350 mg) in 18 ml of DCM and 2 ml of TFA was stirred at rt for 2h, then concentrated under reduced pressure. The residue was dissolved in DCM and washed successively with saturated $NaHCO_3$ aqueous solution (twice) and water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained solid was dried under high vacuum in the presence of phosphorus pentoxide to give the title compound as a white solid (245 mg, 91% yield).

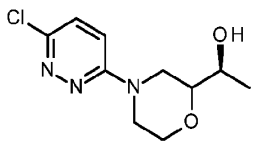
Compound Example 69 was synthesized analogously to Example 68 using OH-phenyl boronic acid instead of OMe-phenyl Pinacolborane for Suzuki coupling and without alkylation step.

Compound 148 was synthesized analogously to Example 68.

Examples 98 and 99: 2 diastereoisomers of 2-[6-[2-[(1S)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



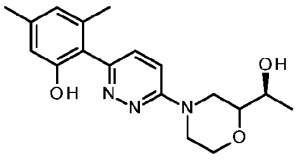
Int 98.1 and Int 99.1: 2 diastereoisomer of (1S)-1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethanol



In a microwave vial, to a solution of 3,6-dichloropyridazine (0.6 mmol, 90 mg) in 3 ml of NMP were added (1S)-1-morpholin-2-ylethanol hydrochloride (0.6 mmol, 100 mg) and DIPEA (0.8 mmol, 0.14 ml). The vial was sealed, and the mixture was heated at 150°C under microwave irradiation for 1h. After cooling down, the solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Heptane/ EOAct (from 100/0 to 70/30) to give the title compound (64 mg, 44%) as a mixture of 2 diastereoisomers:

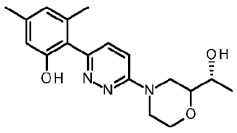
LCMS (**Method S**): Rt = 0,81 min; MS m/z $[M+H]^+$ 244,2

2 diastereoisomers of 2-[6-[2-[(1S)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Examples 98 and 99)

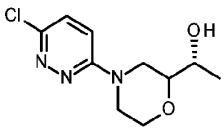


In a microwave vial under Ar, to a mixture of (1S)-1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethanol (0.21 mmol, 51 mg) and 3,5-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.21 mmol , 52 mg) in 0,8 ml of 1,4-dioxane and 0.2 ml of water was added K_3PO_4 (0.63 mol, 135 mg). The solution was purged with Ar for 10 min, then Pd-118 (also named Pd-118 or $PdCl_2$(dtbpf)) (0.02 mmol, 15 mg) was added. The mixture was heated at 120 °C for 18 h. After cooling down, the mixture was filtered through a celite® pad. Water and EtOAc were added to the filtrate. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Isocratic mode MeCN/aq.NH_4HCO_3 0.2% pH=7.9 28/72) to give separately 2 diastereoisomers, first eluting example 99 (Diastereoisomer 1, 12 mg, 17%) and second eluting example 98 (Diastereoisomer 2, 10 mg, 15%).

Examples 108 and 180: 2 diastereoisomers of 2-[6-[2-[(1R)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 108.1: 2 diastereoisomers of (1R)-1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethanol



In a microwave vial, to a solution of 3,6-dichloropyridazine (0.6 mmol, 90 mg) in 3 ml of NMP were added (1R)-1-morpholin-2-ylethanol hydrochloride (0.6 mmol, 100 mg) and DIPEA (0.8 mmol, 0.14 ml). The vial was sealed, and the mixture was heated at 150°C under microwave irradiation for 1h. After cooling down, the solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Heptane/ EtOAc (from 100/0 to 70/30) to give 2 diastereoisomers:

Diastereoisomer 1: (16 mg, 11% yield).

1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.23 (d, J = 9.5 Hz, 1H), 6.92 (d, J = 9.5 Hz, 1H), 4.20 – 4.13 (m, 1H), 4.12 – 4.09 (m, 1H), 4.08 – 4.04 (m, 1H), 3.93 (dt, J = 11.2, 5.6 Hz, 1H), 3.73 (td, J = 11.6, 2.8 Hz, 1H), 3.46 (ddd, J = 10.5, 4.8, 2.8 Hz, 1H), 3.17 – 3.07 (m, 1H), 3.01 (dd, J = 12.9, 10.5 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.27 (d, J = 6.5 Hz, 3H).

Diastereoisomer 2: (24 mg, 17% yield).

1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (d, J = 9.5 Hz, 1H), 6.90 (d, J = 9.5 Hz, 1H), 4.18 (dt, J = 13.0, 2.0 Hz, 1H), 4.16 – 4.08 (m, 1H), 4.03 – 3.96 (m, 1H), 3.82 – 3.75 (m, 1H), 3.75 – 3.69 (m, 1H), 3.38 (ddd, J = 10.7, 6.3, 2.8 Hz, 1H), 3.10 (td, J = 12.3, 3.6 Hz, 1H), 2.87 (dd, J = 12.8, 10.8 Hz, 1H), 2.47 (d, J = 3.8 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H).

2 diastereoisomers of 2-[6-[2-[(1R)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Examples 108 and 180)

Diastereoisomer 1 (Example 108)

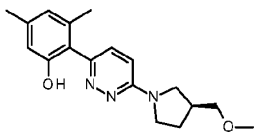
In a microwave vial under Ar, to a solution of (1R)-1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethanol (Diastereoisomer 2 previous Example 108.1, 0.1 mmol, 24 mg) and 3,5-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.11 mmol , 27 mg,) in 0.8 ml of 1,4-dioxane and 0.2 ml of water was added K_3PO_4 (0.3 mol, 63 mg). The solution was purged with Ar for 10 min, then Pd-118 (0.01 mmol, 7 mg) was added. The mixture was heated at 120 °C for 18h. After cooling down, the mixture was filtered through a celite® pad. Water and EtOAc were added to the filtrate. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by reverse phase preparative LC (Column YMC–Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 20/80 to 55/45 15CV), to give after lyophilization the title compound as a white solid (6 mg, 18% yield).

Diastereoisomer 2 (Example 180)

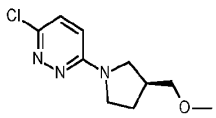
In a microwave vial under Ar, to a solution of (1R)-1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethanol (Diastereoisomer 1 previous Example 108.1, 0.115 mmol, 24 mg) and 2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.172 mmol , 29 mg,) in 1 ml of 1,4-dioxane and 0.25 ml of water was added K_2CO_3 (0.23 mol, 46 mg). The solution was purged with Ar for 10 min, then XPhos (0.00575 mmol, 2.74 mg) and Xphos Pd G2 (0.00575 mmol, 4.52 mg) are added. The mixture was purged again with N_2 and heated at 120 °C for 18h. After cooling down, the mixture was filtered through a celite® pad and concentrated under reduced pressure.

The residue was purified by by flash chromatography on silica gel using DCM/MeOH (from 100/0 to 97/3) to give, after lyophilization, the title compound (7.3 mg, 19%).

Example 82: 2-[6-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 82.1: 3-chloro-6-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazine



In a microwave vial, to a solution of 3,6-dichloropyridazine (2.68 mmol, 400 mg) in 10 ml of NMP are added DIPEA (2.68 mmol, 0.47 ml) and (3S)-3-(methoxymethyl)pyrrolidine (2.60 mol, 300 mg). The vial was sealed, and the mixture was heated at 150°C under microwave irradiation for 1h30. After cooling down, the solution was concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel using Heptane/ EtOAc (from 100/0 to 30/70) to give the title compound as a white solid (450 mg, 75% yield).

1H NMR (400 MHz, DMSO-d6) δ (ppm): 7.46 (d, J = 9.5 Hz, 1H), 6.98 (d, J = 9.5 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.46 – 3.35 (m, 2H), 3.27 (s, 3H), 3.22 – 3.13 (m, 1H), 2.59 – 2.54 (m, 1H), 2.12 – 2.00 (m, 1H), 1.95 – 1.85 (m, 1H), 1.81 – 1.67 (m, 1H).

2-[6-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 82)

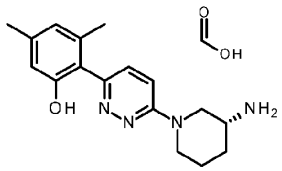
In a microwave vial, under Ar, to a solution of 3-chloro-6-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazine (0.44 mmol, 100 mg,) in 1 ml of 1,4-dioxane and 0.25 ml of water were added. K_3PO_4 (1.32 mmol, 280 mg,) and 3,5-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.44 mol, 110 mg,). The solution was purged with Ar for 10 min, then Pd-118 (0,048 mmol, 31 mg) was added. The mixture was heated at 120 °C for 18h. After cooling down, the mixture was filtered through a celite® pad. Water and EtOAc were added to the filtrate. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel using Heptane/ EtOAc (from 100/0 to 70/30). The fractions containing the compound are combined, evaporated in vacuo and taken-up with MeCN (1 ml), extended with water (3 ml), then freeze-dried over 18h to give the title compound as a white powder (20 mg, 15%).

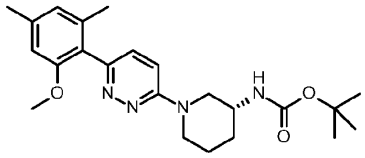
Compound Example 111 was synthesized analogously to Example 82.

Compound Example 88 was synthesized analogously to Example 82 using BuOH instead of NMP at 120°C for n-arylation.

Example 31: 2-[6-[(3R)-3-amino-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol; formic acid



Int 31.1: tert-butyl N-[(3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-piperidyl]carbamate



To a solution of (R)-3-BOC-aminopiperidine (2.2 mmol, 218 mg) and Et_3N (5.03 mmol, 0.7 ml) in 10 ml of ethanol was added 3,6-dichloropyridazine (2.01 mmol, 300 mg) and the mixture was warmed to reflux for 16h. After cooling to rt were added 10 ml of 1,4-dioxane, 2 ml of water, Cesium carbonate (3.0206 mmol, 985 mg) and (2-methoxy-4,6-dimethylphenyl)boronic acid (2.21 mmol, 400 mg). The solution was purged with Ar for 10 min, then was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.2 mmol, 150 mg) and the mixture was warmed to 120°C for 4h. After cooling to rt, the mixture was concentrated under reduced pressure. EtOAc was added and the resulting mixture was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel using cyclohexane/EtOAc (from 100/0 to 0/100) to give the title compound as a white foam (218 mg, 26% yield).

LCMS (**Method I**): Rt = 1,54 min; MS m/z $[M+H]^+$ 413

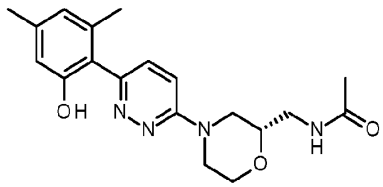
2-[6-[(3R)-3-amino-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol; formic acid (Example 31)

At 0°C, to a solution of tert-butyl N-[(3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-piperidyl]carbamate (0,51 mmol, 210 mg) in 20 ml of DCM was slowly added a 1N solution of boron tribromide in DCM (1.1 mmol, 1.1 ml) and the mixture was stirred at rt

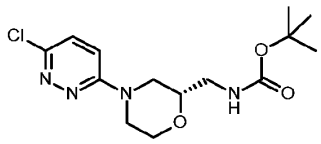
for 3h. Then MeOH was slowly added, and the solution was stirred 20 min. The resulting mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Sunfire prep C18 OBD; 100 * 30 mm * 10 µm; mobile phase: [water (TFA 10^{-2} N)-ACN]; B%: 10%-80% in 18 min. at 50 ml/min) (twice purification) to give the title compound as a light yellow solid (12 mg, 7% yield).

Compound Example 7 was synthesized analogously to Example 31.

Example 105: N-[[(2S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide



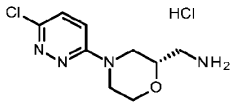
Int 105.1: tert-butyl N-[[(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methyl]carbamate



In a microwave vial, to a solution of 3,6-dichloropyridazine (1.76 mmol, 276 mg) in 5 ml of 1-butanol were added (R)-tert-butyl (morpholin-2-ylmethyl) carbamate (1.76 mmol, 400 mg) and Et_3N (3.9 mmol, 0,55 ml). The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 3h. After cooling down the solution, the mixture was concentrated under reduced pressure, ethyl acetate was added, and the solution was washed with water (3 times) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a light yellow solid (268 mg, 46% yield).

LCMS (**Method G**): Rt = 1,75 min; MS m/z $[M+H]^+$ 329

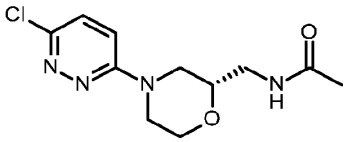
Int 105.2: [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanamine; hydrochloride



To a solution of tert-butyl N-[[(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl] methyl]carbamate (0.39 mmol, 130 mg) in 3 ml of dichloromethane was added 1 ml of a 4M solution of hydrochloric acid in 1,4-dioxane. The solution was stirred for 3h30 at room temperature. The mixture was concentrated under reduced pressure, then 1 ml of MeOH was added and the solution was concentrated under reduced pressure (3 times) to give the titled compound as an oil (145 mg), was used without further purification in the next step.

LCMS (**Method G**): Rt = 0,21 min; MS m/z $[M+H]^+$ 229

Int 105.3: N-[[(2S)-4-(6-chloropyridazin-3-yl) morpholin-2-yl]methyl]acetamide



To a solution of [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanamine; hydrochloride (0.39 mmol, 104 mg) in 2 ml of DCM were added Et_3N (1.0 mmol, 0.14 ml) and acetic anhydride (0.60 mmol, 0.06 ml). The mixture was stirred for 2h30 at room temperature. Then dichloromethane was added, and the mixture was washed with saturated aqueous $NaHCO_3$ solution (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the titled compound as a solid (89 mg, 83% yield).

LCMS (**method L**): Rt = 1.36 min; MS m/z [M+H]+ 271

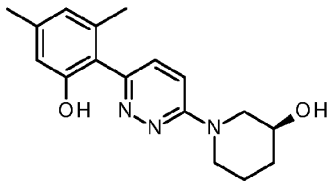
N-[[(2S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl] acetamide (Example 105)

In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.43 mmol, 72 mg) and N-[[(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-

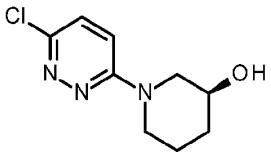
yl]methyl]acetamide (0.34 mmol, 90 mg) in 2 ml of 1,4-dioxane was added a solution of sodium carbonate (1 mmol, 85 mg) in 0.5 ml of water. The mixture was purged with Ar for 10 min, then $Pd(PPh_3)_4$ (0.017 mmol, 20 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling down the solution, the reaction mixture was filtered on a pad of Decalite® and rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure, EtOAc was added, and the resulting mixture was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a white solid (47 mg, 39% yield).

Compounds Examples 106, 211, 212, 216, 267, 275, 276, 279, 280 and 285 were synthesized analogously to Example 105.

Example 67: (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-3-ol



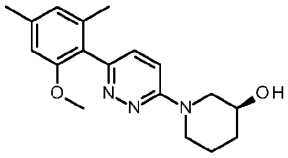
Int 67.1: (3S)-1-(6-chloropyridazin-3-yl)piperidin-3-ol



A solution of 3,6-dichloropyridazine (4.7 mmol, 700 mg), (3S)-piperidin-3-ol;hydrochloride (5.17 mmol, 711 mg) and Et_3N (9.4 mmol, 1.31 ml) in 11 ml of NMP was stirred at 130°C for 5h. The mixture was cooled down, diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc (4 times), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using cyclohexane/EtOAc (10/0 to 0/10) to

give the title compound as a yellow oil (500 mg, 50% yield).
LCMS (**method I**): Rt = 0.96 min; MS m/z $[M+H]^+$ 214

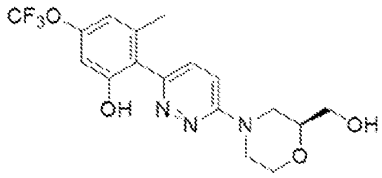
Int 67.2: (3S)-1-[6-(2-methoxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-3-ol



Under Ar, to a solution of (2-methoxy-4,6-dimethyl-phenyl)boronic acid (2.47 mmol, 445 mg) and (3S)-1-(6-chloropyridazin-3-yl)piperidin-3-ol (2.25 mmol, 480 mg) in 8 ml of 1,4-dioxane and 2 ml of water were added cesium carbonate (4.5 mmol, 1.46 g) and then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.22 mmol, 164 mg). The mixture was stirred at 100°C for 2.5h, then another 85 mg (0.47 mmol) of (2-methoxy-4,6-dimethyl-phenyl)boronic acid and 150 mg (0.46 mmol) of cesium carbonate were added and the mixture was stirred at 100°C for another 3h. The mixture was cooled down, diluted with EtOAc and washed with 5% citric acid aqueous solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in diethylether and filtered off to give the title compound as a yellow solid (335 mg, 48% yield).
LCMS (**Method I**): Rt = 1.13 min; MS m/z $[M+H]^+$ 314;

(3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-3-ol (Example 67)
Under Ar, a solution of (3S)-1-[6-(2-methoxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-3-ol (1.07 mmol, 335 mg) in 15 ml of DCM was cooled down to 0°C. A solution of 1N boron tribromide in DCM (2.14 mmol, 2.14 ml) was slowly added. The mixture was stirred at rt for 1h, then quenched by slow addition of 3 ml of MeOH. The resulting solution was stirred for 20 min then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) purified by silica gel chromatography eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound as a white solid (192 mg, 60% yield).

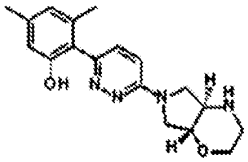
Example 121: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethoxy)phenol



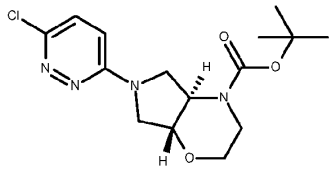
2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethoxy)phenol (Example 121)

In a microwave vial under Ar, to a mixture of [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (Int 8.1) (0.287 mmol, 91.4 mg) in 1 ml of 1,4-dioxane was added 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethoxy)phenol (0.287 mmol, 66.0 mg) and K_3PO_4 (0.862 mmol, 183 mg,) in 0.25 ml of water. The mixture was purged with N_2. Then Pd^{118} (0.0316 mmol, 20.6 mg,) was added and purged again with N_2. The mixture was heated at 120 °C for 24 hours. The reaction mixture was quenched with water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford a residue which was purified by flash chromatography on silica gel using DCM/MeOH (from 100/0 to 90/10). The fractions containing the compound were combined and evaporated under reduced pressure to give a colorless oil (25 mg). This oil was purified by preparative HPLC (YMC –Actus Triart Prep C18-S 150*30mm 5 µm, mobile phase: MeCN/aq.NH_4HCO_3 0.2% pH=7.9; gradient from 25/75 to 65/35) to afford a white solid (11 mg), which was taken-up with MeCN (1 mL), extended with water (3 mL), then lyophilized to give the title compound as a white solid (10 mg, 9% yield).

Example 125: 2-[6-[(4aR,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol



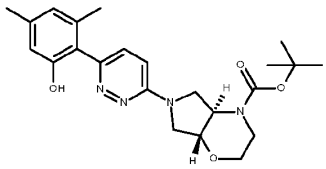
Int 125.1: tert-butyl (4aR,7aR)-6-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate



In a microwave vial, tert-butyl (4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-4-carboxylate (1.01 mmol, 0.230 g), 3,6-dichloropyridazine (1.01 mmol, 0.150 g) and DIPEA (1.01 mmol, 0.175 ml) in 5 ml of butan-1-ol was heated at 120 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2h. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using Hept/AcOEt 100/0 to 30/70 to give the title compound as a white solid (224mg, 65% yield).

LCMS (**method R**): Rt = 1.29min; MS m/z $[M+H]^+$ = 341.4

Int 125.2: tert-butyl (4aR,7aR)-6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate



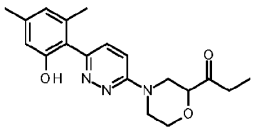
In a microwave vial under Ar, a mixture of tert-butyl (4aR,7aR)-6-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate (0.000205 mol, 0.0700 g), K_2CO_3 (0.000411 mol, 0.0568 g), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.000308 mol, 0.0511 g) in 1 ml of water and 4 ml of 1,4-dioxane was degassed under N_2 flow. XPhos Pd G2 (1.03e-5 mol, 0.00808 g) and XPhos (1.03e-5 mol, 0.00490 g) were added and the mixture was heated at 100 °C for 18h. After cooling at rt, the reaction mixture was filtered through a celite® pad, water was added. The organic layer was extracted with AcOEt, separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give the title compound as a yellow oil (65 mg, 72% yield).

LCMS (**Method S**): Rt = 1.34 min; MS m/z $[M+H]^+$ = 427.4

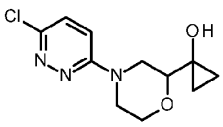
2-[6-[(4aR,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol (Example 125)

To a mixture of tert-butyl (4aR,7aR)-6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate (0.000152 mol, 0.0650 g) in 3 ml of dichloromethane was added TFA (0.00152 mol, 0.174 g). The mixture was then stirred 18h at rt. The mixture was concentrated under reduced pressure. The residue was taken up in water and basified with a 10% aqueous solution of K_2CO_3, then extracted with DCM, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give the title compound as a white solid (20mg, 40% yield).

Example 126: 1-[4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one



Int 126.1: 1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]cyclopropanol



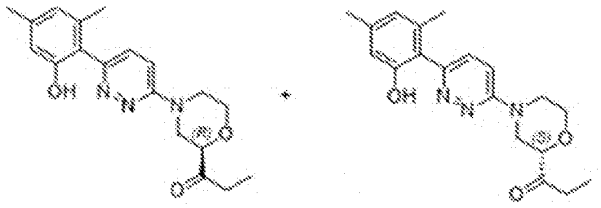
In a microwave vial, 1-morpholin-2-ylcyclopropanol hydrochloride (1.39 mmol, 250 mg), DIPEA (3.15 mmol, 0.539 ml) and 3,6-dichloropyridazine (1.57 mmol, 234 mg) were dissolved in 3.5 ml of NMP. The mixture was then heated at 150°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2 hours. After cooling to rt, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using Hept/AcOEt 100/0 to 50/50, then 30/70 to give the title compound as a pale yellow solid (231mg, 65% yield).

LCMS (**Method R**): Rt = 0.97; MS m/z [M+H]+ = 256.2;

1-[4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one (Example 126)

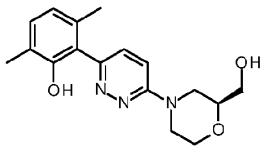
In a microwave vial under Ar, to a mixture of 1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]cyclopropanol (0.903 mmol, 231 mg) in 8 ml of 1,4-dioxane was added 3,5-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.903 mmol, 224 mg) and K_3PO_4 (2.71 mmol, 575 mg) in 2 ml of water. The mixture was purged with N_2. Then Pd^{118} (0.0994 mmol, 64.8 mg) was added and purged again with N_2. The mixture was then heated at 120 °C for 24 hours. The reaction mixture was quenched with water and extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 90/10 to afford a colorless oil (57.6 mg). This oil was purified by preparative HPLC (YMC –Actus Triart Prep C18-S 150*30mm 5 µm, mobile phase: MeCN/aq.NH_4HCO_3 0.2% pH=7.9; gradient from 25/75 to 65/35) to afford a white solid (47 mg), which was triturated in DIPE. The precipitate was filtered and dried under reduced pressure to give the title compound as a white solid (20 mg).

Example 156 and 157: 1-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one and 1-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl) pyridazin-3-yl]morpholin-2-yl]propan-1-one



The filtrate and excess product of 1-[4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one (Example 126) was purified by preparative chiral SFC (column: LuxCell-4 20x250 mm, Mobile phase: CO_2 / (MeOH + 0,3%$iPrNH_2$) 65/35). The fractions containing compound were combined and evaporated in vacuo to give 20 mg of a first fraction and 19 mg of a second fraction. Both fractions were lyophilized to give respectively 17 mg of first enantiomer Example 156 and 16 mg of second enantiomer Example 157 (The absolute configurations cannot be assigned).

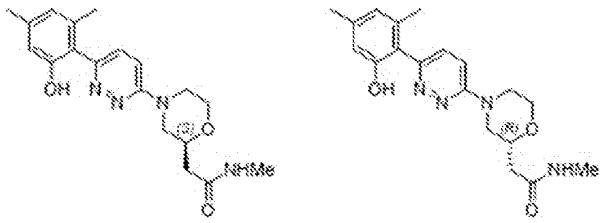
Example 141: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,6-dimethylphenol



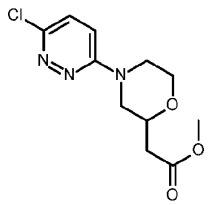
A vial was loaded with [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (0.327 mmol, 75.0 mg), potassium carbonate (0.653 mmol, 90.3 mg,), XPhos Pd G2 (0.0163 mmol, 12.8 mg) and XPhos (0.0163 mmol, 7.78 mg), then purged with nitrogen. A solution of compound 3,6-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.490 mmol, 122 mg) in 2 ml of dioxane and 0.4 ml of water wee added. The resulting mixture was then stirred at 100 °C for 18h. An aqueous solution of HCl 0.05 M was added to the mixture and the product was extracted with DCM (5 times). The aqueous layer was then neutralized to pH = 7 with a solution of 1% sodium bicarbonate and washed with DCM (5 times). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Hept/AcOEt 100/0 to 0/100, then 30/70 to give the title compound as a white solid (51mg, 50% yield).

Compounds Examples 152, 153 and 191 were synthesized analogously to Example 141.

Example 142 and 143: 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide and 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide



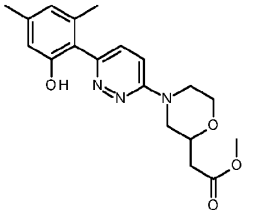
Int 142.1: methyl 2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]acetate



In a microwave vial, a mixture of 3,6-dichloropyridazine (0.00767 mol, 1.14 g), methyl 2-morpholin-2-ylacetate hydrochloride (0.00767 mol, 1.50 g) and DIPEA (0.0115 mol, 1.49 g) in 10 ml of butan-1-ol was heated at 120 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2 hours. After cooling to rt, the mixture was concentrated under reduced pressure and was purified by flash chromatography on silica gel using Hept/AcOEt 100/0 to 30/70 to give the title compound as a yellow oil (1,25 g, 60% yield).

LCMS (**Method R**): Rt = 1,08; MS m/z [M+H]+ = 272.2

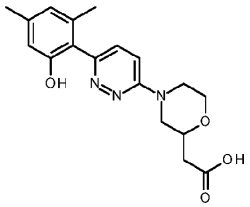
Int 142.2: methyl 2-[4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]acetate



In a microwave vial, under Ar, was added methyl 2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]acetate (2.18 mmol, 592 mg), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (3.27 mmol, 542 mg), XPhos (0.109 mmol, 52.0 mg) and K_2CO_3 (4.36 mmol, 604 mg) in 8 ml of 1,4-dioxane and 2 ml of water. The mixture was purged with N_2, then XPhos Pd G_2 (, 0.109 mmol, 85.9 mg) was added and the mixture was heated at 90 °C for 18h. After cooling to rt, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/05 to give the title compound as a yellow oil (697 mg, 90 % yield).

LCMS (**Method R**): Rt = 1.24 min; MS m/z [M+H]+ = 358.3

Int 142.3: 2-[4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]acetic acid



To a solution of methyl 2-[4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]acetate (1.95 mmol, 696 mg) in 7 ml of tetrahydrofuran and 2,3 ml of water was added LiOH monohydrate (5.84 mmol, 245 mg). The reaction mixture was stirred at rt for 18 hours. The solvent was removed under reduced pressure. The residue was taken up in water, then HCl (3M) was added. After filtration, the filtrate was concentrated under reduced pressure to give the title compound as an orange solid (751 mg).

Product was used crude for next step.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 12.39 (s, 1H), 10.10 (s, 1H), 7.94 (s, 2H), 6.72 (s, 1H), 6.66 (s, 1H), 4.35 (d, J = 13.0 Hz, 1H), 4.17 (d, J = 13.1 Hz, 1H), 4.08 – 3.95 (m, 1H), 3.91 (dt, J = 7.1, 3.5 Hz, 1H), 3.70 – 3.59 (m, 1H), 3.17 (t, J = 12.3 Hz, 1H), 3.00 – 2.89 (m, 1H), 2.58 (dd, J = 15.8, 4.8 Hz, 1H), 2.45 (dd, J = 15.8, 7.9 Hz, 1H), 2.26 (s, 3H), 2.10 (s, 3H).

LCMS (**Method R**): Rt = 0.92 min; purity 94 %, MS m/z $(M+H)^+$ = 344.3

2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide and 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide (Example 142 and Example 143).

To a solution of 2-[4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]acetic acid (0.582 mmol, 200 mg) in 2,5 ml of N,N-dimethylformamide was added methylamine in THF (2 M) (0.641 mmol, 0.320 mL), HATU (0.641 mmol, 244 mg) and DIPEA (0.874 mmol, 0.150 ml). The reaction mixture was stirred at room temperature for 18 hours. Methylamine in THF (2 M) (0.641 mmol, 0.320 ml) was added to the mixture and stirred for another 5 hours. Methylamine in THF (2 M) (0.641 mmol, 0.320 ml) was added to the mixture and stirred for another 3 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/05 to give 32 mg of a colorless oil. This oil purified by preparative chiral SFC (Stationary phase: Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2/(iPrOH + 0,3%$iPrNH_2$) 55/45). The fractions containing compound were combined and evaporated in vacuo to give 10 mg of a first fraction and 8 mg of a second fraction. Both fractions were lyophilized to give respectively 8.5 mg of first enantiomer Example 142 and 7.5 mg of second enantiomer Example 143 (The absolute configurations cannot be assigned).

Example 142 (Enantiomer 1)

LCMS (**Method E**): Rt = 2,25 min; MS m/z [M+H]+ = 357.4; e.e. (by analytical SFC) = 100 %

Example 143 (Enantiomer 2)

LCMS (**Method E**): Rt = 2,25 min; MS m/z [M+H]+ = 357.4; e.e. (by analytical SFC) = 100 %

Example 146 and 147: 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]acetamide and 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]acetamide

To a solution of 2-[4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]acetic acid (Int 142.3) (0.582 mmol, 200 mg) in 2 ml of N,N-dimethylformamide was added HATU (1.16 mmol, 443 mg), TEA (2.33 mmol, 0.325 ml) and HMDS (1.46 mmol, 0.304 ml). The reaction mixture was stirred at room temperature for 18 hours, then quenched with NH_4Cl 10 % and stirred at room temperature for 15 min. The organic layer was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/05 to give 136 mg of a yellowish solid.

This solid was purified by preparative chiral SFC (Stationary phase: Chiralpak® AS-3 4.6x100 mm, Mobile phase: CO_2 / (MeOH + 0,3%$iPrNH_2$) 75/25). The fractions containing compound were combined and evaporated in vacuo to give 48 mg of first enantiomer Example 146 and 45 mg of second enantiomer Example 147 (The absolute configurations cannot be assigned).

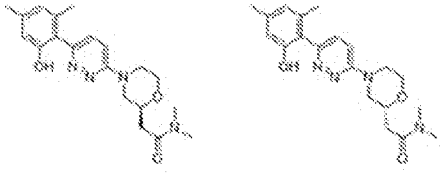
Example 146 (Enantiomer 1):

LCMS (**Method E**): Rt = 2,32 min; MS m/z [M+H]+ = 343.2; e.e. (by analytical SFC) = 99.2 %

Example 147 (Enantiomer 2)

LCMS (**Method E**): Rt = 2,32 min; MS m/z [M+H]+ = 343.2; e.e. (by analytical SFC) = 98.8 %

Example 150 and 151: 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N,N-dimethylacetamide and 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N,N-dimethylacetamide



To a solution of 2-[4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]acetic acid (Int 142.3) (0.495 mmol, 170 mg) in 2 ml of N,N-dimethylformamide were added Dimethylamine (2M) in THF (0.545 mmol, 0.272 ml), HATU (0.545 mmol, 207 mg) and DIPEA (0.743 mmol, 0.127 ml). The reaction mixture was stirred at room temperature for 18 hours, then quenched with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/05 to give 62 mg of a colorless oil.

This oil was purified by preparative chiral SFC (Stationary phase: Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2/(iPrOH + 0,3%$iPrNH_2$) 55/45). The fractions containing compound were combined and evaporated in vacuo to give, after lyophilization, 30 mg of first enantiomer Example 150 and 27 mg of second enantiomer Example 151 (The absolute configurations cannot be assigned).

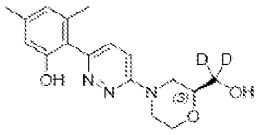
Example 150 (Enantiomer 1)

LCMS (**Method E**): Rt = 2,59 min; MS m/z [M+H]+ = 371.3; e.e. (by analytical SFC) = 100 %

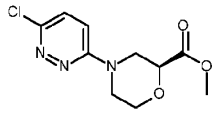
Example 151 (Enantiomer 2)

LCMS (**Method E**): Rt = 2,59 min; MS m/z [M+H]+ = 371.3; e.e. (by analytical SFC) = 100 %

Example 165: 2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol



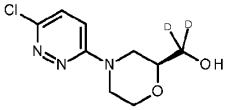
Int 165.1: methyl (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylate



In a microwave vial, a mixture of methyl (2S)-morpholine-2-carboxylate hydrochloride (5.51 mmol, 1.00 g), DIPEA (8.26 mmol, 1.44 ml) and 3,6-dichloropyridazine (5.51 mmol, 0.820 g) in 12 ml of NMP was heated at 150 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1 h. After cooling to rt, the mixture was concentrated under reduced pressure and the residue was purified by reverse phase preparative LC (Cartridge YMC –DispoPack AT ODS_25µm_300g, Flow rate 65ml/min, eluent MeCN/aq.NH_4HCO_3 0.2% pH=7.9, gradient from 10/90 to 30/70). The fractions containing compound were concentrated under reduced pressure to give the title compound as a yellow oil (455 mg, 33% yield).

LCMS (**Method T**): Rt = 4.16 min; MS m/z [M+H]+ = 257.8

Int 165.2: [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]-dideuterio-methanol



At 0°C under Ar, to a stirred solution of methyl (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylate (0.776 mmol, 200 mg) in 7 ml of MeOD was added $NaBD_4$ (1.55 mmol, 65.0 mg). The reaction mixture was stirred at rt for 8h. After cooled down at 0 °C, $NaBD_4$ (1.55 mmol, 65.0 mg) was added. Then, H_2O was slowly added, and the solution was extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

using DCM/MeOH 100/0 to 95/05 to give title compound as a colorless oil (110 mg, 62% yield).

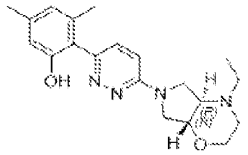
LCMS (**Method R**): Rt = 0.88 min; MS m/z [M+H]+ = 232.2;

2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol (Example 165)

In a microwave vial under Ar., To a solution of ([(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]-dideuterio-methanol (0.129 mmol, 30.0 mg) in 1,6 ml of 1,4-dioxane and 0,4 ml of water was added K_2CO_3 (0.259 mol, 35.8 mg) and (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.94 mmol, 32.2 mg). The reaction mixture was degased with N_2 flow, then XPhos (0.00647 mmol, 3.09 mg) and XPhos Pd G2 (0.00647 mol, 5.09 mg) were added, and the mixture was heated at 90 °C for 18h. After cooling to rt, the reaction mixture was concentrated under reduced pressure, then purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 90/10. The residue obtained was lyophilized to give the title compound as a white solid (13.5 mg, 32% yield).

Compounds Examples 169 and 192 were synthesized analogously to Example 165.

Example 168: 2-[6-[(4aR,7aR)-4-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol

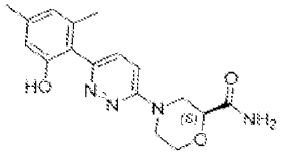


In sealed tube, to a stirred solution of 2-[6-[(4aR,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol (Example 125) (0.0551 mmol, 18.0 mg) in 2 ml of ethanol at rt were added acetaldehyde (0.08.27 mmol, 5.89 µl), acetic acid (0.0551 mmol, 4.03 µ) and $NaBH_3CN$ (0.110 mmol, 6.93 mg). The reaction mixture was stirred at 90°C for 15 min. After cooling to 0°C, ice-cold water and saturated aqueous solution of $NaHCO_3$ were slowly added. The mixture was extracted with AcOEt. The organic layer was washed with water, then brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

using DCM/MeOH 100/0 to 95/5 to give, after lyophilization, the title compound as a white solid (11.9 mg, 47% yield).

Compound Example 185 was synthesized analogously to Example 168.

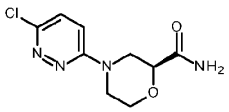
Example 181: (2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholine-2-carboxamide



Int 181.1: (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylic acid

In a microwave vial, to a mixture of 3,6-dichloropyridazine (5.51 mmol, 820 mg) in 12 ml of NMP was added methyl (2S)-morpholine-2-carboxylate hydrochloride (5.51 mmol, 1.00 g) and DIPEA (1.44 ml, 8.26 mmol). The resulting mixture was heated at 150 °C for 1 h, using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W. After cooling to rt, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase preparative LC (Cartridge YMC –DispoPack AT ODS_25µm_300g Flow rate 65ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 10/90 to 30/70) to give the title compound (486 mg, 34%).
1H NMR (400 MHz, DMSO-d6) δ (ppm): 7.55 – 7.51 (m, 1H), 7.37 (d, J = 9.7 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.97 (dt, J = 11.4, 3.6 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.85 – 3.79 (m, 1H), 3.61 – 3. 50 (m, 1H), 3.25 – 3.14 (m, 2H). (COOH not visible)
LCMS (**Method T**): Rt = 1,71 min; MS m/z [M+H]+ = 244.1;

Int 181.2: (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxamide



To a stirred solution of (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylic acid (Int 181.1) (0.821 mmol, 200 mg) in 3 ml of DMF were added HATU (1.23 mmol, 468 mg), TEA (2.46 mmol, 0.343 ml) and HMDS (1.54 mmol, 0.321 ml). The reaction mixture was

stirred at rt for 18h. The mixture was quenched with water and extracted with DCM. The combined organic layers were washed with an aqueous solution of K_2CO_3 (10 %) three times, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give, the title compound as a white solid (65 mg, 43% yield).

LCMS (**Method T**): Rt = 2.73 min; MS m/z [M+H]+ = 242.8;

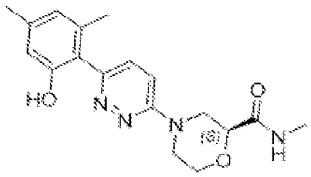
(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholine-2-carboxamide (Example 181)

In a microwave vial under Ar, a mixture of (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxamide (0.251 mmol, 61.0 mg), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.377 mol, 62.6 mg), K_2CO_3 (0.503 mmol, 69.5 mg) in 1,6 ml of 1,4-dioxane and 0,4 ml of water was degassed under N_2. XPhos (0.0126 mmol, 6,0 mg) and XPhos Pd G2 (0.0126 mmol, 9.9 mg) were added, and the mixture was heated at 90°C for 3h. The reaction mixture was then cooling down and concentrated under reduced pressure.

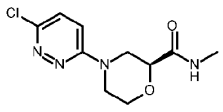
The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give, the title compound as a white solid (48 mg, 58% yield).

Compound Example 183 was synthesized analogously to Example 181.

Example 166: (2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N-methylmorpholine-2-carboxamide



Int 166.1: (2S)-4-(6-chloropyridazin-3-yl)-N-methyl-morpholine-2-carboxamide



In a sealed tube, to a stirred solution of (2S)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylic acid (Int 181.1) (0.821 mmol, 200 mg) in 5 ml of DMF were added, DIPEA (1.23

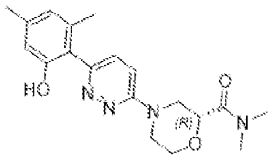
mmol, 0.214 ml), HATU (0.985 mol, 375 mg) and methylanamine hydrochloride (1.64 mmol, 111 mg). The reaction mixture was stirred at rt for 18h. DIPEA (0.821 mmol, 0.143 ml) and methanamine hydrochloride (0.821 mmol, 55.4 mg) was added and the mixture was stirred at rt for additional 18 h. The mixture was quenched with water and extracted with DCM. The combined organic layers were washed with an aqueous solution of K_2CO_3 (10 %) three times then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 97/3 to give the title compound as a white solid (55 mg, 26% yield).
LCMS (**Method T**): Rt = 3.15 min; MS m/z [M+H]+ = 256.9

(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N-methylmorpholine-2-carboxamide (Example 166)

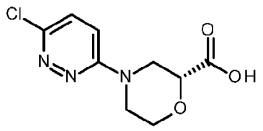
In a microwave vial under Ar, a mixture of (2S)-4-(6-chloropyridazin-3-yl)-N-methyl-morpholine-2-carboxamide (0.156 mmol, 40.0 mg), K_2CO_3 (0.296 mmol, 40.9 mg) and (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.000222 mol, 36.9 mg,) in 0,8 ml 1,4-dioxane and 0.2 ml of water was degassed under N_2. XPhos (0.00740 mmol, 0.929 mg) and XPhos Pd G2 (0.00740 mmol, 1.53 mg) were added, and the mixture was heated at 90 °C for 18 h. The reaction mixture was then cooling down and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 97/3 to give, after lyophilization, the title compound as a white solid (15 mg, 21% yield).

Compound Example 182 was synthesized analogously to Example 166.

Example 184: (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N,N-dimethylmorpholine-2-carboxamide



Int 184.1: (2R)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylic acid

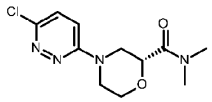


In a microwave vial, 3,6-dichloropyridazine (5.51 mmol, 820 mg) and methyl (2R)-morpholine-2-carboxylate hydrochloride (5.51 mmol, 1.00 g) were dissolved in 10 ml of 1-methylpyrrolidin-2-one, and DIPEA (11.0 mmol, 1.42 g) was added. The mixture was heated at 150 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 1h30. After cooling to rt, the mixture was concentrated under reduced pressure.

The residue was purified by reverse phase preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient 0.2% aq. NH_4+HCO_3- / MeCN from 90:10 to 70:30). The fractions containing the compound were combined and concentrated under reduced pressure. A second purification by reverse phase preparative LC (spherical C18 25 µm, 40 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient 0.2% aq. NH_4+HCO_3- / MeCN 95:5) give the title compound as a white solid (361 mg, 27% yield).

LCMS (**Method Q**): Rt = 1,71 min; MS m/z [M+H]+ = 244.1;

Int 184.2: (2R)-4-(6-chloropyridazin-3-yl)-N,N-dimethyl-morpholine-2-carboxamide



(2R)-4-(6-chloropyridazin-3-yl)morpholine-2-carboxylic acid (0.616 mmol, 150 mg) was dissolved in 2 ml of N,N-dimethylformamide. DIPEA (0.923 mmol,1 58 µl) and HATU (0.739 mmol, 281 mg) were added, and the mixture was stirred for 10 min. N-dimethylamine 2M in THF (1.23 mmol, 616 µl) was added and the mixture was stirred at rt for 36h. The mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

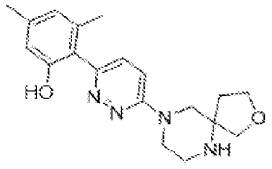
The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 90/10 to give a white solid. After concentration, the residue was taken up in water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a white solid (25 mg, 15%).

LCMS (**Method T**): Rt = 3.45 min; MS m/z [M+H]+ = 270.8

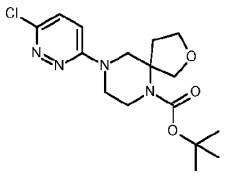
(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N,N-dimethylmorpholine-2-carboxamide (Example 184)

(2R)-4-(6-chloropyridazin-3-yl)-N,N-dimethyl-morpholine-2-carboxamide (0.0923 mmol, 25.0 mg) and (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.139 mmol, 23.0 mg) were dissolved in 0,8 ml of 1,4-dioxane and 0,2 ml of water. K_2CO_3 (0.185 mmol, 25.5 mg) was added, and the mixture was purged with N_2. XPhos (0.00462 mmol, 2.20 mg), XPhos Pd G2 (0.00462 mmol, 3.63 mg) were added, the mixture was purged again with N_2 and the mixture was stirred for 18h at 90 °C. Additional (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.139 mmol, 23.0 mg), K_2CO_3 (0.185 mmol, 25.5 mg), XPhos (0.00462 mmol, 2.20 mg) and XPhos Pd G2 (0.00462 mmol, 3.63 mg,) were added. The mixture was purged with N_2 and stirred for 3 h at 90 °C. After cooling down to rt, water and EtOAc were added. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 90/10 to give the title compound as a white solid (7.6 mg, 23% yield).

Example 196: 3,5-dimethyl-2-[6-(2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]phenol



Int 196.1: tert-butyl 9-(6-chloropyridazin-3-yl)-2-oxa-6,9-diazaspiro[4.5]decane-6-carboxylate

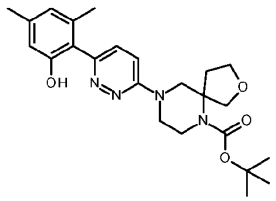


To a stirred solution of 3-bromo-6-chloro-pyridazine (0.825 mmol, 160 mg) in 2 ml of 1,4-dioxane at rt were added tert-butyl 2-oxa-6,9-diazaspiro[4.5]decane-6-carboxylate (0.825 mmol, 200 mg) and sodium tert-butoxide (2.48 mmol, 238 mg). The mixture was purged

with N_2. RuPhos Pd G3 (0.0825 mmol, 69.0 mg) and RuPhos (0.0825 mmol, 0 38.5 mg) were then added, and the mixture was purged with N_2. The reaction mixture was stirred at 90 °C for 4h. After cooling down to rt, the mixture was filtered, and the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give the title compound as a colorless oil (175.4 mg, 56 % yield).

LCMS (**Method R**): Rt = 1.27 min; MS m/z [M+H]+ = 355.4;

Int 196.2: tert-butyl 9-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-oxa-6,9-diazaspiro[4.5]decane-6-carboxylate



In a microwave vial, under inert atmosphere, was added tert-butyl 9-(6-chloropyridazin-3-yl)-2-oxa-6,9-diazaspiro[4.5]decane-6-carboxylate (0.409 mmol, 156 mg), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.409 mmol, 67.8 mg), XPhos (0.0204 mmol, 8.86 mg) and K_2CO_3 (0.817 mmol, 113 mg) in 2 ml of 1,4-dioxane and 0,4 ml of water. The mixture was purged with N_2. Then, XPhos Pd G2 (0.0204 mmol, 16.1 mg) was added, and the mixture was purged with N_2. The mixture was then heated at 90 °C for 4 hours. The mixture was quenched with water and extracted with DCM (twice). The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 97/03 to give the title compound an off-white solid (137 mg, 69% yield).

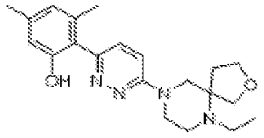
LCMS (**Method S**): Rt = 1.32 min; MS m/z [M+H]+ = 441.4;

3,5-dimethyl-2-[6-(2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]phenol (Example 196)

At 0 °C, to a solution of tert-butyl 9-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-oxa-6,9-diazaspiro[4.5]decane-6-carboxylate (0.296 mmol, 131 mg) in 2 ml of DCM was dropwise added TFA (2.96 mmol, 0.220 ml). The reaction mixture was then stirred at rt for

18 hours. After concentration under reduced pressure, the residue was taken up in water, basified with an aqueous solution of K_2CO_3 10 %, extracted with a 90/10 DCM/MeOH mixture, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 90/10 to give a colorless oil which was triturated in DIPE, filtered, and dried under reduced pressure to give the title compound as a white solid (51 mg, 39% yield).

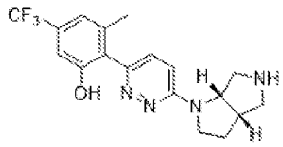
Example 227: 2-[6-(6-ethyl-2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]-3,5-dimethylphenol



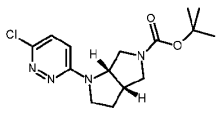
In sealed tube, to a stirred solution of 3,5-dimethyl-2-[6-(2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]phenol (Example 196, 0.0837 mmol, 28.5 mg) in 1 ml of ethanol at rt were added acetaldehyde (0.126 mmol, 0.007 ml), acetic acid (0.0837 mmol, 0.00479 ml) and $NaBH_3CN$ (0.167 mmol, 10.5 mg). The reaction mixture was stirred at rt for 2 hours. After cooling down to rt, ice-cold water and a saturated solution of $NaHCO_3$ were slowly added and the mixture was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by reverse phase (Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 35/65 to 75/25) to give the title compound as an off-white solid (6 mg, 19 % yield).

Compound Example 208 was synthesized analogously to Example 227.

Example 229: 2-[6-[rac-(3aS,6aS)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



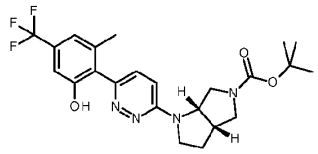
Int 229.1: tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylate



In a microwave vial, a mixture of tert-butyl rac-(3aS,6aS)-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[2,3-c]pyrrole-5-carboxylate (5.03 mmol, 1.07 g), 3,6-dichloropyridazine (5.03 mmol, 0.750 g) and DIPEA (5.03 mmol, 0.862 ml) in 26 ml of NMP was heated at 150 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2 h. NMP was removed with a Genevac. Then, water was added, and the mixture was extracted with DCM (twice). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was triturated with a mixture of DIPE/MeCN (90/10). The precipitate was filtered off and dried to give the title compound a as pale brown solid (740 mg, 45%).

LCMS (**Method T**): Rt = 5.83 min; MS m/z [M+H]+ = 324.9;

Int 229.2: tert-butyl rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b] pyrrole-5-carboxylate



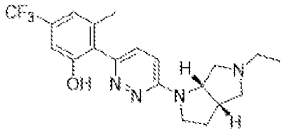
In a microwave vial under Ar, a mixture of tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrole-5-carboxylate (0.308 mmol, 0.100 g), 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenol (0.462 mmol, 0.140 g) and K_2CO_3 (0.616 mmol, 0.0851 g) in 3.3 ml of 1,4-dioxane and 0,8 ml of water was degassed under N_2. XPhos Pd G2 (0.0154 mmol, 12.1 mg) and XPhos (0.0154 mmol, 6.68 mg) were added, and the mixture was heated at 90 °C for 3 h. After cooling to rt, the mixture was filtered and washed with DCM. The filtrate was concentrated under

reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give the title compound (150 mg).
LCMS (**Method S**): Rt = 1.33 min; [M+H]+ = 465.4;

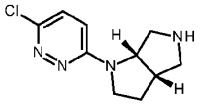
2-[6-[rac-(3aS,6aS)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 229)

TFA (3.23 mmol, 0.240 ml) was added dropwise to a solution of tert-butyl rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]248yridazine-3-yl]-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrole-5-carboxylate (0.323 mmol, 0.150 g) in 8 ml of DCM at room temperature. The mixture was heated at 30 °C overnight. TFA (3.23 mmol, 0.240 ml) was added dropwise, and the mixture was heated at 30 °C for 4h. The mixture was concentrated under reduced pressure. The residue was taken up in DCM and washed with an aqueous solution of K_2CO_3 10%. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via Reverse phase (Stationary phase: YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 25/75 to 55/45) to give, after trituration in DIPE, the title compound as a white solid (23mg, 20% yield).

Example 243: 2-[6-[rac-(3aS,6aS)-5-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



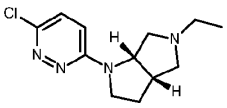
Int 243.1: rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrole



TFA (0.00308 mol, 0.229 ml) was added dropwise to a solution of tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrole-5-carboxylate (Int 229.1, 0.00160 mmol, 0.520 g) in 15 ml of DCM at rt. The mixture was heated at 30 °C for 8h. The mixture was concentrated under reduced pressure. The residue was taken up in

DCM and washed with an aqueous solution of K_2CO_3 10%. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 380 mg of the title compound which was used in the next step without any further purification.
LCMS (**Method S**): Rt = 0,65 min; MS m/z [M+H]+ = 225.1;

Int 243.2: rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-5-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole



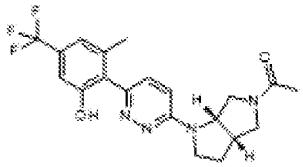
To a stirred solution of rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrole (1.09 mmol, 245 mg) in 10 ml of MeCN were added K_2CO_3 (2.18 mmol, 301 mg) and iodoethane (1.09 mmol, 170 mg). The reaction mixture was stirred at rt for 18h. Water was added to the reaction and the mixture was extracted with DCM. The organics layer was washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 172 mg of the title compound as a white solid, which was used in the next step without any further purification.
LCMS (**Method S**): Rt = 0,75 min; MS m/z [M+H]+ = 253.1

2-[6-[rac-(3aS,6aS)-5-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 243)

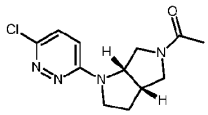
In a microwave vial under Ar, a mixture of rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-5-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole (0.673 mmol, 170 mg), K_2CO_3 (1.35 mmol, 186 mg), 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.673 mmol, 203 mg) in 5 ml of 1,4-dioxane and 1,25 ml of water was degassed under N_2 flow. XPhos (0.0336 mmol, 16.0 mg) and XPhos Pd G2 (0.0336 mmol, 26.5 mg) were added, and the mixture was heated at 90 °C for 4h. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/(MeOH/NH4OH 10%) 100/0 to 90/10. The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by reverse phase chromatography, column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN/aq.

NH_4HCO_3 0.2% pH=7.9 Focused gradient from 40/60 to 60/40. The fractions containing the compound were combined and concentrated under reduced pressure and lyophillizated to give the title compound as a white solid (54 mg, 20% yield).

Example 228: 1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-5-yl]ethanone



Int 228.1: 1-[rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-5-yl]ethanone

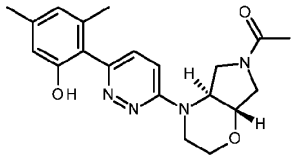


At 0°C, acetyl chloride (0.490 mmol, 0.034 ml) was added dropwise to a solution of (3aS,6aS)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[2,3-c]pyrrole 3 (0.445 mmol, 0.100 g) and DIPEA (0.668 mmol, 0.114 ml) in 6 ml of DCM. The mixture was allowed to warm to rt and stirred for 1h. The mixture was then quenched with water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5 to give the title compound (90 mg).
LCMS (**Method S**): Rt = 0.79 min; MS m/z [M+H]+ = 267.1;

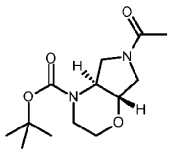
1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-5-yl]ethanone (Example 228)
In a microwave vial under Ar, a mixture of 1-[(3aS1-[(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-5-yl]ethanone (0.292 mmol, 78.0 mg), K_2CO_3 0.585 mmol, 80.8 mg), 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.292 mmol, 88.3 mg) in 3 ml of 1,4-dioxane and 0,8 ml of water was degassed under N_2 flow. XPhos (1.46e-5 mol, 6.97 mg) and XPhos Pd G2 (1.46e-5 mol, 11.5 mg) were added and the mixture was heated at 90 °C for 1h. After cooling to rt, the

reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 90/10 to give, after trituration in DIPE, the title compound (57 mg).

Example 257: 1-[rac-(4aS,7aS)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone



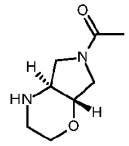
Int 257.1: tert-butyl rac-(4aS,7aS)-6-acetyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate



At 0C°, to a solution of tert-butyl rac-(4aS,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-4-carboxylate (1.18 mmol, 270 mg) in 10 ml of dichloromethane were added triethylamine (1.77 mmol, 247 µl) then acetic anhydride (1.77 mmol, 168 µl). The solution was allowed to warm to rt and stirred for 1 h. DCM was added to the mixture and a 10% aqueous solution of $NaHCO_3$ was also added. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 307 mg of the title compound as a pale yellow oil, which was used in the next step without any further purification.

1H NMR (500 MHz, $CDCl_3$) δ 4.44 – 4.14 (m, 1H), 4.08 – 3.97 (m, 1H), 3.90 (dd, J = 11.2, 7.4 Hz, 1H), 3.86 – 3.65 (m, 2H), 3.63 – 3.55 (m, 1H), 3.52 (td, J = 10.0, 7.5 Hz, 1H), 3.41 – 3.23 (m, 1H), 3.14 (dd, J = 11.9, 9.3 Hz, 1H), 3.07 – 2.93 (m, 1H), 2.04 (d, J = 13.7 Hz, 3H), 1.48 (s, 11H).

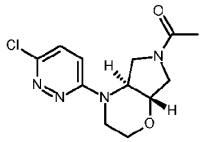
Int 257.2: 1-[rac-(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone ; 2,2,2-trifluoroacetate



At 0 C°, to a solution of tert-butyl (4aS,7aS)-6-acetyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-4-carboxylate (1.11 mmol, 300 mg) in 10 m of dichloromethane was slowly added TFA (11.1 mmol, 824 µl). The solution was allowed to warm to rt and stirred for 1h. The solution was concentrated under reduced pressure, then co-evaporated with toluene to give 530 mg of the title compound as a colorless residue, which was used in the next step without any further purification.

1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.34 – 3.85 (m, 5H), 3.73 – 3.14 (m, 5H), 2.13 (s, 3H).

Int 257.3: 1-[rac-(4aS,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo [3,4-b][1,4]oxazin-6-yl]ethanone



In a sealed tube, a mixture of 3-bromo-6-chloro-pyridazine (1.17 mmol, 227 mg), sodium tertbutoxide (3.17 mmol, 304 mg), RuPhos Pd G3 (0.0528 mmol, 44.1 mg) and RuPhos (0.106 mol, 49.3 mg) was purged with N_2. A solution of 1-[(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-ium-6-yl]ethanone;2,2,2-trifluoroacetate (1.06 mmol, 300 mg) in 6 ml of 1,4-dioxane was added and the mixture was purged again with N2 then heated at 100 °C for 2 h. After cooling to rt, the mixture was diluted with EtOAc, then water was added. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5, then isocratic 95/5 to give 149 mg of the title compound.

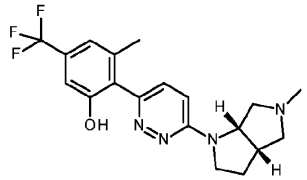
LCMS (**Method S**): Rt = 0.81 min; MS m/z [M+H]+ = 283.1;

1-[rac-(4aS,7aS)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (Example 257)

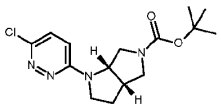
In a sealed tube, a mixture of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.621 mmol, 103 mg), XPhos Pd G2 (0.0414 mmol, 32.6 mg), XPhos (0.0828 mmol, 39.5 mg) and K2CO3 (0.828 mmol, 114 mg) was purged with N_2. 1-[(4aS,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (0.414 mmol, 117 mg) in 5,8 ml of 1,4-dioxane and 1,2 ml of water was added, the mixture was purged again with N2 then heated at 90 °C for 3h. After cooling to rt, the mixture was diluted with EtOAc and water was added. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH 100/0 to 95/5, then isocratic 95/5.

The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 25/75 to 55/45) to give, after lyophilization, 49.0 mg of the title compound as a white fluffy solid.

Example 265: 2-[6-[rac-(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



Int 265.1: tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylate

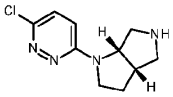


In a microwave vial, a mixture of tert-butyl rac-(3aS,6aS)-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[2,3-c]pyrrole-5-carboxylate (5.03 mmol, 1.07 g), 3,6-dichloropyridazine (5.03 mmol, 0.750 g) and DIPEA (5.03 mmol, 0.862 ml) in 26 ml of NMP was heated at 150 °C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2 h. NMP was removed with a Genevac. Water was added to the residue

and the mixture was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was triturated with a mixture of DIPE/MeCN (90/10). The precipitate was filtered and dried to give 740 mg of the title compound as pale brown solid.

LCMS (**Method T**): Rt = 5,83 min; MS m/z [M+H]+ = 324.9 ;

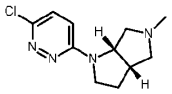
Int 265.2: rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrole



TFA (0.00308 mol, 0.229 ml) was added dropwise to a solution of tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrole-5-carboxylate (0.00160 mmol, 0.520 g) in 15 ml of DCM at room temperature. The mixture was heated at 30 °C for 8h. After cooling to rt, the mixture was concentrated under reduced pressure. The residue was taken up in DCM and washed with an aqueous solution of K_2CO_3 10%. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 380 mg of the title compound, which was used without any further purification.

LCMS (**Method S**): Rt = 0,65 min; MS m/z [M+H]+ = 225.1;

Int 265.3: rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole



Formaldehyde (37% in water) (9.79 mmol, 0.771 ml) was added to a solution of rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[2,3-c]pyrrole (1.96 mmol, 440 mg) in 10 ml of methanol and 10 ml of THF, and stirred at rt. NaBH3CN (1.96 mmol, 123 mg) was added and the resulting mixture was stirred at rt for 2h. The reaction mixture was poured on ice and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/(MeOH/NH_4OH 10%) 100/0 to 90/10 to give 270 mg of the title compound (57% yield).

LCMS (**Method R**): Rt = 0.99 min; MS m/z [M+H]+ = 239.2;

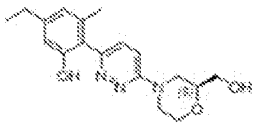
2-[6-[rac-(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 265)

In a microwave vial under Ar, a mixture of rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrole (1.01 mmol, 240 mg), K_2CO_3 (2.01 mmol, 278 mg) and 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (1.51 mmol, 456 mg) in 0,8 ml of 1,4-dioxane and 0,2 ml of water was degassed under N_2 flow. XPhos (0.0503 mmol, 24.0 mg) and XPhos Pd G2 (0.0503 mmol, 39.6 mg) were added, and the mixture was heated at 80 °C for 3h. The reaction mixture was cooled to rt then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/(MeOH/NH_4OH 10%) 100/0 to 80/20. The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 45/55 to 65/35) to give 181 mg of the title compound.

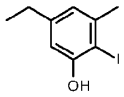
Examples 270 and 271: 2-[6-[(3aR,6aR)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

The 2 enantiomers of compound 2-[6-[(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 265, 360 mg) were separated by preparative chiral SFC chromatography (Stationary phase: Chiralpak® AS-H 20x250 mm, Mobile phase: CO_2 / (iPrOH + 0,3% $iPrNH_2$) 85/15 to give both enantiomers, first eluting Rt 2.64 min, example 270 (66 mg) and second eluting Rt 4.11 min, example 271 (74 mg). The absolute configurations cannot be assigned at this stage.

Example 245: 5-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methylphenol



Int 245.1: 5-ethyl-2-iodo-3-methyl-phenol

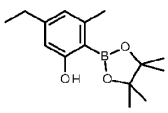


Under Ar, at 0°C, to a stirred solution of 3-ethyl-5-methyl-phenol (1.00 g, 7.34 mmol) in 60 ml of toluene was added portionwise NaH (60% in mineral oil) (0.587 g, 14.7 mmol). The reaction mixture was stirred at 0 °C for 30 min, then was added portionwise I2 (1.86 g, 7.34 mmol). The reaction mixture was stirred at 0 °C for 20 min, then poured into cold water, and extracted with EtOAc. The organic layer was washed with an aqueous solution of $Na_2S_2O_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 80/20). The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by SFC Chiralpak® AD-H 20x250 mm, Chiralpak® IG 30x250 mm, Mobile phase: CO_2 / (iPrOH + 0,3%iPrNH2) 85/15 to give 445 mg of the title compound.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 10.05 (s, 1H), 6.63 (s, 1H), 6.53 (s, 1H), 2.45 (q, J = 7.6 Hz, 2H), 2.31 (s, 3H), 1.12 (t, J = 7.5 Hz, 3H).

LCMS (**Method S**): Rt = 1.33 min; MS m/z [M+H]+ = 261.0;

Int 245.2: 5-ethyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



In a sealed tube, NEt_3 (0.819 mL, 5.88 mmol) was slowly added to a solution of 5-ethyl-2-iodo-3-methyl-phenol (220 mg, 0.839 mmol) and HBpin (537 mg, 4.20 mmol) in 12 ml of 1,4-dioxane. The solution was purged with N_2. $Pd(OAc)_2$ (22.6 mg, 0.101 mmol) and CyJohnPhos (0.7 mg, 0.185 mmol) were added, the mixture was purged again with N2, then

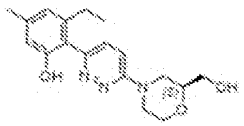
heated at 80 °C for 18 h. After cooling to rt, water was added. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 90/10) to give 164 mg of the title compound.

1H NMR (500 MHz, DMSO-d6) δ (ppm): δ 8.72 (s, 1H), 6.46 (s, 1H), 6.41 (s, 1H), 2.46 (q, J = 7.8 Hz, 2H), 2.26 (s, 3H), 1.30 (s, 12H), 1.12 (t, J = 7.6 Hz, 3H) + undefined impurities

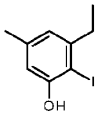
5-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methylphenol (Example 245)

In a microwave vial under Ar, a mixture of [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (88.0 mg, 0.383 mmol), K_2CO_3 (106 mg, 0.766 mmol), 5-ethyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (140 mg, 0.534 mol) in 3 ml of 1,4-dioxane and 0.75 ml of water was degassed under N_2. XPhos (9.34 mg, 0.0196 mmol) and XPhos Pd G2 (15.1 mg, 0.0192 mmol) were added, and the mixture was heated at 80 °C for 6h. After cooling to rt, the mixture was filtrated over celite® and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5). The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by reverse phase preparative LC Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 (Focused gradient from 25/75 to 65/35) to give, after lyophilisation, 22 mg of the title compound.

Example 246: 3-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methylphenol



Int 246.1: 3-ethyl-2-iodo-5-methyl-phenol

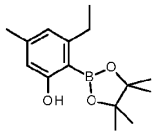


Under Ar, at 0°C, to a stirred solution of 3-ethyl-5-methyl-phenol (1.00 g, 7.34 mmol) in 60 ml of toluene was added portionwise NaH (60% in mineral oil) (0.587 g, 14.7 mmol). The reaction mixture was stirred at 0 °C for 30 min, then was added portionwise I2 (1.86 g, 7.34 mmol). The reaction mixture was stirred at 0 °C for 20 min, then poured into cold water, and extracted with EtOAc. The organic layer was washed with an aqueous solution of $Na_2S_2O_3$.The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure.The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 80/20). The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by SFC Chiralpak® AD-H 20x250 mm, Chiralpak® IG 30x250 mm, Mobile phase: CO_2 / (iPrOH + 0,3%iPrNH2) 85/15 to give 181 mg of the title compound.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 10.03 (s, 1H), 6.57 (s, 1H), 6.52 (s, 1H), 2.62 (q, J = 7.5 Hz, 2H), 2.17 (s, 3H), 1.10 (t, J = 7.5 Hz, 3H).

LCMS (**Method S**): Rt = 1.32 min; MS m/z [M+H]+ = 261.0;

Int 246.2: 3-ethyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



In a sealed tube, NEt_3 (0.670 mL, 4.81 mmol) was slowly added to a solution of 3-ethyl-2-iodo-5-methyl-phenol (180 mg, 0.687 mol) and HBpin (0.498 mL, 3.43 mmol) in 8 ml of 1,4-dioxane. The solution was purged with N_2. $Pd(OAc)_2$ (18.5 mg, 0.0824 mmol) and CyJohnPhos (53.0 mg, 0.151 mmol) were added, the mixture was purged again with N_2 then heated at 80 °C for 18h. After cooling to rt, water was added. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 90/10) to give 93 mg of the title compound.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 8.81 (s, 1H), 6.44 (s, 1H), 6.40 – 6.35 (m, 1H), 2.59 – 2.50 (m, 2H), 2.17 (s, 3H), 1.29 (s, 12H), 1.08 (t, J = 7.5 Hz, 3H) + undefined impurities.

3-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methylphenol (Example 246)

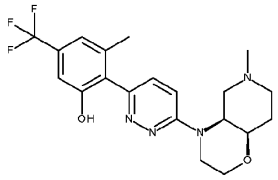
In a microwave vial under Ar, a mixture of [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (55.0 mg, 2.39 mmol), K_2CO_3 (66.2 mg, 0.479 mmol), 3-ethyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (94.2 mg, 0.359 mmol) in 2 ml of 1,4-dioxane and 0.5 ml of water was degassed under N_2 flow. XPhos (5.71 mg, 0.012 mmol) and XPhos Pd G2 (9.42 mg, 0.012 mmol) were added, and the mixture was heated at 80 °C for 6h. After cooling to rt, the mixture was filtrated over celite® and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5). The fractions containing the compound were combined and concentrated under reduced pressure. The residue was purified by reverse phase preparative LC Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 (Focused gradient from 25/75 to 65/35) to give, after lyophilisation, 14 mg of the title compound.

Examples 260 and 261: 3-methyl-2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol and 3-methyl-2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol

The 2 enantiomers of compound 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 226, 101 mg) were separatedby Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD-H, 250×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 20%; flow rate: 200 mL/min; outlet pressure: 100 bar; 2 injections; UV detection: 265 nm) to provide 3-methyl-2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol, first eluting enantiomer at Rt = 4.3 min (22 mg, **Example 260**, Enantiomer 1) as a white solid, and 3-methyl-2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol, second eluting enantiomer at Rt = 6 min (20 mg, **Example 261**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Compounds Examples 310, 311 were obtained by preparative chiral SFC separation analogously to Example 260 and 261. The absolute configurations were assigned a posteriori (see **Chiral synthesis of example 311**).

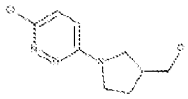
Example 260: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



To a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (2.23 mmol, 674 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** – 1.49 mmol, 400 mg) in 60 ml of 1,4-dioxane and 10 ml of water was added a 2N sodium carbonate aqueous solution (4.47 mmol, 2.23 ml). Argon was bubbling through the solution for 10 min then tetrakis(triphenylphosphine)palladium(0) (0.149 mmol, 172 mg) was added and the solution was stirred at 100°C for 2h. After cooling down to rt, the mixture was concentrated under reduced pressure and the residue was diluted with 100 ml of DCM and 100 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 2X50 ml of DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2) to give, after trituation in diethylether, the title compound as a white solid (390 mg, 64% yield).

Example 127: 5-chloro-2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-phenol

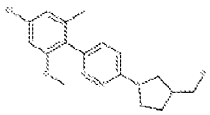
Int 127.1: [(3S)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]methanol



Under Ar, to a solution of 3,6-dichloropyridazine (250 mg, 1.6781 mmol) and triethylamine

(515 µl, 3.6918 mmol) in 20 ml of n-butanol was added [(3S)-pyrrolidin-3-yl]methanol (187 mg, 1459 mmol) and the mixture was heated at 120°C for 4h. After cooling to rt, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized in diethyl ether and filtrated off to give the title compound as a beige solid (m= 190 mg, 52% yield)
LCMS (**Method L**): Rt = 0,34 min; MS m/z [M+H]+ = 213 ;

Int 127.2: [(3S)-1-[6-(4-chloro-2-methoxy-6-methyl-phenyl)pyridazin-3-yl]pyrrolidin-3-yl]methanol



In a microwave vial, under Ar, to a solution of [(3S)-1-(6-chloropyridazin-3-yl)pyrrolidin-3-yl]methanol (100 mg, 0.468 mmol), 2-(4-chloro-2-methoxy-6-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (172 mg, 0.6084 mmol), carbonate sodium (117 mg, 1.4041 mmol) in 6.23 ml of 1,4-dioxane and 1.56 ml of Water was add tetrakis(triphenylphosphine)palladium(0) (38 mg , 0.0328 mmol). The mixture was heated at 120°C under microwave irradiation for 3h. After cooling to rt, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography SiO_2 DCM/MeOH (from 100/0 to 95/5) to give the title compound as an amorphous solid (76 mg, 48% yield).
LCMS (**Method L**) Rt = 0,54 min MS m/z [M+H]+ = 334 ;

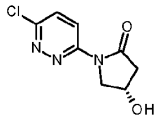
5-chloro-2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-phenol (Example 127)

At -5 °C, to a solution of [(3S)-1-[6-(4-chloro-2-methoxy-6-methyl-phenyl)pyridazin-3-yl]pyrrolidin-3-yl]methanol (76 mg, 0.2277 mmol) in 10 ml of dichloromethane was slowly added Tribromoboron (455 µl, 0.4553 mmol, 1 mol/l in hexane) and the reaction mixture was stirred at -5°C for 1h15. Additional Tribromoboron (200 µl) was added, and the mixture was stirred for 1h15 more at -5°C. Then at -5°C few drops of methanol were slowly added, and the mixture was basified with aqueous NaOH 5N, stirred 5mn, then acidified with an aqueous solution of aqueous SO_2 6%. The mixture was diluted with water and extracted with

DCM. The organic layer was washed with brine, dried over Mg_2SO_4, filtered, and concentrated under reduce pressure. The residue was crystallized in diethyl ether, filtered off, and purified by reverse phase chromatography (H_20/CH_3CN) (C18, water/MeCN, gradient 95/5 to 5/95) to give the title compound as a beige solid (7 mg, 10% yield).

Example 130: (4S)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one

Int 130.1: (4S)-1-(6-chloropyridazin-3-yl)-4-hydroxy-pyrrolidin-2-one



In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (2.25 mmol, 335 mg) and (S)-4-hydroxy-2-pyrrolidinone (2.56 mmol, 259 mg) in 5 ml of 1,4-dioxane was added potassium phosphate tribasic (4.27 mmol, 907 mg), 1-1'-bis(diphenylphosphino)ferrocene (0.26 mmol, 142 mg), palladium acetate (0.09 mmol, 19 mg). The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1.5h. After cooling to rt, the reaction mixture was diluted with EtOAc and CH_2Cl_2 then filtered, the solid part was washed with EtOAc and CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 50/50) to give the title compound as a brown solid (145 mg, 32% yield).

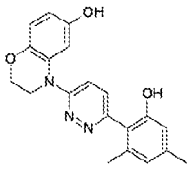
LCMS (**Method M**): Rt = 0.76 min; MS m/z [M+H]+ 214;

(4S)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one (Example 130)

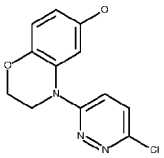
In a microwave vial, under Ar, to a solution of (4S)-1-(6-chloropyridazin-3-yl)-4-hydroxy-pyrrolidin-2-one (0.35 mmol, 75 mg) and (4-chloro-2-hydroxy-6-methylphenyl)boronic acid (0.37 mmol, 69 mg) in 1.8 ml of 1,2-dimethoxyethane were added sodium carbonate (0.88 mmol, 93 mg) and 0.45 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.02 mmol, 20 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc and water and filtered. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered

and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 93/3.5/3.5) to give the title compound as a white solid (27 mg, 24% yield).

Example 162 :4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3-dihydro-1,4-benzoxazin-6-ol



Int 162.1: 4-(6-chloropyridazin-3-yl)-2,3-dihydro-1,4-benzoxazin-6-ol



In a microwave vial, under Ar, a suspension of 3,6-dichloropyridazine (5.97 mmol, 889 mg), 3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ol hydrochloride (0.75 mmol, 140 mg) and diisopropylethylamine (1.64 mmol, 0.28 ml) in 1 ml of n-butanol was heated at 150°C under microwave irradiation for 7.5h. After addition of DCM, the organic layer was washed with water, filtered on hydrophobic column and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 94/3/3) to give the title compound as a brown solid (63 mg, 32% yield).

LCMS (**Method U**): Rt = 1,17 min; MS m/z [M+H]+ = 264;

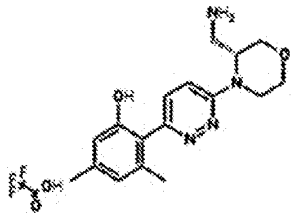
4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3-dihydro-1,4-benzoxazin-6-ol (Example 162)

In a microwave vial, under Ar, to a solution of 4-(6-chloropyridazin-3-yl)-2,3-dihydro-1,4-benzoxazin-6-ol (0.24 mmol, 62 mg) and (2-hydroxy-4,6-dimethylphenyl)boronic acid (0.26 mmol, 43 mg) in 1.65 ml of 1,2-dimethoxyethane were added sodium carbonate (0.59 mmol, 62 mg) and 0.4 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.02 mmol, 19 mg) was added. The vial was sealed, and the mixture was heated at 100°C under

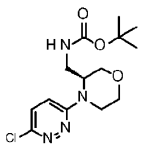
microwave irradiation for 1h. After cooling to rt, the reaction mixture was diluted with EtOAc and filtered. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give a brown solid (45 mg). This one was further purified by reverse phase chromatography (Column XSelect CSH C18 5µm OBD from Waters, 250x50mm, Flow rate 80ml/min, eluent: acetonitrile /water + 0.1% formic acid (from 34/66 to 100/0), to give the title compound as an off white solid (30 mg, 37% yield).

Compounds Examples 193, 215 and 362 were synthesized analogously to Example 162.

Example 123: 2-[6-[(3R)-3-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid



Int 123.1: tert-butyl N-[[(3R)-4-(6-chloropyridazin-3-yl) morpholin-3-yl]methyl]carbamate

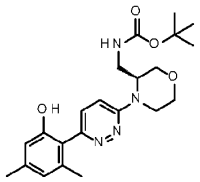


In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (2.57 mmol, 404 mg) in 3 ml of NMP was added (R)-tert-butyl (morpholin-3-ylmethyl) carbamate (2.57 mmol, 586 mg) and DIPEA (5.15 mmol, 0.907 mL). The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 2.5h. After cooling to rt, DCM and brine were added. The aqueous layer was extracted twice with DCM. The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give an orange oil (356 mg). This oil was purified by flash chromatography on

silica gel using DCM/AcOEt (from 10/0 to 6/4) to give the title compound as a white solid (120 mg, 14% yield).

LCMS (**Method L**): Rt = 0,79 min; [M+H]+ = 329;

Int 123.2: tert-butyl N-[[(3R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl) pyridazin-3 yl] morpholin-3-yl]methyl] carbamate



In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl) boronic acid (0.197 mmol, 32.8 mg) and tert-butyl N-[[(3R)-4-(6-chloropyridazin-3-yl) morpholin-3-yl]methyl] carbamate (0.152 mmol, 50 mg) in 0.94 ml of dioxane were added sodium carbonate (0.456 mmol, 37 mg) and 0.23 ml of water. The solution was purged with Ar, then Pd(PPh3)4 (7.6 µmol, 8.8 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. After cooling to rt, the reaction mixture was filtered. The filtrate was diluted with EtOAc and washed with water (3 times), and brine. The organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a white solid (59 mg, 93% yield).

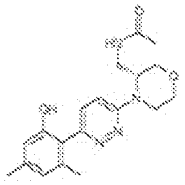
LCMS (**Method L**): Rt = 0,69 min; MS m/z [M+H]+ = 415

2-[6-[(3R)-3-(aminomethyl) morpholin-4-yl] pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid (Example 123)

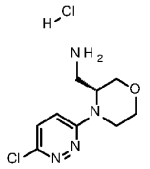
To a solution of tert-butyl N-[[(3R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl) pyridazin-3 yl] morpholin-3-yl]methyl] carbamate (0.14 mmol, 59 mg) in 1 ml of dichloromethane was added dropwise TFA (1.42 mmol, 0.111 mL). The resulting solution was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, diluted in methanol and concentrated under reduced pressure. The residue was suspended in diethyl ether and stirred for 10 min at room temperature. The suspension was filtered off and dried to give the title compound as a light-yellow solid (41.9 mg, 69% yield).

Compounds Example 124 was synthesized analogously to Example 123.

Example 129: N-[[(3R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-3-yl]methyl]acetamide



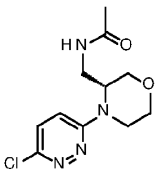
Int 129.2: [(3R)-4-(6-chloropyridazin-3-yl) morpholin-3-yl]methanamine; hydrochloride



To a solution of tert-butyl N-[[(3R)-4-(6-chloropyridazin-3-yl)morpholin-3-yl]methyl] carbamate (Int 123-1) (0.26 mmol, 88 mg) in 2 ml of DCM was added dropwise HCl 4M/dioxane (2.67 mmol, 0.67 ml). The resulting solution was stirred at room temperature 2 h. The mixture was concentrated under reduced pressure to give [(3R)-4-(6-chloropyridazin-3-yl) morpholin-3-yl]methanamine; hydrochloride as a light-yellow solid (80 mg, 100% yield).

LCMS (**Method L**): Rt = 0,19 min; MS m/z [M+H]+ = 228

Int 129.3: N-[[(3R)-4-(6-chloropyridazin-3-yl) morpholin-3-yl]methyl]acetamide



To a solution of [(3R)-4-(6-chloropyridazin-3-yl) morpholin-3-yl]methanamine;hydrochloride (0.301 mmol, 80 mg) in 2 ml of DCM was added dropwise triethylamine (0.745 mmol, 0.105 mL), then acetic anhydride (0.452 mmol, 42.5 µL) was added. The resulting solution was stirred at room temperature 2h 30. The mixture was diluted

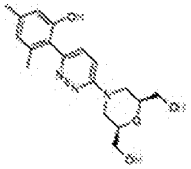
with DCM, washed with a with saturated aqueous solution of $NaHCO_3$ (3 times). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a white solid (52 mg, 63% yield).
LCMS (**Method L**): Rt = 0,47 min; MS m/z [M+H]+ = 271

N-[[(3R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-3-yl] methyl] acetamide (Example 129)

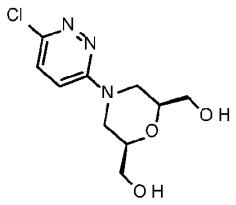
In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl) boronic acid (0.255 mmol, 42.3 mg) and N-[[(3R)-4-(6-chloropyridazin-3-yl)morpholin-3-yl]methyl]acetamide (0.196 mmol, 52 mg) in 1.2 ml of dioxane were added sodium carbonate (0.588 mmol, 48 mg) and 0.30 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (9.8 µmol, 11.4 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling to rt, the reaction mixture was filtered. The filtrate was diluted with EtOAc and washed with water (3 x), and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2), then suspended in pentane and stirred 10 min at room temperature. The suspension was filtered off and dried to give the title compound as a white solid (21 mg, 30% yield).

Compound Example 154 was synthesized analogously to Example 129.

Example 173: 2-[6-[(2R,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 173.1: [(2S,6R)-4-(6-chloropyridazin-3-yl)-6-(hydroxymethyl) morpholin-2-yl] methanol



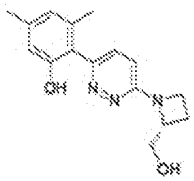
In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (1.30 mmol, 200 mg) in 3 ml of 1-butanol was added [(2S,6R)-6-(hydroxymethyl) morpholin-2-yl] methanol hydrochloride (1.30 mmol, 251 mg) and DIPEA (2.60 mmol, 0.458 mL). The vial was sealed, and the mixture was heated at 130°C under microwave irradiation for 1h. After cooling to rt, the mixture was concentrated under reduced pressure and DCM was added. The heterogenous mixture was stirred for 10 min, filtered off and dried under vacuum at 40°C to give the title compound as an orange-yellow solid (125 mg, 71% yield).
LCMS (**Method L**): Rt = 0,43 min; MS m/z [M+H]+ = 260

2-[6-[(2R,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 173)

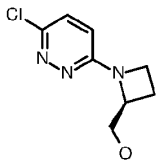
In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl) boronic acid (0.175 mmol, 29 mg) and [(2S,6R)-4-(6-chloropyridazin-3-yl)-6-(hydroxymethyl) morpholin-2-yl] methanol (0.134 mmol, 35 mg) in 0.84 ml of dioxane were added sodium carbonate (0.404 mmol, 33 mg) and 0.21 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (6.7 µmol, 7.8 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling to rt, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. MeOH was added, the mixture was filtered, and the filtrate was concentrated under reduced pressure and the residue was purified by reverse phase chromatography, Column Waters XSelect CSH, C18 5µ 50x250 mm, eluent: acetonitrile/water (+ 0,1% HCOOH) from 2/98 to 100/0, Flow rate 120 ml/min to give the titled compound as an orange solid (13 mg, 28% yield).

Compounds Examples 178, 198, 199, 200, 201, 258 and 259 were synthesized analogously to Example 173.

Example 118: 2-[6-[(2R)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 118.1: [(2R)-1-(6-chloropyridazin-3-yl)azetidin-2-yl]methanol



In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (1.68 mmol, 250 mg) and (R)-2-azetidinmethanol (1.8459 mmol, 166 mg) in 2 ml of n-butanol was added N,N-diisopropylamine (3.69 mmol, 477 mg). The vial was sealed, and the mixture was heated at 130°C under microwave irradiation for 2h. After cooling to rt, the solvent was concentrated under reduced pressure. DCM was added, the organic layer was washed with water and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using AcOEt /MeOH 9/1 to give the title compound as a colorless oil (200 mg, 60% yield).

LCMS (**Method U**): Rt = 0,66 min; MS m/z [M+H]+ = 200;

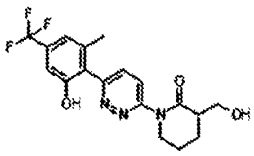
2-[6-[(2R)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 118)

In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethylphenyl)boronic acid (1.04 mmol, 174 mg) and [(2R)-1-(6-chloropyridazin-3-yl)azetidin-2-yl]methanol (0.95 mmol, 190 mg) in 6 ml of 1,4-dioxane were added sodium carbonate (2.85 mmol, 302 mg) and 1.5 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.06 mmol, 66 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 2h. After cooling to rt, the solvent was concentrated under reduced pressure. EtOAc was added and the organic layer was washed with water (3 times), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash

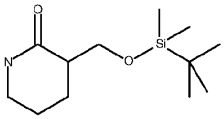
chromatography on silica gel using DCM/MeOH/ACN (97/1.5/1.5) to give the title compound as a white solid (85 mg, 31% yield).

Compound Example 134 was synthesized analogously to Example 118 using Int 8.1 ([(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol).

Example 273: 3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]piperidin-2-one



Int 273.1: 3-[[tert-butyl(dimethyl)silyl]oxymethyl]piperidin-2-one



Under Ar, to a solution of 3-(hydroxymethyl)piperidin-2-one (4.5 mmol, 600 mg) in 3.6 ml of DMF are added 4-dimethylaminopyridine (1.35 mmol, 165 mg) and triethylamine (5.4 mmol, 550 mg). tert-Butyldimethylchlorosilane (4.96mmol, 762 mg) was slowly added. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was diluted with AcOEt and poured into 5% aqueous $NaHCO_3$ solution. The organic layer was washed with 5% aqueous $NaHCO_3$ solution (twice) and with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using AcOEt/MeOH (100/0 to 90/10) to give the title compound as a colorless oil (840 mg, 77% yield).

LCMS (**Method L**): Rt = 1.09 min; MS m/z $[M+H]^+$ = 244.1;

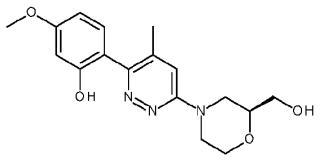
3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one (Example 273)

Under Ar, a solution of 3-[[tert-butyl(dimethyl)silyl]oxymethyl]-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one (obtained similarly to Example

130 from 3-[[tert-butyl(dimethyl)silyl]oxymethyl]piperidin-2-one, 1.39 mmol, 900 mg) in 3 ml of THF was cooled at +5°C, then a solution of 6 ml of acetic acid and 1 ml of water was added dropwise. The reaction mixture was stirred at room temperature overnight then heated at 50°C for 48h. After cooling to rt, the reaction mixture was poured into DCM and water. The organic layer was washed with $NaHCO_3$ saturated solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Heptane/(AcOEt 3/1 EtOH) 8/2 to give the title compound as a white solid (420 mg, 79% yield).

Compound Examples 286, 316 and 368 were synthesized analogously to Example 273. Compound Examples 419 and 420 were separated enantiomerically from Compound Example 368, analogously to Compound Examples 287 and 288, using a column ChiralPak® IC.

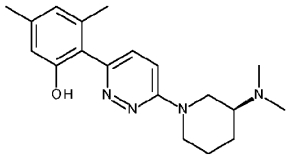
Example 116: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methoxy-phenol



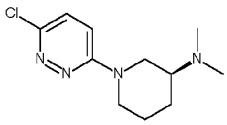
Under Ar, to a solution of 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.2 mmol, 300 mg) and [(2S)-4-(6-chloro-5-methyl-pyridazin-3-yl)morpholin-2-yl]methanol (**Int 85.1** - 0.8 mmol, 195 mg) in 5 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (2.16 mmol, 1.08 ml) then tetrakis(triphenylphosphine)palladium(0) (0.04 mmol, 46 mg). The mixture was stirred at 100°C for 3h. After cooling down, the resulting mixture was diluted with EtOAc and the aqueous layer extracted again with a 70/30 mixture of dichloromethane/isopropanol. The combined organic layers were washed successively with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in methanol, filtered off and the solid washed with diethylether to give the title compound (170 mg, 64% yield) as a yellow solid.

Compounds Examples 149 and 177 were synthesized analogously to Example 116.

Example 128: 2-[6-[(3S)-3-(dimethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 128.1: (3S)-1-(6-chloropyridazin-3-yl)-N,N-dimethyl-piperidin-3-amine



A solution of 3,6-dichloropyridazine (1.42 mmol, 211 mg), (3S)-N,N-dimethylpiperidin-3-amine dihydrochloride (1.7 mmol, 342 mg) and triethylamine (4.53 mmol, 632 µl) in 14 ml of n-butanol was stirred at 120 °C for 18 h. The mixture was cooled down, concentrated under reduced pressure and the residue was diluted with 50 ml of EtOAc then washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of methanol in dichloromethane to give the title compound (165 mg, 48% yield) as a beige solid.

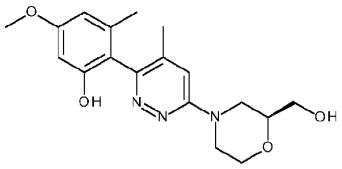
LCMS (**Method L**): Rt = 0.46 min; MS m/z $[M+H]^+$ 241;

2-[6-[(3S)-3-(dimethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 128)

Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.02 mmol, 169 mg) and (3S)-1-(6-chloropyridazin-3-yl)-N,N-dimethyl-piperidin-3-amine (0.68 mmol, 163 mg) in 4 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.83 mmol, 914 µl) then tetrakis(triphenylphosphine)palladium(0) (0.034 mmol, 39 mg). The mixture was stirred at 100°C for 3 h. After cooling down, the resulting mixture was diluted with 20 ml of EtOAc and the organic layer was washed successively with water and brine. The

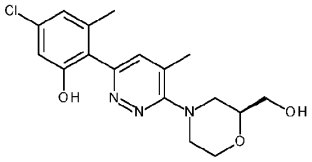
organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 15% of MeOH in DCM to give a yellow solid residue which was triturated in a mixture of dichloromethane and pentane to give the title compound (120 mg, 54% yield) as a as a beige solid.

Example 119: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methoxy-3-methyl-phenol

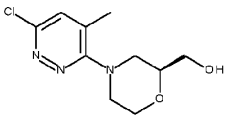


Following procedure of **Example 85**, [(2S)-4-(6-chloro-5-methyl-pyridazin-3-yl)morpholin-2-yl]methanol (**Int 85.1** - 1.026 mmol, 250 mg) and 5-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **(Int 96.2** - 1.54 mmol, 406 mg) give the title compound as an orange oil (30 mg, 8% yield)

Example 133: 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-3-methyl-phenol



Int 133.1: [(2S)-4-(6-chloro-4-methyl-pyridazin-3-yl)morpholin-2-yl]methanol



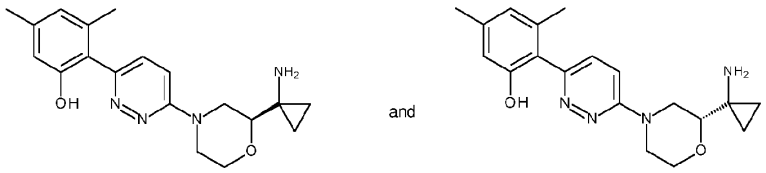
A solution of 3,6-dichloro-4-methyl-pyridazine (24.5 mmol, 4 g), [(2S)-morpholin-2-yl]methanol;hydrochloride (24.5 mmol, 3.77 g) and triethylamine (54 mmol, 7.52 ml) in 50 ml of n-butanol was stirred at 130°C for 11h. The mixture was cooled down, diluted with EtOAc and diethylether then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a gradient of

0 to 100% of a 99/1 mixture EtOAc/MeOH in cyclohexane to give the title compound (376 mg, 6% yield) as a white solid.
LCMS (**Method L**): Rt = 0.51min; MS m/z $[M+H]^+$ 244;

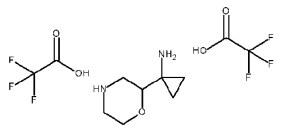
5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-3-methyl-phenol (Example 133)

Under Ar, to a solution of (4-chloro-2-hydroxy-6-methyl-phenyl)boronic acid (0.74 mmol, 138 mg) and [(2S)-4-(6-chloro-4-methyl-pyridazin-3-yl)morpholin-2-yl]methanol (**Int 133.1** - 0.49 mmol, 120 mg) in 4 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.33 mmol, 665 µl) then tetrakis(triphenylphosphine)palladium(0) (0.025 mmol, 28 mg). The mixture was stirred at 100°C for 3h. After cooling down, the resulting mixture was diluted with EtOAc and diethylether. The organic layer was washed successively with a saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 98/1/1 to 94/3/3) to give the title compound as a yellow solid (29 mg, 17% yield).

Examples 135 and 136: 2-[6-[(2S)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(2R)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



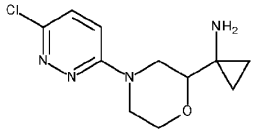
Int 135.1: 1-morpholin-2-ylcyclopropanamine;2,2,2-trifluoroacetic acid



To a solution of tert-butyl 2-(1-aminocyclopropyl)morpholine-4-carboxylate (2.48 mmol, 600 mg) in 9 ml of dichloromethane was added 1 ml of trifluoroacetic acid and the mixture was stirred for 5h at rt then concentrated under reduced pressure to give the title compound (300 mg, 85% yield) as a yellow oil.

LCMS **(Method H)** : Rt = 0.24 min; MS m/z $[M+H]^+$ 143.

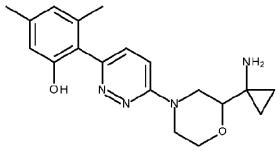
Int 135.2: 1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]cyclopropanamine



Following procedure of **Int 128.1,** 1-morpholin-2-ylcyclopropanamine;2,2,2-trifluoroacetic acid (3.69 mmol, 525 mg) and 3,6-dichloropyridazine (3.36 mmol, 500 mg) give the title compound as a yellow oil (850 mg, 99% yield).

LCMS **(Method H)** : Rt = 0.80 min; MS m/z $[M+H]^+$ 255

Int 135.3: 2-[6-[2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (racemate)



Following procedure of **Example 85**, 1-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]cyclopropanamine (1.77 mmol, 450 mg) give the title compound as an orange oil (70 mg, 11% yield).

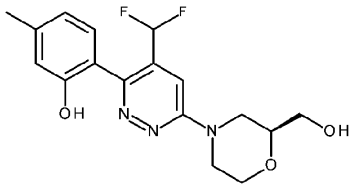
LCMS **(Method L):** Rt = 0.57 min; MS m/z $[M+H]^+$ 341

2-[6-[(2S)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(2R)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 135 : Enantiomer 1 and Example 136 : Enantiomer 2)

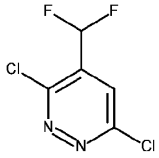
The 2 enantiomers of compound 2-[6-[2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol were separated by chiral normal phase chromatography (Column: Daicel Chiralpcel® OD, 350x30 mm I.D., 5 µm particle size; Mobile phase: Eluent B: EtOH (0.1% TEA), Isocratic elution: 80% Phase B; Flow rate: 45 ml/min) to give both enantiomers, first one eluting at Rt = 7.9 min (13.5 mg, **Example 135**, Enantiomer 1) as a

white solid, and second eluting at Rt = 15.3 min (14.2 mg, **Example 136**, Enantiomer 2) as a white solid. (The absolute configurations cannot be assigned).

Example 144: 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol



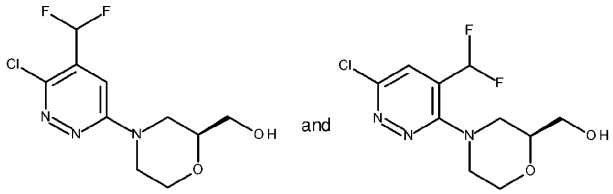
Int 144.1: 3,6-dichloro-4-(difluoromethyl)pyridazine



To a suspension of 3,6-dichloropyridazine (13.42 mmol, 2 g) in 20 ml of water was added 2,2-difluoroacetic acid (18.8 mmol, 1.18 ml) and the mixture was stirred at 55°C. Then was added silver nitrate (2.68 mmol, 456 mg) solubilized in 2 ml of water and trifluoroacetic acid (2.68 mmol, 200 µl). To the mixture stirred at 55°C was added dropwise a solution of ammonium persulfate (21.5 mmol, 4.9 g) in 9 ml of water and the mixture was stirred for 2h at 75°C then cooled to rt and quenched with 50 ml of a saturated aqueous sodium bicarbonate solution and 100 ml of dichloromethane under stirring. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of diisopropylether in petroleum ether to give the title compound (820 mg, 31% yield) as a colorless liquid.

LCMS **(Method L):** Rt = 0.96 min; MS m/z $[M+H]^+$ 199.

Int 144.2 and Int 170.1: [(2S)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol (Int 144.2) and [(2S)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol (Int 170.1)



Int 144.2 and Int 170.1

A solution of 3,6-dichloro-4-(difluoromethyl)pyridazine (7.94 mmol, 1.58 g), [(2S)-morpholin-2-yl]methanol;hydrochloride (7.94 mmol, 1.22 g) and triethylamine (17.5 mmol, 1.43 ml) in 20 ml of n-butanol was stirred at 130°C for 6h. The mixture was cooled down, concentrated under reduced pressure and the residue was taken with 50 ml of EtOAc and filtered off. The solid was rinsed with EtOAc and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of a 99/1 mixture EtOAc/MeOH in cyclohexane to give the title compounds **Int 144.2** (1.44 g, 65% yield) and **Int 170.1** (555 mg, 25% yield) as a yellow solid.

LCMS **(Method L):**

Int 144.2: Rt = 0.84 min; MS m/z $[M+H]^+$ 280

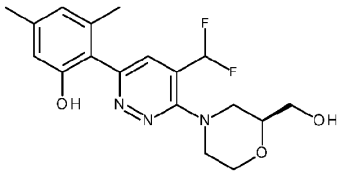
Int 170.1: Rt = 0.87 min; MS m/z $[M+H]^+$ 280

2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol (Example 144)

Following procedure of **Example 133**, [(2S)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol (**Int 144.2** – 0.715 mmol, 200 mg) gave the title compound as white solid (136 mg, 54% yield)

Compound Example 145 was synthesized analogously to Example 144.

Example 170: 2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

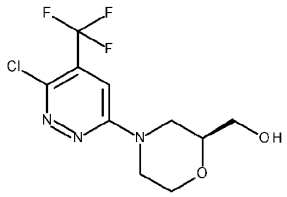


Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.43 mmol, 237 mg) and [(2S)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol (**Int 170.1** - 0.715 mmol, 200 mg) in 10 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.93 mmol, 0.965 ml) then Tetrakis(triphenylphosphine)palladium(0) (0.036 mmol, 41 mg). The mixture was stirred at 100°C for 3h. After cooling down, EtOAc and diethylether were added and the resulting mixture was washed successively with aqueous saturated $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH/ACN (from 98/1/1 to 94/3/3) to give a yellow solid residue which was again purified by prep-HPLC (column: Sunfire prep C18 OBD ; 250 * 50 mm * 10 µm; mobile phase: [water (TFA 10^{-2} N)-ACN]; B%: 10%-100% in 35 min. at 50 ml/min) to give the title compound as a white solid (111 mg, 42% yield).

Compounds Examples 171, 172, 194, 247, 248 and 249 were synthesized analogously to Example 170.

Example 155: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-(trifluoromethyl)pyridazin-3-yl]-5-methyl-phenol

Int 155.1: [(2S)-4-[6-chloro-5-(trifluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol



A solution of 3,6-dichloro-4-(trifluoromethyl)pyridazinel (4.61 mmol, 1 g), [(2S)-morpholin-2-yl]methanol;hydrochloride (5.07 mmol, 778 mg) and triethylamine (10.14

mmol, 1.41 ml) in 10 ml of n-butanol was stirred at 120°C for 4h. The mixture was cooled down, concentrated under reduced pressure and the residue was diluted with 250 ml of EtOAc then washed with 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH/ACN (from 98/1/1 to 94/3/3) to give the title compound (772 mg, 56% yield) as a yellow oil.

LCMS **(Method X):** Rt = 0.68 min; MS m/z $[M+H]^+$ = 298.

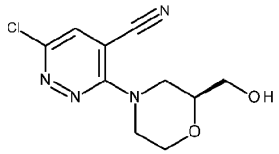
2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-(trifluoromethyl)pyridazin-3-yl]-5-methyl-phenol (Example 155)

Following procedure of **Example 133** [(2S)-4-[6-chloro-5-(trifluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol (**Int 155.1** – 0.67 mmol, 200 mg) gave the title compound as white solid (186 mg, 74% yield).

Compound Example 160 was synthesized analogously to Example 155.

Example 158: 6-(2-hydroxy-4,6-dimethyl-phenyl)-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile

Int 158.1: 6-chloro-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile



Following procedure of **Int 155.1,** 3,6-dichloropyridazine-4-carbonitrile (4.02 mmol, 700 mg) give the title compound as yellow oil (779 mg, 76% yield).

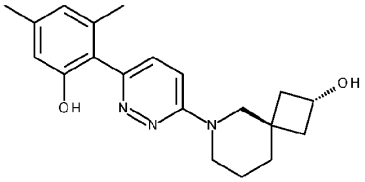
LCMS **(Method X):** Rt = 0.92 min; MS m/z $[M+H]^+$ 255.

6-(2-hydroxy-4,6-dimethyl-phenyl)-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile (Example 158)

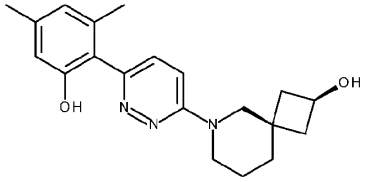
Following procedure of **Example 133,** 6-chloro-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile (**Int 158.1** – 0.785 mmol, 200 mg) gave the title compound as white solid (154 mg, 58% yield).

Compounds Examples 159 and 163 was synthesized analogously to Example 158.

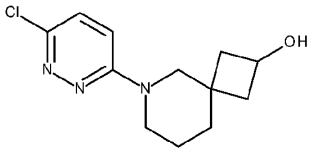
Examples 175 and 176: 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 1 and 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 2



and



Int 175.1: 6-(6-chloropyridazin-3-yl)-6-azaspiro[3.5]nonan-2-ol



A solution of 3,6-dichloropyridazine (3.02 mmol, 450 mg), 6-azaspiro[3.5]nonan-2-ol;hydrochloride (3.32 mmol, 590 mg) and triethylamine (6.64 mmol, 0.93 ml) in 5 ml of n-butanol was stirred at 130°C for 3h. The mixture was cooled down, concentrated under reduced pressure and the residue was diluted with 150 ml of EtOAc then washed with 150 ml of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give the title compound (452 mg, 59% yield) as a beige solid.

LCMS (**Method L**): Rt = 1.23 min; MS m/z $[M+H]^+$ 254.

6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 1 and 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-

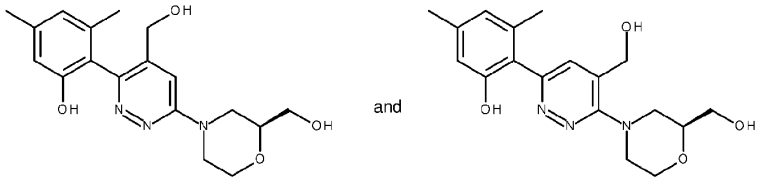
azaspiro[3.5]nonan-2-ol Isomer 2 (Example 175 : isomer 1 and Example 176 : isomer 2)

Under Ar, to a solution of 6-(6-chloropyridazin-3-yl)-6-azaspiro[3.5]nonan-2-ol (1.78 mmol, 452 mg) and (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (2.67 mmol, 444 mg) in 8 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (4.81 mmol, 2.4 ml) then tetrakis(triphenylphosphine)palladium(0) (0.09 mmol, 103 mg). The mixture was stirred at 100°C for 3h. After cooling down, EtOAc and diethylether were added and the resulting mixture was washed successively with aqueous saturated $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give a mixture of 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give a mixture of 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol 2 and 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 1. Isomer 2 and 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 1.

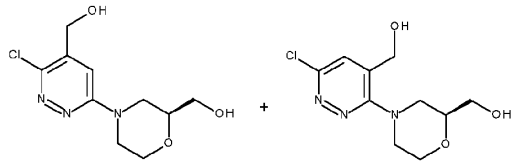
LCMS **(Method L):** Rt = 0.70 min and 0.74 min; MS m/z $[M+H]^+$ = 340.

The isomeric mixture Isomer 1 / Isomer 2 was separated by semi-preparative chiral normal phase chromatography (Column: Daicel Chiralpak® IC, 350 x76,5 mm, 20 um particle size; Mobile phase: Eluent B: EtOH (0.1% TEA), Isocratic elution: 80% Phase B; Flow rate: 400 ml/min) to provide the 2 stereoisomers, first one eluting at Rt = 16.6 min (175 mg, Example 175, isomer 1) as a white solid, and second one eluting at Rt = 17.8 min (219 mg, Example 176, isomer 2) as a white solid.

Examples 186 and 187: 2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol.



Int 186.1 and Int 187.1: [3-chloro-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-4-yl]methanol (Int 186.1) and [6-chloro-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-4-yl]methanol (Int 187.1)



Int 186.1 Int 187.1

A solution of (3,6-dichloropyridazin-4-yl)methanol (13 mmol, 2.3 g), (3S)-N,N-dimethylpiperidin-3-amine dihydrochloride (14 mmol, 2.2 g) and triethylamine (28 mmol, 3.9 ml) in 40 ml of n-butanol was stirred at 130°C for 3h. The mixture was cooled down, concentrated under reduced pressure and the residue was diluted with 200 ml of EtOAc then washed with 150 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of methanol in dichloromethane to give the title compounds as a mixture (165 mg, 36% yield) and as yellow oil.

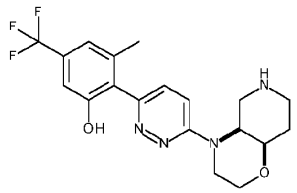
LCMS **(Method L):** Int 186.1 and Int 187.1: Rt = 0.83 min; MS m/z $[M+H]^+$ 260.

2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 186 and Example 187)

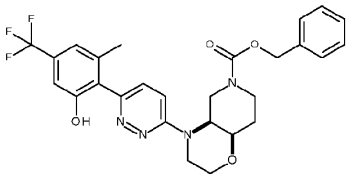
Following procedure of **Example 133,** a mixture of [3-chloro-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-4-yl]methanol **(Int 186.1)** and [6-chloro-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-4-yl]methanol **(Int 187.1)** (2.5 mmol, 1.3 g) gives 2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (**Example 186** – 385 mg, 45% yield) and 2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (**Example 187** – 96 mg, 11% yield) as white solids.

Compounds examples 188 and 189 were synthesized analogously to Example 186 and 187.

Examples 197: 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



Int 197.1: benzyl rac-(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate



Following procedure of **Example 133**, benzyl rac-(4aR,8aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 10.8** – 2.57 mmol, 1 g) give the title compound (1.38 g, 82% yield) as a yellow oil.

LCMS **(Method V):** Rt = 1.14 min; MS m/z $[M+H]^+$ 529.

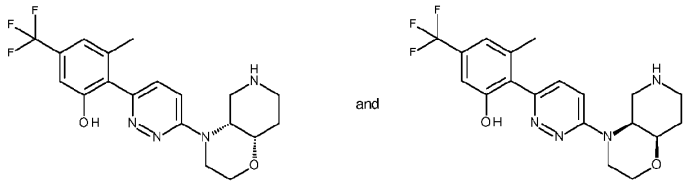
3-methyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (Example 197)

To a suspension of benzyl rac-(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazine-6-carboxylate (2.61 mmol, 1.38 g) in 40 ml of EtOH was added ammonium formate (7.83 mmol, 494 mg) and 10% Pd/C (494 mg) and the resulting mixture was stirred at 80 °C under microwave irradiation for 1 h. After cooling down to RT, the mixture was filtered off over a pad of Decalite® and the cake rinsed with 50 ml of EtOH. The organic layer was concentrated under reduced pressure and the residue was diluted with 200 ml of dichloromethane and washed twice with 200 ml of an aqueous saturated sodium bicarbonate

solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a white solid (660 mg, 64% yield).

Compounds Examples 195 and 221 were synthesized analogously to Examples 197.

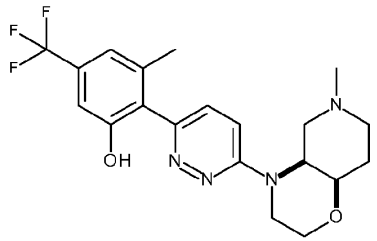
Example 251 and 252: 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol.



3-methyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (**Example 197** - 174 mg) was separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD-H, 250×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 40%; flow rate: 200 mL/min; outlet pressure: 100 bar; 8 injections; UV detection : 265 nm) to provide 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol, first eluting enantiomer at Rt = 5.9 min (62 mg, **Example 251**, Enantiomer 1), as a white solid, and 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl) phenol, second eluting enantiomer at Rt = 13.2 min (70 mg, **Example 252**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Compounds Examples 314, 315 and 308, 309 were obtained by preparative chiral SFC separation analogously to Example 251 and 252.

Examples 226: 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

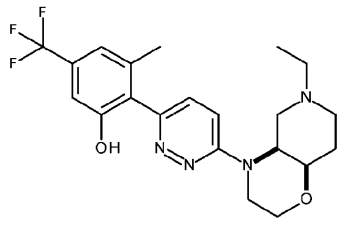


To a solution of 3-methyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (**Examples 197** - 0.62 mmol, 246 mg) in 20 ml of dichloromethane under argon, was added acetic acid (9.36 mmol, 535 µl) and a 37% weight aqueous solution of formaldehyde (3.12 mmol, 253 mg) and the resulting mixture was stirred at rt for 5 min. Then was added portionwise sodium triacetoxyborohydride (1.12 mmol, 238 mg) and the mixture was stirred at rt for 3h then diluted with 100 ml of dichloromethane. The organic layer was washed with 100 ml of an aqueous saturated sodium bicarbonate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a white solid (111 mg, 44% yield).

Compounds Examples 224 and 225 were synthesized analogously to Example 226 starting from Examples 221 and 195 respectively.

Compound Example 299 were synthesized analogously to Example 226 starting from Intermediate 354.1.

Example 210: 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

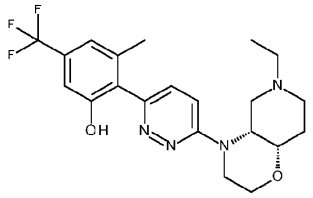


To a solution of 3-methyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (**Examples 197** - 0.51 mmol,

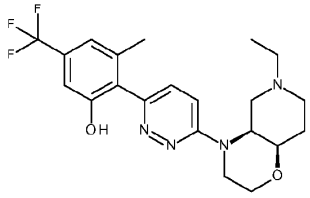
200 mg) in 10 ml of dichloromethane under argon, was added acetic acid (7.6 mmol, 435 µl) and acetaldehyde (2.54 mmol, 142 µl) and the resulting mixture was stirred at rt for 5 min. Then was added portion wise sodium triacetoxyborohydride (0.91 mmol, 193 mg) and the mixture was stirred at rt for 3h then diluted with 100 ml of dichloromethane. The organic layer was washed with 100 ml of an aqueous saturated sodium bicarbonate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a white solid (155 mg, 72% yield).

Compounds Examples 209 and 223 were synthesized analogously to Examples 210 starting from Examples 195 and 221 respectively.

Examples 255 and 256: 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

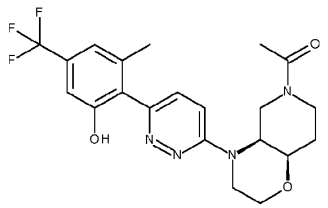


and

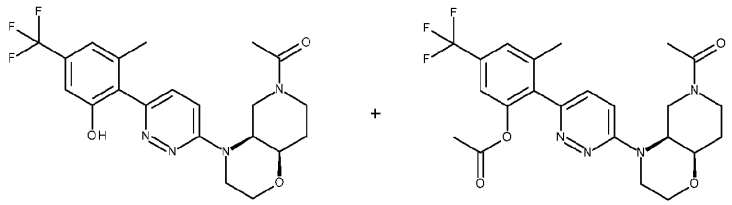


2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (**Example 210** - 147 mg) was separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD-H, 250×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 20%; flow rate: 200 mL/min; outlet pressure: 100 bar; 6 injections; UV detection : 265 nm) to provide 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol, first eluting enantiomer at Rt = 6.8 min (58 mg, Example 255, Enantiomer 1) as a white solid, and 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol, second eluting enantiomer at Rt = 9.3 min (57 mg, Example 256, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 214: 1-[rac-(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl] ethenone.



Int 214.1: 1-[rac-(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl] ethanone and 3-methyl-2-[6-[rac-(4aS,8aR)-6-acetyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl) phenyl] acetate



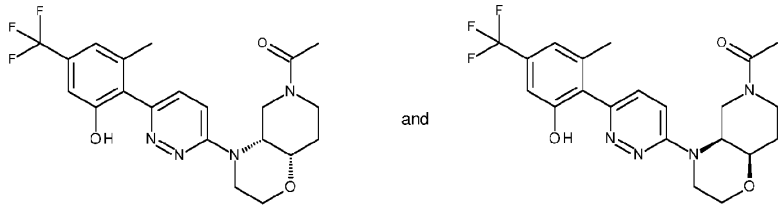
To a solution of 3-methyl-2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (**Examples 197** - 0.49 mmol, 194 mg) in 8 ml of dichloromethane, was added acetic anhydride (0.74 mmol, 69 µl), N,N-diethylethanamine (0.49 mmol, 67 µl) and N,N-dimethylpyridin-4-amine (0.025 mmol, 3 mg) and the resulting mixture was stirred at rt for 30 min. then diluted with 100 ml of dichloromethane. The organic layer was washed with 100 ml of an aqueous saturated sodium bicarbonate solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a mixture of title compounds as a yellow oil, which was used without further purification in the next step.

1-[rac-(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (Example 214)

The residue Int214.1 was taken in a solution of 10 ml of methanol and 1 ml of a 1N aqueous sodium hydroxide solution and the mixture was stirred at rt for 30 min then neutralized with a 1N aqueous HCl solution until pH = 7. The mixture was diluted with 50 ml of dichloromethane and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of 0 to 10% of methanol in dichloromethane to give the title compound as a white foam (133 mg, 62% yield).

Compounds Examples 213 and 222 were synthesized analogously to Examples 214 starting from Examples 195 and 221 respectively.

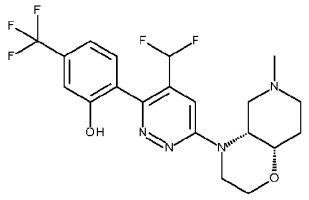
Examples 262 and 263: 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone and 1-[(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone.



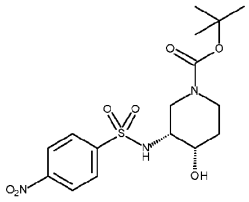
1-[rac-(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (**Example 214** - 125 mg) was separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD-H, 250×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 20%; flow rate: 200 mL/min; outlet pressure: 100 bar; 2 injections; UV detection: 265 nm) to provide 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone, first eluting enantiomer at Rt = 7.5 min (47 mg, Example 262, Enantiomer 1) as a white solid, and 1-[(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-

b][1,4]oxazin-6-yl]ethanone, second eluting enantiomer at Rt = 13.2 min (48 mg, Example 261, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 268: 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol

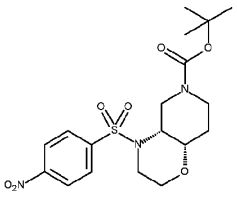


Int 268.1: tert-butyl (3R,4S)-4-hydroxy-3-[(4-nitrophenyl)sulfonylamino]piperidine-1-carboxylate.



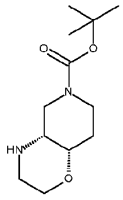
To a cooled (0-5°C) solution of tert-butyl (3R,4S)-3-amino-4-hydroxy-piperidine-1-carboxylate (4.62 mmol, 1 g) in 20 ml of dichloromethane was added triethylamine (12.5 mmol, 1.74 ml) and 4-nitrobenzenesulfonyl chloride (5.09 mmol, 1.13 g) and the mixture was stirred for 30min at rt then diluted with 100 ml of dichloromethane and 100 ml of water. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.5 g, 81% yield) as a yellow solid.
LCMS **(Method L):** Rt = 0.85 min; MS m/z $[M+H]^+$ 402.

Int 268.2: tert-butyl (4aR,8aS)-4-(4-nitrophenyl)sulfonyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate.



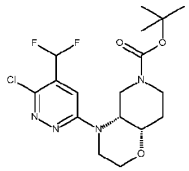
To a cooled (0-5°C) solution of tert-butyl (3R,4S)-4-hydroxy-3-[(4-nitrophenyl)sulfonylamino]piperidine-1-carboxylate (3.7 mmol, 1.5 g) in 160 ml of anhydrous dichloromethane under argon was added sodium hydride 60% dispersion in oil (20 mmol, 810 mg) by portions and the mixture was stirred at 0-5°C for 5 min. Then was added (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (10 mmol, 4.4 g) and the mixture was allowed to stir 18h at RT. Then, triethylamine (9.7 mmol, 1.4 ml) was added and the mixture was stirred at rt for another 2h then diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane and the pooled organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 40% of EtOAc in cyclohexane to give the title compound (668 mg, 42% yield) as a white foam.
LCMS **(Method L):** Rt = 1.01 min; MS m/z $[M+H]^+$ 428.

Int 268.3: **tert-butyl (4aR,8aS)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate.**



To a solution of tert-butyl (4aR,8aS)-4-(4-nitrophenyl)sulfonyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (1.56 mmol, 668 mg) in 10 ml of N,N-dimethylformamide was added 2-sulfanylacetic acid (3.75 mmol, 345 mg) and lithium hydroxide;hydrate (8.72 mmol, 366 mg) and the mixture was stirred 18h at rt then diluted with EtOAc and washed with water (4 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in dichloromethane to give the title compound (346 mg, 91% yield) as a colourless oil.
LCMS **(Method V)**: Rt = 0.35 min; MS m/z $[M+H]^+$ 243

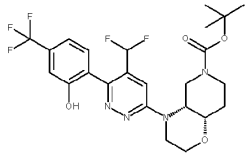
Int 268.4: tert-butyl (4aR,8aS)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate.



A solution of 3,6-dichloro-4-(difluoromethyl)pyridazine (**Int 144.1** - 1.43 mmol, 284 mg), tert-butyl (4aR,8aS)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (1.43 mmol, 346 mg) and triethylamine (3.14 mmol, 438 µl) in 5 ml of n-butanol was stirred at 130°C for 30h. The mixture was cooled down, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 20% of EtOAc in cyclohexane to give the title compound (122 mg, 21% yield) as a yellow oil.

LCMS (**Method L):** Rt = 1.03 min; MS m/z $[M+H]^+$ 405

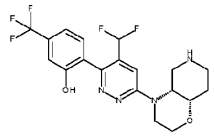
Int 268.5: **tert-butyl (4aR,8aS)-4-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate.**



Following procedure of **Example 133,** tert-butyl (4aR,8aS)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (0.3 mmol, 122 mg) gave the title compound (101 mg, 51% yield) as a white solid.

LCMS (**Method L):** Rt = 1.23 min; MS m/z $[M+H]^+$ 531

Int 268.6: **2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol.**



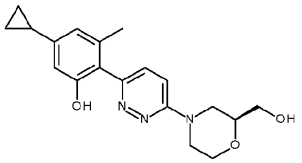
To a solution of tert-butyl (4aR,8aS)-4-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazine-6-carboxylate (0.19 mmol, 101 mg) in 9 ml of dichloromethane was added 1 ml of trifluoroacetic acid and the mixture was stirred for 2h at rt then concentrated under reduced pressure. The residue was diluted with 50 ml of dichloromethane and washed with 50 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of water then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (79 mg, 96% yield) as a yellow solid.

LCMS **(Method L):** Rt = 0.97 min; MS m/z $[M+H]^+$ 431

2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol (Example 268).

Following procedure of **Example 226,** 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol (0.18 mmol, 79 mg) gave the title compound (29 mg, 36% yield) as a white solid.

Example 204: 5-cyclopropyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol



Under Ar, to a solution of 5-cyclopropyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.37 mmol, 376 mg) and [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (**Int 8.1** - 0.65 mmol, 150 mg) in 8 ml of 1,4-dioxane and 2 ml of water was added a 2N sodium carbonate aqueous solution (1.96 mmol, 980 µl) then TETRAKIS(triphenylphosphine)palladium(0) (0.065 mmol, 75 mg). The mixture was stirred at 90°C for 1h. After cooling down, the resulting mixture was diluted with dichloromethane and the organic layer was washed successively with a saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over Na_2SO_4, filtered

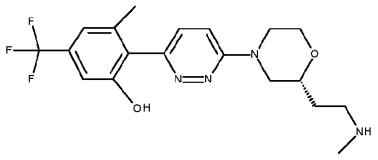
and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give a yellow solid residue which was again purified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [water (TFA 10^{-2} N)-ACN]; B%: 10%-100% in 35 min. at 50 ml/min). The pure fractions were diluted with 10 ml of dichloromethane and washed with 2 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in 4 ml of diethylether/pentane: 50 / 50 to give after filtration the title compound as a white solid (20 mg, 9% yield).

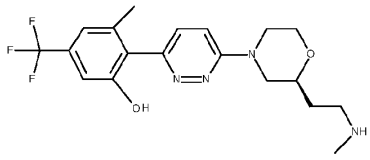
Compound Example 274 was synthesized analogously to Example 204.

Examples 287 and 288: (3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one and (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one.
The 2 enantiomers of compound 3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one (**Example 273**, 420 mg) were separated by semi-preparative chiral normal phase chromatography (Column: Chiralpak® AD, 350x76,5 mm, 20 µm particle size; Mobile phase: Heptane 50/EtOH 50) +0.1% TEA ; Flow rate: 400 ml/min) to provide the 2 enantiomers, first one eluting at Rt = 5.5 min (180 mg, **Example 287**) as a white solid, and second one eluting at Rt = 8.5 min (181 mg, **Example 288**) as a white solid. The absolute configurations cannot be assigned at this stage.

Compounds Examples 292 and 293 were synthesized and separated enantiomerically analogously to Examples 287 and 288.

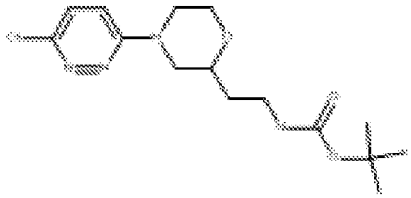
Examples 331 and 332: 3-methyl-2-[6-[(2R)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol and 3-methyl-2-[6-[(2S)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol





and

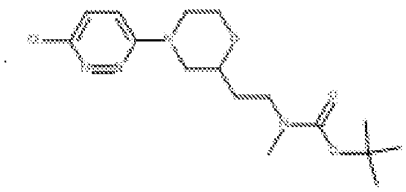
Int 331.1: tert-butyl N-[2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethyl]carbamate



To a solution of 3,6-dichloropyridazine (150 mg, 1.0069 mmol) and tert-butyl N-(2-morpholin-2-ylethyl)carbamate in 3 ml of 1-Butanol was added Triethylamine (0.309 ml, 2.2151 mmol). The mixture was heated at 130°C for 2h30. After cooling down to rt, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Hept/AcOEt (from 100/0 to 50/50) to give the title compound as a white solid (253 mg, 73% yield).

LCMS **(Method L)**: Rt = 0.84; MS m/z $[M+H]^+$ = 343

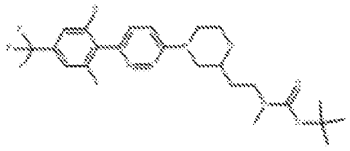
Int 331.2: tert-butyl N-[2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethyl]-N-methyl-carbamate



Solution of tert-butyl N-[2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethyl]carbamate (253 mg, 0.738 mmol) in 3 ml of THF was cooled with an ice bath. Sodium hydride (33 mg, 0.8118 mmol, 60 mass%) was added and the resulting mixture was stirred for 20 min. Then Iodomethane (0.100 ml, 1.4718 mmol) was added. After 2h, additional Sodium hydride (10 mg, 0.2500 mmol, 60 mass%) was added, and 10 min after 2 drops of Iodomethane. The mixture was stirred for 30 min. The reaction mixture was diluted with AcOEt, washed with

water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a yellow oil (258 mg, 97% yield).
LCMS (**Method L**): Rt = 0.94; MS m/z [M+H]+ = 357

Int 331.3: tert-butyl N-[2-[4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]-N-methyl-carbamate



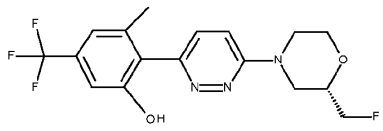
The reaction was carried out in two vials in parallel.
In a microwave vial, under Ar, to a solution of tert-butyl N-[2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]ethyl]-N-methyl-carbamate (258 mg, 0.723 mmol), 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (262 mg, 0.8676 mmol), carbonate sodium (192 mg, 1.8075 mmol) in 8 ml of 1,2-Dimethoxyethane and 2 ml of water was added tetrakis(triphenylphosphine)palladium(0) (42 mg; 0.0361 mmol). This procedure was repeated in a second vial. The mixture was heated at 100°C under microwave irradiation for 1h30. After cooling down to rt, the mixture of the two vials were joined together, diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (from 100/0 to 97/2) to give the title compound as an oil (140 mg, 39% yield).
LCMS (**Method L**): Rt = 1.03; MS m/z $[M+H]^+$ = 497

3-methyl-2-[6-[(2R)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol and 3-methyl-2-[6-[(2S)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (Examples 331 and 332)

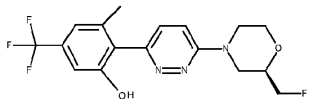
At 5°C, to a solution of tert-butyl N-[2-[4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]-N-methyl-carbamate (140 mg, 0.282 mmol) in 6 ml of DCM was add 0.7 ml of a solution of HCl 4N in dioxane. After stirring 2 h at rt, the reaction was concentrated under reduce pressure. The residue was precipitated in Et_2O, filtered and washed with acetone to give 3-methyl-2-[6-[2-[2-(methylamino) ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol as a white

solid (60 mg, 54% yield). The 2 enantiomers of compound were separated by chiral phase LC (Column Amylose1 5µm, 250x30 mm, Flow rate 40ml/min, eluent n-heptane/ethanol (85/15) + 0,1% TEA, detection 265nm) to give both enantiomers, first eluting Rt = 28 mn, **Example 331** (11.3 mg, 10% yield) and second eluting Rt = 41 mn, **Example 332** (16.8 mg, 15% yield). The absolute configurations cannot be assigned at this stage.

Examples 283 and 284: 2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



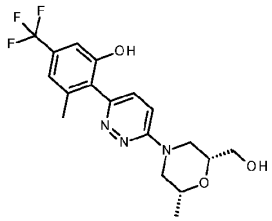
and



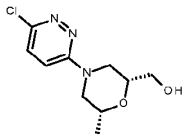
2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (22 mg), obtained similarly to Example 114 was purified by preparative chiral SFC similarly to Examples 237 and 238 using a chiralcel OJ-H column, to give (7 mg, 22%) of a first enantiomer and (6 mg, 19%) of the second one. The absolute configurations cannot be assigned at this stage.

Compounds examples 338 and 339 were enantiomerically separated, analogously to examples 283 and 284 using a Chiralpak® IG column, from a racemic mixture which one was synthesized similarly to Example 114.

Example 302: 2-[6-[(2R,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



Int 302.1: [(2R,6R)-4-(6-chloropyridazin-3-yl)-6-methyl-morpholin-2-yl]methanol



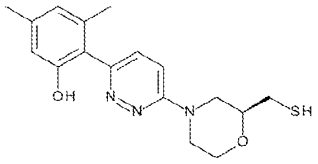
In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (0,651 mmol, 100 mg) in 5 ml of 1-butanol was added [(2R,6R)-6-methylmorpholin-2-yl]methanol hydrochloride (0.651 mmol, 114 mg) and DIPEA (1.30 mmol, 0.229 mL). The vial was sealed, and the mixture was heated at 130°C under microwave irradiation for 1h. After cooling down to rt, the mixture was concentrated under reduced pressure to give the title compound, as an oil (312 mg, 100% yield), which was used in the next step without further purification.
LCMS (**Method H**): Rt = 0.94 min; MS m/z $[M+H]^+$ = 244

2-[6-[(2R,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 302)

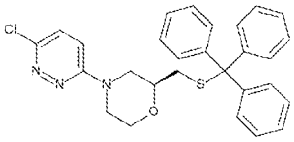
In a microwave vial, under Ar, to a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.846 mmol, 256 mg) and [(2R,6R)-4-(6-chloropyridazin-3-yl)-6-methyl-morpholin-2-yl]methanol (0.651 mmol, 159 mg) in 4,1 ml of dioxane were added sodium carbonate (1.950 mmol, 162 mg) and 1,02 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (32.6 µmol, 38 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling down to rt, the reaction mixture was filtered. DCM was added the resulting solution was washed with water (3 times), and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 94/3/3). The solid obtained was triturated in pentane then filtered off and dried to give the title compound as a white solid (80.4 mg, 32% yield).

Compound Examples 296, 297, 359, 365 and 390 were synthesized analogously to Example 302.

Example 303: 3,5-dimethyl-2-[6-[(2S)-2-(sulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol



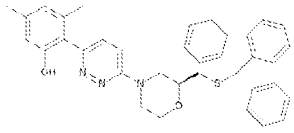
Int 303.1: (2S)-4-(6-chloropyridazin-3-yl)-2-(tritylsulfanylmethyl)morpholine



Under Ar, to a solution of [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (**Int 8.1** - 0.94 mmol, 217 mg) and triphenylmethanethiol (2.46 mmol, 679 mg) in 10 ml of THF was added dropwise tributylphosphane (1.98 mmol, 0.51 ml). The mixture was stirred at rt for 10 min. and then was added 1,1'-(azodicarbonyl)dipiperidine (ADDP – 1.98 mmol, 501 mg) in one portion. The mixture was stirred for another 5 min then diluted with 5 ml of pentane and filtered off. The white precipitate was washed with 3 ml of pentane and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of EtOAc in dichloromethane to give the title compound (628 mg, 136% yield) as a yellow oil containing by-products and used as it for the next step.

LCMS (**Method L**): Rt = 1.21; MS m/z $[M+H]^+$ = 488

Int 303.2: 3,5-dimethyl-2-[6-[(2S)-2-(tritylsulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol



Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.57 mmol, 95 mg) and (2S)-4-(6-chloropyridazin-3-yl)-2-(tritylsulfanylmethyl)morpholine (**Int 303.1** - 0.38 mmol, 186 mg) in 5 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.03 mmol, 514 µl) then Tetrakis(triphenylphosphine)palladium(0) (0.019 mmol, 22 mg). The mixture was stirred at 100°C for 2h. After cooling down, the mixture was diluted with 20 ml of EtOAc and the organic layer was washed successively with water and brine then

dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of EtOAc in DCM to give the title compound (113 mg, 52% yield – 70% for the 2 steps) as a yellow oil.

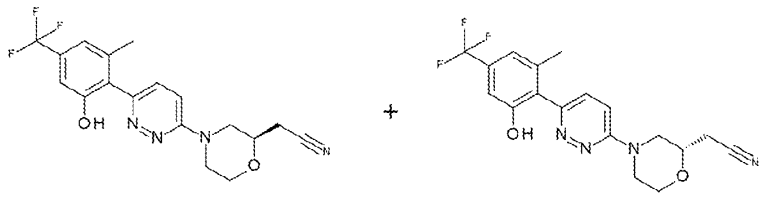
LCMS (**Method L**) Rt = 1.07; MS m/z $[M+H]^+$ = 574

3,5-dimethyl-2-[6-[(2S)-2-(sulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol (Example 303)

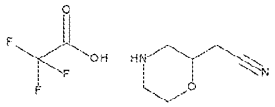
To a cooled (0°C) solution of 3,5-dimethyl-2-[6-[(2S)-2-(tritylsulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol (**Int 303.2** - 0.19 mmol, 111 mg) in 2 ml of DCM were added triisopropylsilane (0.93 mmol, 190 µl) and trifluoroacetic acid (7.74 mmol, 575 µl) and the mixture was stirred at rt for 10 min then concentrated under reduced pressure. The residue was co-evaporated twice with 5 ml of toluene then purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound (60 mg, 94% yield) as a yellow gum.

Compound Example 305 was synthesized analogously to Example 303.

Examples 327 and 328: 2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile and 2-[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile



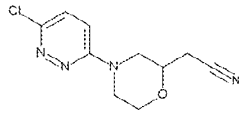
Int 327.1: (rac)- 2-morpholin-2-ylacetonitrile;2,2,2-trifluoroacetic acid



At 0°C, to a solution of (rac)-tert-butyl 2-(cyanomethyl)morpholine-4-carboxylate (4.42 mmol, 1 g) in 40 ml of DCM was added trifluoroacetic acid (44.2 mmol, 3.28 ml) and the mixture was stirred at rt for 1h, then concentrated under reduced pressure. The residue was

co-evaporated with 3x50 ml of toluene, then triturated in diethylether to give the title compound (1.12g, 106% yield) as a white solid used without further purification in the next step.

Int 327.2: (rac)- 2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]acetonitrile



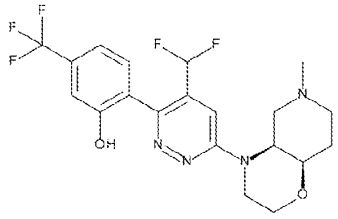
A solution of 3,6-dichloropyridazine (3.89 mmol, 580 mg), (rac)- 2-morpholin-2-ylacetonitrile; 2,2,2-trifluoroacetic acid (4.67 mmol, 1.12 g) and triethylamine (8.56 mmol, 1.19 ml) in 35 ml of 1-butanol was stirred at 120°C for 45h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was diluted with 50 ml of DCM then washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a light brown solid (198 mg, 21% yield).
LCMS (**Method Q**): Rt = 0.51; MS m/z $[M+H]^+$ = 239

2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile and 2-[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]morpholin-2-yl]acetonitrile (Example 327 and Example 328)

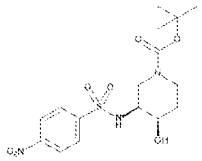
Under Ar, to a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (1.24 mmol, 376 mg) and (rac)-2-[4-(6-chloropyridazin-3-yl)morpholin-2-yl]acetonitrile (**Int 327.2** - 0.83 mmol, 198 mg) in 5 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (2.24 mmol, 1.12 ml) then tetrakis(triphenylphosphine)palladium(0) (0.042 mmol, 48 mg). The mixture was stirred at 100°C for 1h. After cooling down, the mixture was diluted with 40 ml of EtOAc and the organic layer was washed successively with water and brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50% of EtOAc in cyclohexane to give (rac)-2-[4-

[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile (218 mg, 69% yield) as a white solid. This racemate was separated by SFC (Column: Daicel Chiralpak® IG, 250×30 mm I.D., 5 µm particle size; Mobile phase: Eluent B: MeOH (0.1% TEA), Isocratic elution: 18% Phase B in Supercritical CO_2; Flow rate: 120 ml/min; (UV detection: 265 nm; 30 injections) to provide the 2 enantiomers, first one eluting at Rt = 8.06 min (21 mg, **Example 327**, Enantiomer 1) as a white solid, and second one eluting at Rt = 9.43 min (15 mg, **Example 328**, Enantiomer 2) as a white solid. The absolute configurations cannot be assigned.

Example 298: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol



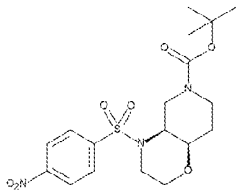
Int 298.1: tert-butyl (3S,4R)-4-hydroxy-3-[(4-nitrophenyl)sulfonylamino]piperidine-1-carboxylate.



To a cooled solution (0-5°C) of tert-butyl (3S,4R)-3-amino-4-hydroxy-piperidine-1-carboxylate (46.2 mmol, 10 g) in 300 ml of dichloromethane was added triethylamine (125 mmol, 17.4 ml) and 4-nitrobenzenesulfonyl chloride (50.9 mmol, 11.3 g) and the mixture was stirred for 30 min at rt. The mixture was then diluted with 600 ml of diethylether and 500 ml of water. The organic layer was washed with 250 ml of water, 250 ml of a 5% aqueous citric acid solution and 100 ml of brine (twice), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (19.6 g, 100% yield) as a pale yellow solid.

LCMS (**Method V**): Rt = 0.96; MS m/z$[M+H]^+$ = 400

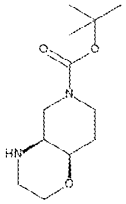
Int 298.2: tert-butyl (4aS,8aR)-4-(4-nitrophenyl)sulfonyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate.



Under Ar, a suspension of tert-butyl (3S,4R)-4-hydroxy-3-[(4-nitrophenyl)sulfonylamino]piperidine-1-carboxylate (24.9 mmol, 10 g), potassium carbonate (100 mmol, 13.8 g) and 1,2-dibromoethane (249 mmol, 21.8 ml) in 500 ml of acetonitrile was stirred at reflux for 30h. After cooling down to rt, the mixture was filtered, the cake rinsed with 50 ml of acetonitrile and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give the title compound (7.35 g, 73% yield on the 2 steps) as a yellow foam.

LCMS (**Method V**): Rt = 1.18; MS m/z $[M+H]^+$ = 428

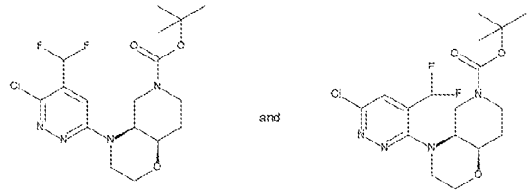
Int 298.3: tert-butyl (4aS,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate.



To a solution of tert-butyl (4aS,8aR)-4-(4-nitrophenyl)sulfonyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (34.4 mmol, 14.7 g) and 2-sulfanylacetic acid (82.5 mmol, 5.76 ml) in 200 ml of N,N-dimethylformamide were added lithium hydroxide hydrate (193 mmol, 8.08 g) and the mixture was stirred at rt for 18h. The mixture was then diluted with 1 L of EtOAc and washed successively with 500 ml of water, 500 ml then 250 ml of a 0.1 N sodium hydroxide aqueous solution. The aqueous layers were pooled and successively extracted with 2x500 ml of EtOAc and 2x250 ml of a mixture of chloroform / isopropanol: 90 / 10. All the organic layers were pooled and washed with 100 ml of a 0.1 N

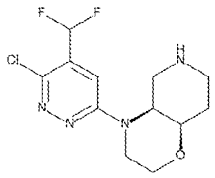
sodium hydroxide aqueous solution, then dried over Na_2SO_4, filtered and concentrated under reduced pressure at 70°C to give the title compound (7.22 g, 87% yield) as a yellow oil.
LCMS (**Method W**): Rt = 0.42; MS m/z $[M+H]^+$ = 243

Int 298.4: **tert-butyl (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate and**
Int 291.1: **tert-butyl (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate**



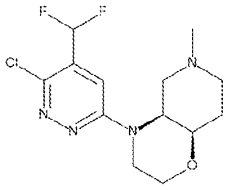
To a mixture of tert-butyl (4aS,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (9.90 mmol, 2.3 g) and 3,6-dichloro-4-(difluoromethyl)pyridazine (**Int 144.1**, 14.9 mmol, 3 g) was added triethylamine (19.8 mmol, 2.8 ml). The mixture was stirred at 140°C for 10 min (while removing the excess of triethylamine under a flow of argon), then for another 30 min. The neat solution was then cooled to rt, diluted with 50 ml of DCM and purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of a mixture of EtOAc/MeOH: 99/1 in cyclohexane to give successively tert-butyl (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate - **Int 291.1** (1.17 g, 29% yield) and tert-butyl (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate - **Int 298.4** (1.71 g, 43% yield) as yellow oils.
LCMS (**Method V**):
Int 291.1: Rt = 1.17; MS m/z $[M+H]^+$ = 405
Int 298.4: Rt = 1.15 ; MS m/z $[M+H]^+$ = 405

Int 298.5: **(4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine**



To a solution of tert-butyl (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (1.31 mmol, 530 mg) in 45 ml of dichloromethane were added 5 ml of trifluoroacetic acid and the mixture was stirred for 2h at RT then concentrated under reduced pressure. The residue was diluted with 50 ml of dichloromethane and washed with 50 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of water then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (400 mg, 100% yield) as a yellow solid.
LCMS (**Method V**): Rt = 0.39; MS m/z $[M+H]^+$ = 305

Int 298.6: (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,4a,5,7,8,8a -hexahydro-2H-pyrido[4,3-b][1,4]oxazine

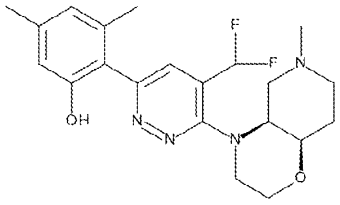


To a solution of (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (1.91 mmol, 581 mg) and a 37% weight formaldehyde aqueous solution (9.53 mmol, 774 mg) in 40 ml of DCM were added 1.63 ml of acetic acid and the mixture was stirred for 10 min at rt. Then was added sodium triacetoxyborohydride (3.43 mmol, 727 mg) and the mixture was stirred 2h at rt, then diluted with 100 ml of DCM and washed with 100 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 95/2.5/2.5) to give the title compound as a yellow oil (401 mg, 66% yield).
LCMS (**Method V**): Rt = 0.41; MS m/z $[M+H]^+$ = 319

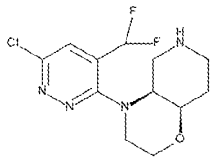
2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol (Example 298)

Under Ar, to a solution of [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (0.47 mmol, 97 mg) and (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 298.6** - 0.31 mmol, 100 mg) in 5 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (0.85 mmol, 424 µl) then Tetrakis(triphenylphosphine)palladium(0) (0.016 mmol, 18 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 20 ml of EtOAc and 20 ml of diethylether and the organic layer was washed successively with 2x15 ml of a saturated aqueous sodium bicarbonate solution and 15 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5), then repurified by prep-HPLC (column: Sunfire prep C18 OBD ; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (45 mg, 32% yield).

Example 291: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol



Int 291.2: (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine

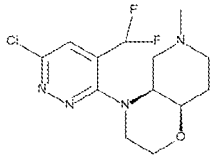


To a solution of tert-butyl (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 291.1** - 2.89 mmol, 1.17 g) in 18 ml of dichloromethane were added 2 ml of trifluoroacetic acid and the

mixture was stirred for 2h at rt, then diluted with 50 ml of dichloromethane and washed with a mixture of 20 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of a 2N aqueous Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (810 mg, 92% yield) as a yellow gum.

LCMS (**Method V**): Rt = 0.39; MS m/z $[M+H]^+$ = 305

Int 291.3: (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine



To a solution of (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (1.31 mmol, 401 mg) and a 37% weight formaldehyde aqueous solution (6.56 mmol, 533 mg) in 30 ml of DCM were added 1.3 ml of acetic acid and the mixture was stirred for 10 min at RT. Then was added sodium triacetoxyborohydride (2.36 mmol, 501 mg) and the mixture was stirred 1h at rt, then diluted with 20 ml of DCM and washed with 20 ml of a 2N aqueous Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in DCM to give the title compound (342 mg, 82% yield) as a yellow oil.

LCMS (**Method V**): Rt = 0.39; MS m/z $[M+H]^+$ = 319

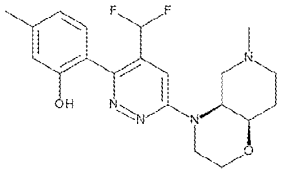
2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol (Example 291)

Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.72 mmol, 119 mg) and (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 291.3** - 0.36 mmol, 114 mg) in 4 ml of 1,4-dioxane and 0.75 ml of water was added a 2N sodium carbonate aqueous solution (1.07 mmol, 537 µl) then tetrakis(triphenylphosphine)palladium(0) (0.036 mmol, 41 mg). The mixture was stirred at 100°C for 2h30. After cooling down to rt, the mixture was diluted

with 20 ml of DCM and 20 ml of saturated aqueous sodium bicarbonate. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 89/5/5/1) to give the title compound as a white solid (114 mg, 79% yield).

Compound Example 425 was synthesized analogously to Example 291.

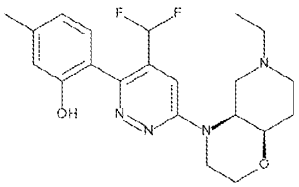
Example 295: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol



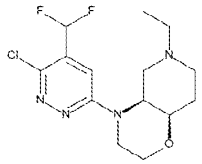
Under Ar, to a solution of (2-hydroxy-4-methyl-phenyl)boronic acid (0.47 mmol, 71.5 mg) and (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 298.6** - 0.31 mmol, 100 mg) in 8 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (0.85 mmol, 424 µl), then tetrakis(triphenylphosphine)palladium(0) (0.016 mmol, 18 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 20 ml of EtOAc and 20 ml of diethylether and the organic layer was washed successively with 2x15 ml of a saturated aqueous sodium bicarbonate solution and 15 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) to give the title compound as a white solid (58 mg, 38% yield).

Compounds Examples 306 and 351 were synthetized analogously to Example 295

Example 323: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol



Int 323.1: (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine



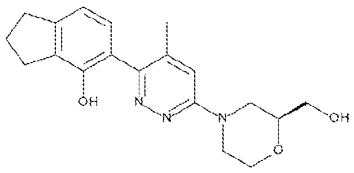
To a solution of (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 298.5 –** 0.69 mmol, 211 mg) and acetaldehyde (3.46 mmol, 152 mg) in 20 ml of DCM was added 0.594 ml of acetic acid and the mixture was stirred for 10 min at RT. Then was added sodium triacetoxyborohydride (1.25 mmol, 264 mg) and the mixture was stirred 2h at rt, then diluted with 50 ml of DCM and washed with 50 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a yellow solid (138 mg, 60% yield).

LCMS (**Method V**): Rt = 0.42; MS m/z $[M+H]^+$ = 333

2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol (Example 323)

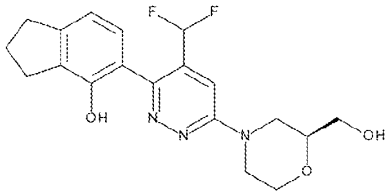
Following procedure of **Example 298**, (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.41 mmol, 138 mg) gave the title compound as a white solid (73 mg, 43% yield).

Example 324: 5-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]indan-4-ol



Under Ar, to a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indan-4-ol (**Int 324.2** - 0.92 mmol, 276 mg) and [(2S)-4-(6-chloro-5-methyl-pyridazin-3-yl)morpholin-2-yl]methanol (**Int 85.1** – 0.62 mmol, 150 mg) in 5 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.66 mmol, 831 µl) then tetrakis(triphenylphosphine)palladium(0) (0.031 mmol, 36 mg). The mixture was stirred at 100°C for 3h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM and the solid obtained was triturated in 2 ml of acetonitrile to give the title compound as a white solid (58 mg, 28% yield).

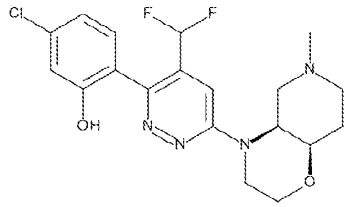
Example 345: 5-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]indan-4-ol



Under Ar, to a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indan-4-ol (**Int 324.2** - 0.86 mmol, 257 mg) and [(2S)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]morpholin-2-yl]methanol (**Int 144.2** – 0.57 mmol, 160 mg) in 5 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.54 mmol, 772 µl) then tetrakis(triphenylphosphine)palladium(0) (0.029 mmol, 33 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over

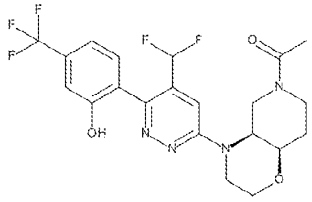
Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM then repurified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 25 min. at 50 ml/min) to give the title compound as a white solid (98 mg, 45% yield).

Example 350: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol

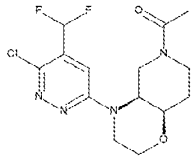


Under Ar, to a solution of 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.94 mmol, 240 mg) and (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 298.6** - 0.63 mmol, 200 mg) in 8 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.69 mmol, 847 µl), then tetrakis(triphenylphosphine)palladium(0) (0.031 mmol, 36 mg). The mixture was stirred at 100°C for 1 h. After cooling down to rt, the mixture was diluted with 20 ml of EtOAc and 20 ml of diethylether and the organic layer was washed successively with 2x15 ml of a saturated aqueous sodium bicarbonate solution and 15 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5), then repurified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N /ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (49 mg, 19% yield).

Example 386: 1-[(4aS,8aR)-4-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6yl]ethanone



Int 386.1: **1-[(4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone**



To a solution of (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 298.5** – 0.66 mmol, 200 mg), DMAP (0.033 mmol, 4 mg) and triethylamine (0.66 mmol, 90 µl) in 16 ml of DCM was added acetic anhydride (0.98 mmol, 92 µl). The mixture was stirred for 4h at rt, then diluted with 10 ml of DCM. The organic layer was washed with 10 ml of a saturated aqueous sodium bicarbonate solution and 15 ml of water, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a yellow oil (222 mg, 98% yield).

LCMS (**Method V**): Rt = 0.78; MS m/z $[M+H]^+$ = 347

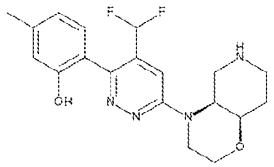
1-[(4aS,8aR)-4-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (Example 386)

Under Ar, to a solution of [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (0.58 mmol, 119 mg) and 1-[(4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (**Int 386.1** - 0.29 mmol, 100 mg) in 6 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (0.78 mmol, 389 µl), then tetrakis(triphenylphosphine)palladium(0) (0.014 mmol, 17 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 15 ml of EtOAc and 20 ml of diethylether and the organic layer was washed successively with 2x15 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was

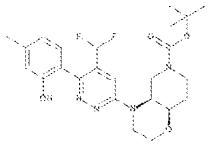
purified by flash chromatography on silica gel using a gradient of DCM / MeOH / ACN / NH_3 7N sol. in MeOH (from 100/0/0/0 to 78/10/10/2) to give the title compound as a white solid (53 mg, 39% yield).

Compound Examples 387 and 442 were synthetized analogously to Example 386.

Example 322: 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol



Int 322.1: **tert-butyl (4aS,8aR)-4-[5-(difluoromethyl)-6-(2-hydroxy-4-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate**



Under Ar, to a solution of 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.74 mmol, 173 mg) and tert-butyl (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 298.4** - 0.49 mmol, 200 mg) in 8 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.33 mmol, 667 µl), then tetrakis(triphenylphosphine)palladium(0) (0.025 mmol, 29 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 20 ml of EtOAc and 20 ml of diethylether and the organic layer was washed successively with 2x15 ml of a saturated aqueous sodium bicarbonate solution and 15 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 40% of EtOAc in cyclohexane to give the title compound (202 mg, 86% yield) as a yellow oil.

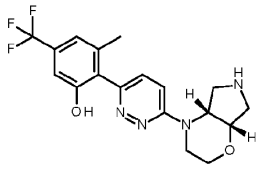
LCMS (**Method V**): Rt = 1.19; $[M+H]^+$ = 477

2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol (Example 322)

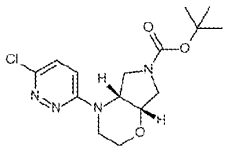
Following procedure of **Int 268.6**, 1-[(4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (0.38 mmol, 180 mg) gave the title compound as a white solid (101 mg, 51% yield) after purification by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10).

Compound Example 382 was synthetized analogously to Example 322

Example 320: 3-methyl-2-[6-[rac-(4aR,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol



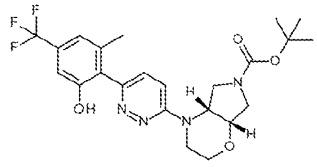
Int 320.1: tert-butyl rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate



In a sealed tube, a mixture of 3-bromo-6-chloro-pyridazine (1.2 eq., 1.31 g, 0.0068 mol), tert-butyl rac-(4aR,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxylate hydrochloride (1.00 g, 0.00378 mol), sodium tert-butoxide (1.09 g, 0.0113 mol), RuPhos Pd G3 (0.158 g, 0.189 mmol) and RuPhos (0.176 g, 0.378 mmol) was purged with N_2. 20 ml of 1,4-dioxane was added, the mixture was purged again with N_2 then heated at 100 °C for 2 h. After cooling down to rt, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (100/0 to 90/10) to give the title compound as a white solid (1.00 g, 78 %).

LCMS (**Method S**): Rt = 1.29; MS m/z [M+H]+ = 285.1

Int 320.2: tert-butyl rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate



In a sealed tube, a mixture of tert-butyl rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate (200 mg, 0.587 mmol), K_2CO_3 (243 mg, 1.76 mmol) and 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (266 mg, 0.880 mmol) in 2 ml of 1,4-dioxane and 0.5 ml of water was purged with N_2. XPhos Pd G2 (23.1 mg, 0.0293 mmol) and XPhos (14.0 mg, 0.0293 mmol) were added, the mixture was purged again with N_2 then heated at 90 °C for 3h. After cooling down to rt, the mixture was quenched with water and extracted twice with a 80/20 DCM/MeOH mixture. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give the title compound as a yellow solid (247 mg, 88 %).

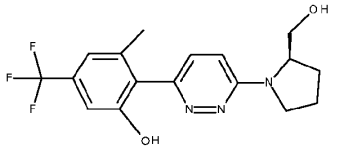
LCMS (**Method S**): Rt = 1.73; S MS m/z [M+H]+ = 481.4

3-methyl-2-[6-[rac-(4aR,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (Example 320)

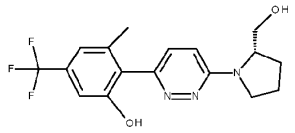
At 0°C, to a solution of tert-butyl rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4] oxazine-6-carboxylate (247 mg, 0.514 mmol) in 5 ml of 1,4-dioxane was added dropwise 0.65 ml of HCl (4 M in dioxane) and the mixture was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure to give a residue which was triturated in diethyl ether to afford a yellow gum. This gum was taken up in MeOH and toluene and concentrated under reduced pressure, then taken up in MeOH and concentrated under reduced pressure to afford the title compound as a yellow solid (9 mg, 5% yield).

Compound example 318 was synthesized analogously to example 320.

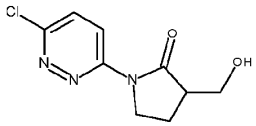
Examples 325 and 326: (3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one and (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one



and



Int 325.1: 1-(6-chloropyridazin-3-yl)-3-(hydroxymethyl)pyrrolidin-2-one



In a microwave vial, under Ar, a suspension of 3,6-dichloropyridazine (2.14 mmol, 335 mg), 3-(hydroxymethyl)pyrrolidin-2-one (2.56 mmol, 295 mg), potassium phosphate tribasic (4.27 mmol, 907 mg), 1-1'-bis(diphenylphosphino)ferrocene (0.26 mmol, 142 mg) and palladium acetate (0.09 mmol, 19 mg) in 5 ml of 1,4-dioxane was heated at 110°C under microwave irradiation for 1 h 30. After cooling down to rt, the reaction mixture was diluted with EtOAc and CH_2Cl_2, then filtered. The solid part was washed with EtOAc and CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 60/40) to give the title compound as a brown solid (176 mg, 36% yield).

LCMS (**Method B**): Rt = 0.88; MS m/z [M+H]+ = 228

Int 325.2: 3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]pyrrolidin-2-one

In a microwave vial, under Ar, to a solution of 1-(6-chloropyridazin-3-yl)-3-(hydroxymethyl)pyrrolidin-2-one (0.72 mmol, 164 mg) and 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.76 mmol, 229 mg) in 4 ml of 1,2-dimethoxyethane were added sodium carbonate (1.80 mmol, 191 mg) and 1 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.04 mmol, 42 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h.

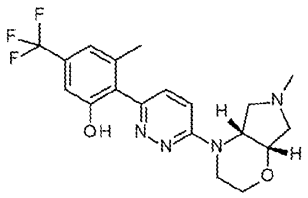
After cooling down to rt, the reaction mixture was diluted with EtOAc and water, then filtered. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (100/0/0 to 90/5/5) to give the title compound as a beige solid (148 mg, 56% yield).

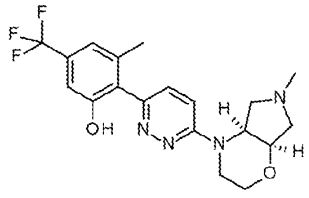
LCMS (**Method B**): Rt = 1.36; MS m/z [M+H]+ = 368

(3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazine-3-yl]pyrrolidin-2-one and (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one (Example 325 and Example 326)

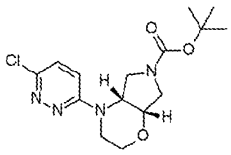
The 2 enantiomers of 3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one (146 mg) were separated by chiral phase LC (Column Chiralcel OJ-H 5µm, 350x76.5mm, Flow rate 400ml/min, eluent (n-heptane/ethanol 80/20) + 0,1% TEA, to give both enantiomers, first eluting Rt = 13.1 min, **Example 325** (43.4mg, yield 29%) and second eluting Rt = 17.7 min, **Example 326** (69.4 mg, yield 47%). The absolute configurations cannot be assigned at this stage.

Examples 333 and 334: 2-[6-[(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(4aS,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol





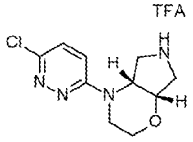
Int 333.1: tert-butyl rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate



In a sealed tube, a mixture of 3-bromo-6-chloro-pyridazine (1.31 g, 6.8 mmol), tert-butyl rac-(4aR,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxylate hydrochloride (1.00 g, 3.78 mmol), sodium tert-butoxide (1.09 g, 11.3 mmol), RuPhos Pd G3 (0.158 g, 0.189 mmol) and RuPhos (0.176 g, 0.378 mmol) was purged with N_2. 20 ml of 1,4-dioxane was added, the mixture was purged again with N_2 then heated at 100 °C for 2h. After cooling down to rt, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (100/0 to 90/10) to give the title compound as a white solid (1.00 g, 78 %).

LCMS (**Method S**): Rt = 1.29 min; MS m/z [M+H]+ = 285.1

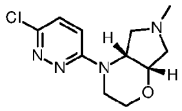
Int 333.2: rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine;2,2,2- trifluoroacetic acid



To a solution of tert-butyl rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate (100 mg, 0.293 mmol) in 3 ml of dichloromethane was slowly added TFA (0.218 mL, 2.93 mmol). The solution was stirred at rt for 18 h. The reaction mixture was concentrated under reduced pressure to give the title compound as a TFA salt (194 mg), which was used without further purification in the next step.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 9.00 (s, 1H), 7.66 (d, J = 9.6 Hz, 1H), 7.41 (d, J= 9.6 Hz, 1H), 5.01 (td, J = 9.2, 3.6 Hz, 1H), 4.21 (t, J = 3.6 Hz, 1H), 4.04 (dd, J = 11.8, 3.5 Hz, 1H), 3.84 (dd, J = 13.1, 2.8 Hz, 1H), 3.67 (td, J = 12.0, 2.9 Hz, 1H), 3.53 – 3.40 (m, 2H), 3.36 – 3.28 (m, 1H), 3.24 – 3.15 (m, 1H), 3.14 – 3.07 (m, 1H).

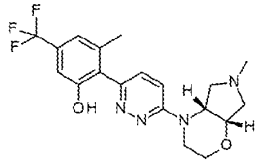
Int 333.3: rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine



formaldehyde (37% in water) (0.262 mL, 0.00332 mol) was added to a solution of rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4] oxazine; 2,2,2- trifluoroacetic acid (0.160 g, 0.000665 mol) in 0.8 ml of methanol and 0.8 ml of tetrahydrofuran. The solution was stirred for 15 min, then $NaBH_3CN$ (0.0418 g, 0.000665 mol) was added. The solution was stirred at rt for 1h. Then, EtOAc was added to the mixture. The mixture was then quenched with a small amount of water and basified with a 1N aqueous solution of NaOH until pH 8. The aqueous layer was separated then extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 90/10) to give the title compound (0.0740 g, 44 %).

LCMS (**Method S**): Rt = 0.75 min; MS m/z [M+H]+ = 255.2

Int 333.4: 3-methyl-2-[6-[rac-(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol



In a sealed tube, a mixture of rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine (0.0720 g, 0.000283 mol), K_2CO_3 (0.0781 g, 0.000565 mol) and 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.128 g, 0.000424 mol) in 1.6 ml of 1,4-dioxane and 0.4 ml of water was purged with N_2. XPhos Pd G2 (0.0111 g, 1.41e-5 mol) and XPhos (0.00674 g, 1.41e-5 mol) were added, the mixture was purged again with N_2 then heated at 90°C for 3h. After cooling down to rt, EtOAc and water were added. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous solution of NaCl then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using

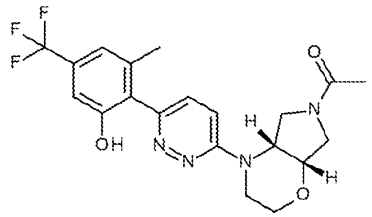
DCM/(MeOH/aq NH3 (9:1)) (100/0 to 0/100) to give the title compound as an off-white solid (0.0780 g, 70 %).
LCMS (**Method E**): Rt = 2.49 min; MS m/z [M+H]+ = 395.4

2-[6-[(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl] pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(4aS,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 333 and Example 334)

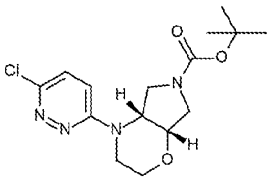
3-methyl-2-[6-[rac-(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol was purified by chiral SFC (Stationary phase: Chiralpak® AD-H 20x250 mm, Mobile phase: CO_2 / (EtOH + 0,3%$iPrNH_2$) 80/20). The fractions containing compound were combined and evaporated in vacuo to give 2 fractions. The fractions containing each compound were combined and concentrated under reduced pressure to give two residues. The first residue was lyophilized to provide 2-[6-[(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (20 mg, 18%). The second residue was lyophilized to provide 2-[6-[(4aS,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (23 mg, 21%). The absolute configurations cannot be assigned at this stage.

Compounds Example 289, 361 and 376 were synthesized analogously to compound Example 334 without chiral separation.

Example 335: 1-[rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone



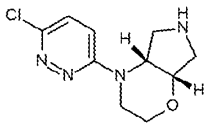
Int 335.1: tert-butyl rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate



In a sealed tube, a mixture of 3-bromo-6-chloro-pyridazine (1.31 g, 6.8 mmol), tert-butyl rac-(4aR,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxylate hydrochloride (1.00 g, 3.78 mmol), sodium tert-butoxide (1.09 g, 11.3 mmol), RuPhos Pd G3 (0.158 g, 0.189 mmol) and RuPhos (0.176 g, 0.378 mmol) was purged with N_2. 20 ml of 1,4-dioxane was added, the mixture was purged again with N_2 then heated at 100 °C for 2 h. After cooling down to rt, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (100/0 to 90/10) to give the title compound as a white solid (1.00 g, 78 %).

LCMS (**Method S**): Rt = 1.29; MS m/z [M+H]+ = 285.1

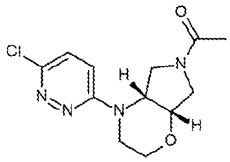
Int 335.2: rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine



To a solution of tert-butyl rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate (100 mg, 0.293 mmol) in 3 ml of dichloromethane at rt was slowly added TFA (0.218 mL, 2.93 mmol) and the solution was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure to give the title compound (194 mg) which was used without further purification.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 9.00 (s, 1H), 7.66 (d, J = 9.6 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 5.01 (td, J = 9.2, 3.6 Hz, 1H), 4.21 (t, J = 3.6 Hz, 1H), 4.04 (dd, J = 11.8, 3.5 Hz, 1H), 3.84 (dd, J = 13.1, 2.8 Hz, 1H), 3.67 (td, J = 12.0, 2.9 Hz, 1H), 3.53 – 3.40 (m, 2H), 3.36 – 3.28 (m, 1H), 3.24 – 3.15 (m, 1H), 3.14 – 3.07 (m, 1H).

Int 335.3: 1-[(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone



At 0°C, acetyl chloride (0.0650 mL, 0.914 mmol) was added dropwise to a solution of rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine (200 mg, 0.831 mmol) and DIPEA (0.217 mL, 1.25 mmol) in 4 ml of DCM and the mixture was stirred for 1h at rt. The mixture was then quenched with water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (231 mg, yield:98%).

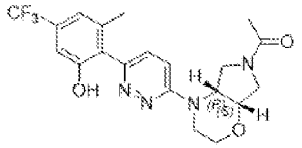
LCMS (**Method R**): Rt = 0.89; MS m/z [M+H]+ = 283.2

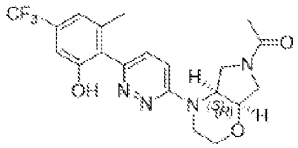
1-[rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (Example 335)

In a microwave vial, under N_2, a mixture of 1-[rac-(4aR,7aS)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (230 mg, 0.814 mmol), K_2CO_3 (225 mg, 1.63 mmol), 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (369 mg, 01.22 mmol) in 4 ml of 1,4-dioxane and 1 ml of water was degazed under N_2 flow. XPhos (19.4 mg, 0.0407 mmol) and XPhos Pd G2 (32.0 mg, 0.0407 mmol) were added, and the mixture was heated at 90°C for 3h. After cooling down to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give a yellow solid residue which was again purified by prep-HPLC (Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 35/65 to 55/45. The pure fractions were diluted with dichloromethane and washed with a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a white solid (170 mg, 47% yield).

Compound Example 337 was synthesized analogously to Example 335

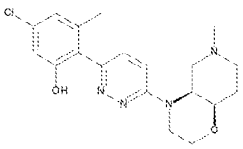
Examples 348 and 352: 1-[(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone and 1-[(4aS,7aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone



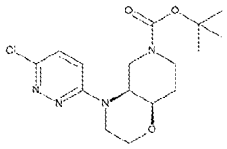


1-[rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (example 335 - 160 mg) was purified by preparative chiral SFC (Stationary phase: Chiralpak® AD-H 20x250 mm, Mobile phase: CO_2/iPrOH 70/30. The fractions containing each compound were combined and concentrated under reduced pressure to give two residues. The first residue was lyophilized to provide 1-[(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (28 mg, 8%). The second residue (40 mg, 11%) was purified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 25/75 to 50/50 15CV) to give after concentration under reduced pressure 1-[(4aS,7aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone (13 mg, 4%). The absolute configurations cannot be assigned at this stage.

Example 321: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol



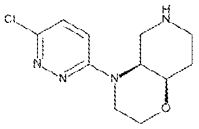
Int 321.1: tert-butyl (4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate



A solution of tert-butyl (4aS,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 298.3** – 24.76 mmol, 6g), 3,6-dichloropyridazine (37.14 mmol, 5.53g) and triethylamine (74.28 mmol, 10.4 ml) in 20 ml of 1-butanol was stirred at 150°C for 1h while removing 1-butanol and triethylamine under a stream of argon. The mixture was stirred at 150°C for another 1 h 30 then cooled down to rt. The mixture was triturated with 200 ml of EtOAc and filtered. The cake was rinsed with 2x50 ml of EtOAc and the filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give the title compound (3.57g, 41% yield) as a yellow oil.

LCMS (**Method V**): Rt = 1.07; MS m/z $[M+H]^+$ = 355

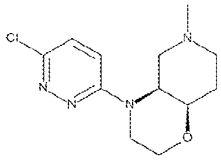
Int 321.2: (4aS,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine



A solution of tert-butyl (4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (7.05 mmol, 2.5g) in 45 ml of dichloromethane and 5 ml of trifluoroacetic acid was stirred at rt for 18h, then concentrated under reduced pressure. The residue was diluted with 50 ml of dichloromethane and washed with 50 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of a 2N aqueous sodium carbonate solution. The pooled aqueous layers were extracted with 4x30 ml of DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (1.79 g, 100% yield) as a colorless oil.

LCMS (**Method W**): Rt = 0.58; MS m/z $[M+H]^+$ = 255

Int 321.3: **(4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine**



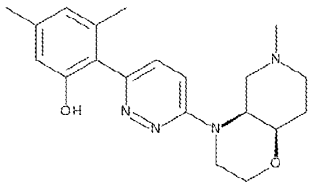
Under Ar, to a solution of (4aS,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (7.05 mmol, 1.79 g) cooled to 0-5°C were successively added 7 ml of acetic acid, a 37% aqueous solution of formaldehyde (35 mmol, 2.7 ml) and sodium triacetoxyborohydride (13 mmol, 2.7g) portion wise. The mixture was stirred at rt for 1h30). 100 ml of dichloromethane, 100 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of a 2N aqueous sodium carbonate solution were added. The aqueous layer was extracted with 100 ml of dichloromethane and the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (1.86 g, 98% yield) as a yellow oil.

LCMS (**Method W**): Rt = 0.60; MS m/z $[M+H]^+$ = 269

2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol (Example 321)

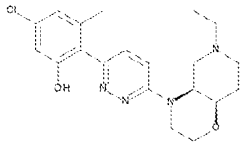
Under Ar, to a solution of 5-chloro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (2.54 mmol, 683 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** – 1.41 mmol, 380 mg) in 20 ml of 1,4-dioxane was successively added a 2N sodium carbonate aqueous solution (3.82 mmol, 1.91 ml) and tetrakis(triphenylphosphine)palladium(0) (0.071 mmol, 82 mg). The mixture was stirred at 100°C for 2 h. After cooling down to rt, the mixture was diluted with 100 ml of EtOAc and 100 ml of diethylether. The organic layer was washed successively with 2x100 ml of a saturated aqueous sodium bicarbonate solution and 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give, after trituration in diethylether, the title compound as a white solid (207 mg, 39% yield).

Example 311: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

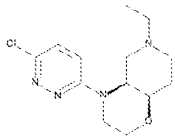


Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (2.23 mmol, 371 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** – 1.49 mmol, 400 mg) in 20 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (4.02 mmol, 2 ml) then tetrakis(triphenylphosphine)palladium(0) (0.074 mmol, 86 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 100 ml of EtOAc and 100 ml of diethylether and the organic layer was washed successively with 2X100 ml of a saturated aqueous sodium bicarbonate solution and 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) to give a solid that was triturated in the minimum of acetonitrile to give the title compound as a white solid (214 mg, 40% yield).

Example 313: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol



Int 313.1: **(4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine**



To a solution of (4aS,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 321.2** - 2.81 mmol, 720 mg) in 10 ml of dichloromethane were added successively 2.4 ml of acetic acid, acetaldehyde (14 mmol, 787

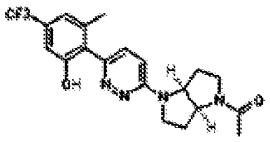
µl) and sodium triacetoxyborohydride (5.07 mmol, 1.07g) portionwise. The mixture was stirred at rt for 18h. The mixture was diluted with 100 ml of dichloromethane and 100 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 100 ml of DCM then with 2x100 ml of a mixture DCM/isopropanol: 90/10. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM / MeOH / ACN (from 100/0/0/0 to 80/10/10) to give the title compound as a white solid (795 mg, 99% yield).

LCMS (**Method V**): Rt = 0.64; MS m/z $[M+H]^+$ = 283

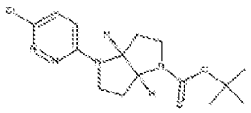
2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl] pyridazin-3-yl]-5-chloro-3-methyl-phenol (Example 313)

Under Ar, to a solution of (4-chloro-2-hydroxy-6-methyl-phenyl)boronic acid (2.48 mmol, 463 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 313.1** – 1.38 mmol, 390 mg) in 20 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (3.72 mmol, 1.86 ml) and tetrakis(triphenylphosphine)palladium(0) (0.069 mmol, 80 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 100 ml of EtOAc and 100 ml of diethylether and the organic layer was washed successively with 2x100 ml of a saturated aqueous sodium bicarbonate solution and 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0/0 to 95/2.5/2.5) to give the title compound as a white solid (240 mg, 45% yield).

Example 377: 1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]ethanone



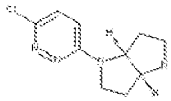
Int 377.1: tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrole-4-carboxylate



To a solution of 3,6-dichloropyridazine (400 mg, 2.685 mmol) in 7 ml of 1-Butanol was added tert-butyl rac-(3aS,6aS)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrole-4-carboxylate (627 mg, 2.9535 mmol) and Triethylamine (0.823ml, 5.9069 mmol). The mixture was heated at 130°C for 5h. After cooling down to rt, the mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of Hept/AcOEt (from 100/0 to 50/50) to give the title compound as a white solid (575 mg, 66% yield).

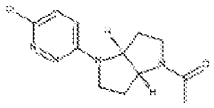
LCMS (**Method L**): Rt = 0.88 min; MS m/z [M+H]+ = 325

Int 377.2: rac-(3aS,6aS)-4-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo [3,2-b]pyrrole;dihydrochloride



To a solution of tert-butyl rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrole-4-carboxylate (575 mg, 1.7703 mmol) in 10 ml of DCM was added a solution of HCl 4N dioxane (8.85 ml, 35.4058 mmol). After stirring 4h at rt, the mixture was concentrated under reduce pressure to give the title compound as a beige solid (m=600mg), which was used without further purification in the next step.

Int 377.3: 1-[rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydropyrrolo [3,2-b]pyrrol-4-yl]ethanone



To a suspension of rac-(3aS,6aS)-4-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrole;dihydrochloride (200 mg, 0.672 mmol) in 40 ml of DCM was added

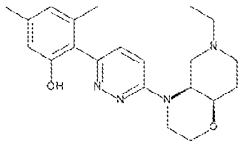
N,N-dimethylpyridin-4-amine (4 mg, 0.0336 mol) and triethylamine (0.28ml, 2.016 mmol). Acetic anhydride (0.10 ml, 1.01 mmol) was added and the mixture was stirred at rt for 4 h. The mixture was diluted with water, extracted with DCM. The organic layer was washed with an aqueous saturated solution of $NaHCO_3$, brine, dried over Mg_2SO_4, filtered, and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH (100/0 to 95/5) to give the title compound as a solid (101 mg, 56% yield).

LCMS (**Method L**): Rt = 0.46 min; MS m/z [M+H]+ = 267

1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]ethanone (Example 377)

In a microwave vial, under Ar, to a solution of 1-[rac-(3aS,6aS)-1-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]ethanone (145 mg, 0.5436 mmol), 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (180 mg, 0.598 mmol) and Sodium carbonate (144 mg, 1.3591 mmol) in 4 ml of 1,2-Dimethoxyethane and 1 ml of water was added tetrakis(triphenylphosphine)Palladium(0) (31 mg, 0.0272 mmol). The mixture was heated at 100°C under microwave irradiation for 1h30. After cooling down to rt, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH (100/0 to 95/5) to give, after crystallization in diethylether, the title compound as a white solid (103 mg, 47% yield).

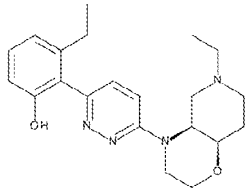
Example 404: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (2.55 mmol, 423 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 313.1** – 1.42 mmol, 402 mg) in 20 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (3.82 mmol, 1.91 ml) and

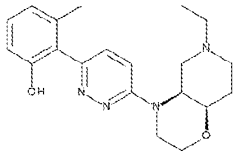
tetrakis(triphenylphosphine)palladium(0) (0.071 mmol, 82 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 100 ml of EtOAc and 100 ml of diethylether and the organic layer was washed successively with 2x100 ml of a saturated aqueous sodium bicarbonate solution and 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0/0 to 95/2.5/2.5) to give the title compound as a white solid (201 mg, 39% yield).

Example 408: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol



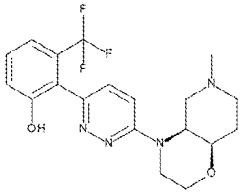
Under Ar, to a solution of (2-ethyl-6-hydroxy-phenyl)boronic acid (**Int 358.2** - 1.01 mmol, 167 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 313.1** – 0.67 mmol, 190 mg) in 20 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (1.81 mmol, 0.91 ml) and tetrakis(triphenylphosphine)palladium(0) (0.034 mmol, 39 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0/0 to 95/2.5/2.5) to give the title compound as a white solid (68 mg, 27% yield).

Example 412: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol



Under Ar, to a solution of (2-hydroxy-6-methyl-phenyl)boronic acid (**Int 354.1** - 1.01 mmol, 153 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 313.1** – 0.67 mmol, 190 mg) in 20 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (1.81 mmol, 0.91 ml) and tetrakis(triphenylphosphine)palladium(0) (0.034 mmol, 39 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 95/2.4/2.4/0.2) to give the title compound as a white solid (58 mg, 24% yield).

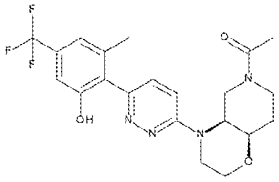
Example 402: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol



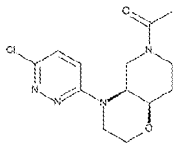
Under Ar, to a solution of [2-hydroxy-6-(trifluoromethyl)phenyl]boronic acid (0.41 mmol, 84 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** – 0.23 mmol, 61 mg) in 3 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (0.61 mmol, 306 µl) and tetrakis (triphenylphosphine)palladium(0) (0.011 mmol, 13 mg). The mixture was stirred at 100°C for 2h30. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 30 ml of water. The aqueous layer was extracted with a mixture of 35 ml of DCM and 15 ml of isopropanol and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on

silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 95/2.4/2.4/0.2) to give the title compound as a pale yellow solid (74 mg, 82% yield).

Example 398: 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone



Int 398.1: **1-[(4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido [4,3-b][1,4]oxazin-6-yl]ethanone**



To a solution of (4aS,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 321.2** – 5.69 mmol, 1.45 g), DMAP (0.285 mmol, 35 mg) and triethylamine (5.69 mmol, 780 µl) in 40 ml of DCM was added acetic anhydride (8.54 mmol, 802 µl). The mixture was stirred for 24h at rt, then diluted with 100 ml of DCM. The organic layer was washed with 100 ml of a saturated aqueous sodium bicarbonate solution and 50 ml of water, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound as a yellow solid (1.69 g, 100% yield).

LCMS (**Method V**): Rt = 0.63; MS m/z $[M+H]^+$ = 297

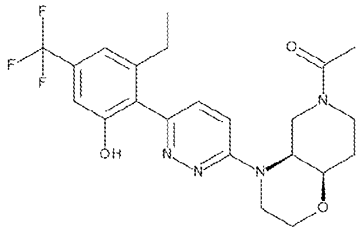
1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethenone (Example 398)

Under Ar, to a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (3.64 mmol, 1.1 g) and 1-[(4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (**Int 398.1** – 2.02 mmol, 600 mg) in 20 ml of 1,4-dioxane were successively added a 2N sodium carbonate

aqueous solution (5.46 mmol, 2.72 ml) and tetrakis(triphenylphosphine)palladium(0) (0.1 mmol, 117 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 200 ml of EtOAc and 200 ml of diethylether and the organic layer was washed successively with 2x150 ml of a saturated aqueous sodium bicarbonate solution and 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 95/2.5/2.5) to give the title compound as a yellow oil (506 mg, 57% yield).

Compounds Example 397, 409, 424, 462 and 463 were synthetized analogously to Example 398. Chiral separation of Examples 462 and 463 were realized using Chiralpak® IG column.

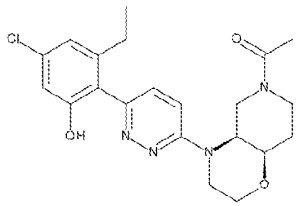
Example 380: 1-[(4aS,8aR)-4-[6-[2-ethyl-6-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone



Under Ar, to a solution of 3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.67 mmol, 213 mg) and 1-[(4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (**Int 398.1** – 0.34 mmol, 100 mg) in 8 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (0.91 mmol, 455 µl) and tetrakis(triphenylphosphine)palladium(0) (0.017 mmol, 19 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 80/9.8/9.8/0.4) then repurified by prep-HPLC (column: Sunfire prep C18 OBD ; 250 * 50 mm * 10 µm; mobile phase:

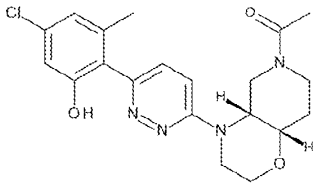
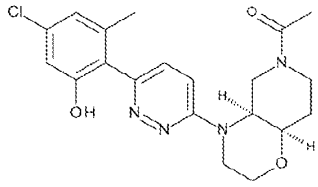
[aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (49 mg, 32% yield).

Example 381: 1-[(4aS,8aR)-4-[6-(4-chloro-2-ethyl-6-hydroxy-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone



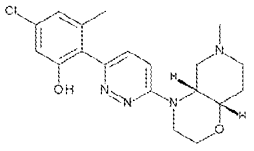
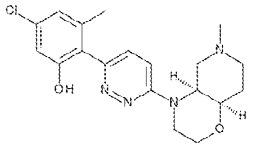
Under Ar, to a solution of 5-chloro-3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**Int 381.3** – 0.67 mmol, 190 mg) and 1-[(4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (**Int 398.1** – 0.34 mmol, 100 mg) in 8 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (0.91 mmol, 455 µl) and tetrakis(triphenylphosphine)palladium(0) (0.017 mmol, 19 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 80/9.8/9.8/0.4) then repurified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (53 mg, 38% yield).

Example 304 and 397: 1-[(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone and 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone


and


1-[rac-(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (**Example 222** - 57 mg) was separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD, 300×50 mm I.D., 20 µm particle size; Mobile phase: CO_2/Methanol (+0.1% Triethylamine) 35%; flow rate: 250 mL/min; outlet pressure: 100 bar; 4 injections; UV detection : 265 nm) to provide the first enantiomer 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone eluting at Rt = 23 min (7 mg, **Example 397**, Enantiomer 1), as a white solid, and the second enantiomer 1-[(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido [4,3-b][1,4]oxazin-6-yl] ethanone, eluting at Rt = 12.5 min (7 mg, **Example 304**, Enantiomer 2), as a white solid. The absolute configurations were assigned *a posteriori* (see Chiral synthesis of example 398).

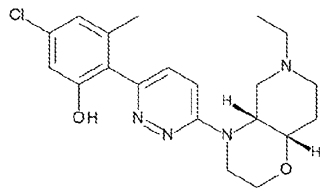
Example 307 and 321: 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol and 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol


and


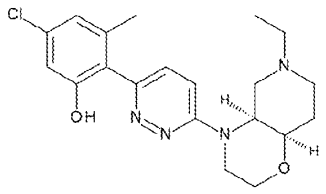
5-chloro-3-methyl-2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol (**Example 224** - 18 mg) was separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD, 300×50 mm I.D., 20 µm particle size; Mobile phase: CO_2/Methanol (+0.1% Triethylamine) 25%; flow rate: 250 mL/min; outlet pressure: 100 bar; 1 injections; UV detection : 265 nm) to provide the first enantiomer 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-

b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, eluting at Rt = 5.37 min (8.4 mg, **Example 307**, Enantiomer 1), as a white solid, and the second enantiomer 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, eluting at Rt = 8.84 min (9.1 mg, **Example 321**, Enantiomer 2), as a white solid. The absolute configurations were assigned *a posteriori* (see **Chiral synthesis of example 321**).

Example 312 and 313: 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol and 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol

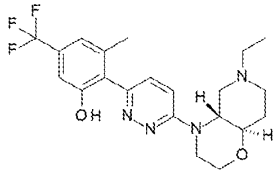


and

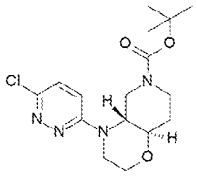


5-chloro-3-methyl-2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol (**Example 223** - 53 mg) was separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD, 300x50 mm I.D., 20 µm particle size; Mobile phase: CO_2/Methanol (+0.1% Triethylamine) 25%; flow rate: 250 mL/min; outlet pressure: 100 bar; 1 injections; UV detection : 265 nm) to provide the first enantiomer 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, first eluting enantiomer at Rt = 4.7 min (22 mg, **Example 312**, Enantiomer 1), as a white solid, and the second enantiomer 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, second eluting enantiomer at Rt = 6.94 min (22 mg, **Example 313**, Enantiomer 2), as a white solid. The absolute configurations were assigned *a posteriori* (see **Chiral synthesis of example 313**).

Example 344: 2-[6-[(4aR,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



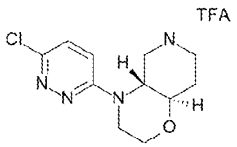
Int 344.4: tert-butyl (4aR,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate



To a stirred solution of 3-bromo-6-chloro-pyridazine (2.05 g, 10.6 mmol) in 40 ml of 1,4-dioxane were added tert-butyl (4aR,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (Int 344.4 - 1.71 g, 7.06 mmol) and NaOtBu (2.03 g, 21.2 mmol). The mixture was purged with N_2. RuPhos Pd G3 (590 mg, 0.706 mmol) and Catacxium A (253 mg, 0.706 mmol) were then added, and the mixture was purged with N_2. The reaction mixture was stirred at 85°C for 2h. After cooling down to room temperature, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (100/0 to 80/20) to give the title compound as a yellow oil (220 mg, 9 %).

LCMS (**Method T**): Rt = 6.08; MS m/z [M+H]+ = 355

Int 344.5: (4aR,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine;2,2,2- trifluoroacetic acid

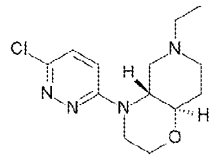


At 0°C, to a stirred solution of tert-butyl (4aR,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (220 mg, 0.620 mmol) in 4 ml of dichloromethane was added TFA (0.461 mL, 6.20 mol) and the reaction was stirred at rt for 18 h. The mixture was concentrated under reduced pressure to afford the

title compound as a yellow oil (296 mg) which was used without further purification in the next step.

LCMS (**Method T**): Rt = 2.43; MS m/z [M+H]+ = 254.9

Int 344.6: (4aR,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine



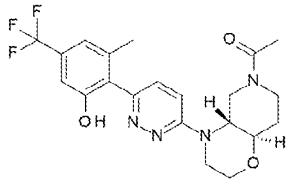
To a stirred solution of (4aR,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine;2,2,2- trifluoroacetic acid (155 mg, 0.321 mmol) in 5 ml of MeCN were added K_2CO_3 (443 mg, 3.21 mmol) and iodoethane (0.0258 mL, 0.321 mmol). The reaction mixture was stirred at 80°C for 18h. After cooling down to rt, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 80/20) to give the title compound as a yellow oil (46 mg, 51 %).

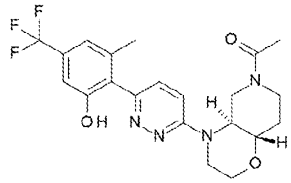
LCMS (**Method R**): Rt = 0.84; MS m/z [M+H]+ = 283.2

2-[6-[(4aR,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl] pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 344)

In a sealed tube, a mixture of (4aR,8aR)-4-(6-chloropyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (46.0 mg, 0.163 mmol), K_2CO_3 (67.4 mg, 0.488 mmol) and 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) phenol (73.7 mg, 0.244 mmol) in 1.6 ml of 1,4-dioxane and 0.4 ml of water was purged with N_2. XPhos Pd G2 (6.40 mg, 0.00813 mmol) and XPhos (3.88 mg, 0.00813 mmol) were added, the mixture was purged with N_2 and heated at 90°C for 3h. After cooling down to rt, water was added, and the resulting mixture was extracted twice with a 80/20 DCM/MeOH mixture. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give, after lyophilization, the title compound as a yellow oil (40 mg, 58 %).

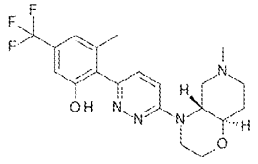
Examples 336 and 349: 1-[(4aR,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl] ethanone and 1-[(4aS,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-6-yl]ethanone

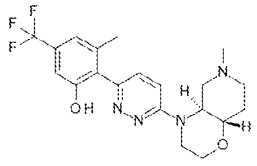




1-[rac-(4aR,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (75 mg), obtained similarly to ex 398 (with tert-butyl rac-(4aR,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate instead of tert-butyl (4aS,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate) was purified by preparative chiral SFC (Stationary phase: Chiralpak® AD-H 20x250 mm, Mobile phase: CO_2/iPrOH 80/20). The fractions containing each enantiomer were combined and concentrated under reduced pressure to give two residues. These two residues were respectively taken-up with MeCN, extended with water, then lyophilized overnight to give (22 mg, 12%) of a first enantiomer and (10 mg, 6%) of the second one. The absolute configurations cannot be assigned at this stage.

Examples 301 and 343: 2-[6-[(4aR,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(4aS,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl] pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

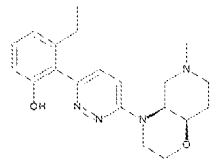




2-[6-[rac-(4aR,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl] pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (43 mg), obtained similarly to Example

358 (with tert-butyl rac-(4aR,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate instead of tert-butyl (4aS,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate) was purified by preparative chiral SFC (Stationary phase: Chiralpak® IC 20x250 mm, Mobile phase: CO_2/(iPrOH + 0,3%$iPrNH_2$) 75/25). The fractions containing each enantiomer were combined and concentrated under reduced pressure to give two residues. These two residues were respectively taken-up with MeCN, extended with water, then lyophilized overnight to give (12 mg, 15%) of a first enantiomer and (15 mg, 19%) of the second one. The absolute configurations cannot be assigned at this stage.

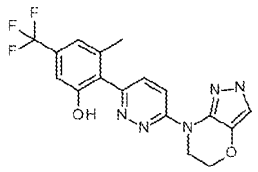
Example 358: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol



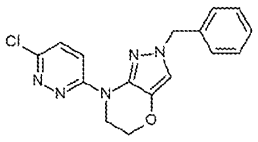
Under Ar, to a solution of (2-ethyl-6-hydroxy-phenyl)boronic acid (**Int 358.2** – 1.49 mmol, 247 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** – 0.74 mmol, 200 mg) in 8 ml of 1,4-dioxane were successively added a 2N sodium carbonate aqueous solution (2 mmol, 1 ml) and tetrakis (triphenylphosphine)palladium(0) (0.037 mmol, 43 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x50 ml of a saturated aqueous sodium bicarbonate solution and 50 ml of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2) to give the title compound as a white solid (125 mg, 47% yield).

Compounds Examples 353 and 354 were synthesized analogously to Example 358 starting from Int 353.2 and Int 354.1 respectively.

Example 360: 2-[6-(5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazin-7-yl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



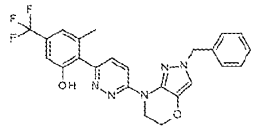
Int 360.7: 2-benzyl-7-(6-chloropyridazin-3-yl)-5,6-dihydropyrazolo[4,3-b][1,4]oxazine



In a sealed tube, a mixture of 3-bromo-6-chloro-pyridazine (0.178 g, 0.000920 mol), RuPhos Pd G3 (0.0321 g, 3.83e-5 mol), RuPhos (0.0358 g, 7.67e-5 mol) and NaOtBu (0.221 g, 0.00230 mol) was purged with N_2. 2-benzyl-6,7-dihydro-5H-pyrazolo[4,3-b][1,4]oxazine (0.165 g, 0.000767 mol) in 8 ml of 1,4-dioxane was added, the mixture was purged again with N_2 then heated at 100°C for 2h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 70/30) to give the title compound as an off-white solid (0.149 g, 59 %).

LCMS (**Method S**): Rt = 1.40; MS m/z [M+H]+ = 328.1

Int 360.8: 2-[6-(2-benzyl-5,6-dihydropyrazolo[4,3-b][1,4]oxazin-7-yl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



In a sealed tube, a mixture of 2-benzyl-7-(6-chloropyridazin-3-yl)-5,6-dihydropyrazolo[4,3-b][1,4]oxazine (0.120 g, 0.000366 mol), 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.166 g, 0.000549 mol) and K_2CO_3 (0.101 g, 0.000732 mol) in 2.7 ml of 1,4-dioxane and 0.9 ml water was purged with N_2. XPhos Pd G2 (0.0144 g, 1.83e-5 mol) and XPhos (0.00873 g, 1.83e-5 mol) were added, the mixture was purged again with N_2 then heated at 90 °C for 18 h. After cooling down to rt, EtOAc and water were added. The aqueous layer was separated and extracted twice with EtOAc.

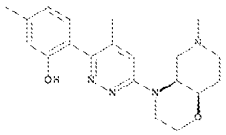
The combined organic layers were concentrated under reduced pressure, then coevaporated with toluene. The residue was purified by flash chromatography on silica gel using DCM to give 174 mg of pale yellow solid. This solid was triturated in Et_2O then filtered off to give the title compound as an off-white solid (0.149 g, 87 %).

LCMS (**Method E**): Rt = 3.45; MS m/z [M+H]+ = 468.4

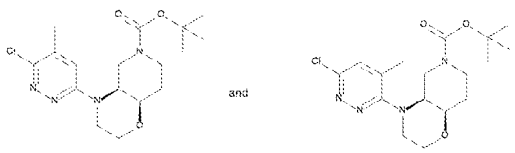
2-[6-(5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazin-7-yl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 360)

Under N_2, DMSO (0.152 mL, 0.00214 mol) was added to 2-[6-(2-benzyl-5,6-dihydropyrazolo[4,3-b][1,4]oxazin-7-yl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl) phenol (0.100 g, 0.214 mmol). tBuOK 1M in THF (1.00 mol/L, 1.50 mL, 0.00150 mol) was added and the mixture was purged with O_2 and stirred at rt for 18h. The solution was diluted with EtOAc and slowly neutralized with a 1N aqueous solution of HCl. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 90/10) to give 42 mg of a yellow solid. This solid was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 50/50) to give the title compound as a pale yellow solid (20 mg, 25 %).

Example 373: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol



Int 373.1 and Int 434.1: tert-butyl (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (Int 373.1) and tert-butyl (4aS,8aR)-4-(6-chloro-4-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (Int 434.1)



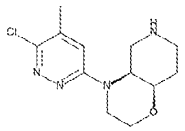
To a mixture of tert-butyl (4aS,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 298.3** – 3.30 mmol, 800 mg) and 3,6-dichloro-4-methyl-pyridazine (4.95 mmol, 807 mg was added triethylamine (6.6 mmol, 928 µl). The mixture was stirred at 150°C for 10 min under a flow of argon, then stirred at 150°C for 5 h. The neat solution was cooled to rt, diluted with 10 ml of DCM and purified by flash chromatography on silica gel eluting with a gradient of 0 to 60% of EtOAc in cyclohexane to give successively tert-butyl (4aS,8aR)-4-(6-chloro-4-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 434.1**) (50 mg, 4% yield) and tert-butyl (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 373.1**) (460 mg, 38% yield) as yellow oils.

LCMS (**Method V**)

Int 434.1: Rt = 0.97; MS m/z $[M+H]^+$ = 369

Int 373.1: Rt = 0.98; MS m/z $[M+H]^+$ = 369

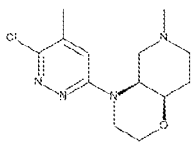
Int 373.2: (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine



A solution of tert-butyl (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (1.21 mmol, 445 mg) in 18 ml of dichloromethane and 2 ml of trifluoroacetic acid was stirred at rt for 4h, then concentrated under reduced pressure to give the title compound (324 mg, 100% yield) as a brown oil.

LCMS (**Method V**): Rt = 0.33; MS m/z $[M+H]^+$ = 269

Int 373.3: (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine



Under argon, to a solution of (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (0.89 mmol, 240 mg) in 10 ml of DCM were successively added 767 µl of acetic acid, a 37% aqueous solution of formaldehyde (4.46 mmol, 362 mg) and sodium triacetoxyborohydride (1.6 mmol, 341 mg). The mixture was stirred at rt for 18 h, then diluted with 20 ml of dichloromethane and 20 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give the title compound as a yellow oil (214 mg, 85% yield).

LCMS (**Method V**): Rt = 0.34; MS m/z $[M+H]^+$ = 283

2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol (Example 373)

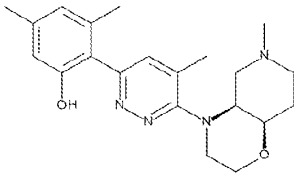
Under Ar, to a solution of 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.53 mmol, 124 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.35 mmol, 100 mg) in 8 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (0.95 mmol, 477 µl). tetrakis(triphenylphosphine)palladium(0) (0.018 mmol, 20 mg) was added and the solution was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 80/9.8/9.8/0.4) to give the title compound as a white solid (23 mg, 18% yield).

Compound Example 356 was synthetized analogously to Example 373

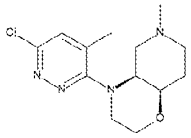
Compounds Examples 403, 421, 438 and 448 were synthesized starting from dichloropyridazine with conditions for N-arylation and boronate coupling analogously to Example 373.

Compounds Examples 443 and 470 were synthesized analogously to Example 373, starting from 3,6-dichloro-4-ethyl-pyridazine.

Example 434: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol



Int 434.2: **(4aS,8aR)-4-(6-chloro-4-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine**



Following procedures of **Int 373.2** and **Int 373.3**, tert-butyl (4aS,8aR)-4-(6-chloro-4-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 434.1** - 0.136 mmol, 50 mg) give (4aS,8aR)-4-(6-chloro-4-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (27 mg, 70% yield) as a yellow oil.

LCMS (**Method V**): Rt = 0.68; MS m/z $[M+H]^+$ = 283

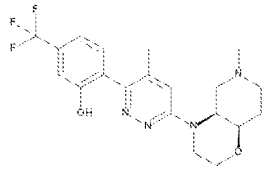
2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol (Example 434)

Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.19 mmol, 32 mg) and (4aS,8aR)-4-(6-chloro-4-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.096 mmol, 27 mg) in 1 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (0.29 mmol, 143 µl) and tetrakis(triphenylphosphine)palladium(0) (0.01 mmol, 11 mg). The solution was stirred at 90°C for 4h. After cooling down, the mixture was diluted with 20 ml of DCM and 5 ml of a saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with 5 ml of DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2) to give the title compound as a white solid (23 mg, 65% yield).

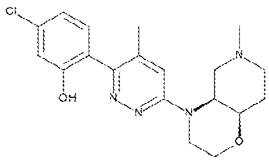
Compounds Examples 439 was synthesized analogously to Example 434.

Example 430: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol



Under Ar, to a solution of [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (1.36 mmol, 281 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 373.3** – 0.76 mmol, 214 mg) in 8 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (2.04 mmol, 1.02 ml) and tetrakis(triphenylphosphine)palladium(0) (0.038 mmol, 44 mg). The mixture was stirred at 100°C for 2h. After cooling down, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give a solid that was triturated in 2 ml of acetonitrile to give the title compound as a white solid (60 mg, 19% yield).

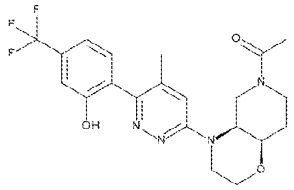
Example 379: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol



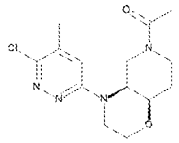
Under Ar, to a solution of 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.53 mmol, 135 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-

3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 373.3** – 0.35 mmol, 100 mg) in 8 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (0.91 mmol, 455 µl). tetrakis(triphenylphosphine)palladium(0) (0.018 mmol, 20 mg) was then added and the mixture was stirred at 100°C for 1 h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2), then repurified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (25 mg, 19% yield).

Example 363: 1-[(4aS,8aR)-4-[6-[2-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone



Int 363.1: **1-[(4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone**



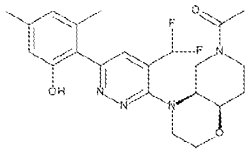
To a solution of (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 373.2** – 0.89 mmol, 240 mg), DMAP (0.045 mmol, 5.5 mg) and triethylamine (0.89 mmol, 120 µl) in 10 ml of DCM was added acetic anhydride (1.34 mmol, 126 µl). The mixture was stirred for 24 h at rt. The mixture was then diluted with 50 ml of DCM. The organic layer was washed with 50 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound as a yellow solid (269g, 97% yield).
LCMS (**Method V**): Rt = 0.64; MS m/z $[M+H]^+$ = 311

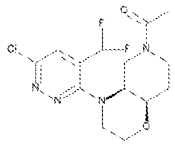
1-[(4aS,8aR)-4-[6-[2-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethenone (Example 363)
Under Ar, to a solution of [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (1.29 mmol, 265 mg) and 1-[(4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (0.64 mmol, 200 mg) in 8 ml of 1,4-dioxane was successively added a 2N sodium carbonate aqueous solution (1.74 mmol, 869 µl) and tetrakis(triphenylphosphine)palladium(0) (0.032 mmol, 37 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 80/9.8/9.8/0.4) to give the title compound as a white solid (59 mg, 21% yield).

Compounds Example 357 and 431 were synthetized analogously to Example 363

Example 405: 1-[(4aS,8aR)-4-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone



Int 405.1: **1-[(4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone**

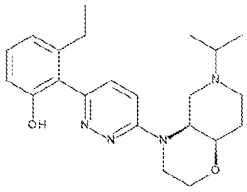


Following procedure of **Int 386.1**, (4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 291.2** – 1.31 mmol, 400 mg) gave (1-[(4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (410 mg, 90% yield) as a yellow oil.
LCMS (**Method V**): Rt = 0.79; MS m/z $[M+H]^+$ = 347

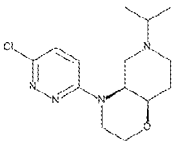
1-[(4aS,8aR)-4-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethenone (Example 405)

Following procedure of **Example 291**, 1-[(4aS,8aR)-4-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (0.63 mmol, 220 mg) gave 1-[(4aS,8aR)-4-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone (225 mg, 82% yield) as a yellow oil.

Example 432: 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol



Int 432.1: **(4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine**



To a solution of (4aS,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 321.2** – 1.69 mmol, 430 mg) in 20 ml of

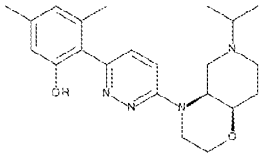
dichloromethane were added successively 1.45 ml of acetic acid, acetone (8.44 mmol, 625 µl) and sodium triacetoxyborohydride (3.04 mmol, 644 mg) portionwise. The mixture was stirred at rt for 18h, heated to 40°C for 2h then diluted with 100 ml of dichloromethane and 100 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 4x100 ml of a mixture DCM/isopropanol: 90/10 and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was solubilized in 20 ml of dichloromethane and then were added again 1.5 ml of acetic acid, acetone (8.44 mmol, 625 µl) and sodium triacetoxyborohydride (3.04 mmol, 644 mg) portion wise. The mixture was stirred at rt for 18h. Acetone (6.75 mmol, 500 µL) and sodium triacetoxyborohydride (1.69 mmol, 358 mg) were added and the mixture was stirred at rt for 3h, then diluted with 100 ml of dichloromethane and 100 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give the title compound as a yellow oil (425 mg, 85% yield).

LCMS (**Method V**): Rt = 0.58; MS m/z $[M+H]^+$ = 297

2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl] pyridazin-3-yl]-3-ethyl-phenol (Example 432)

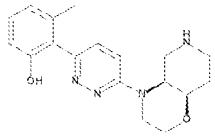
Under Ar, to a solution of (2-ethyl-6-hydroxy-phenyl)boronic acid (**Int 358.2** - 1.27 mmol, 211 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.71 mmol, 210 mg) in 8 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.91 mmol, 955 µl) and tetrakis(triphenylphosphine)palladium(0) (0.035 mmol, 41 mg). The mixture was stirred at 100°C for 2h. After cooling down, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 95/2.5/2.5) to give the title compound as a white solid (63 mg, 23% yield).

Example 433: 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



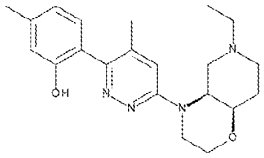
Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.27 mmol, 211 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 432.1** - 0.71 mmol, 210 mg) in 8 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.91 mmol, 955 µl) and tetrakis(triphenylphosphine)palladium(0) (0.035 mmol, 41 mg). The mixture was stirred at 100°C for 2h. After cooling down, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 95/2.5/2.5) to give the title compound as a white solid (135 mg, 50% yield).

Example 411: 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol

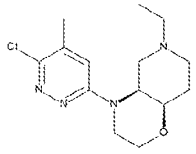


Following procedures of **Int 322.1** and **Example 322,** tert-butyl (4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 321.1** – 0.42 mmol, 150 mg) gave 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol (410 mg, 45% yield) as a white solid.

Example 435: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol



Int 435.1: (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine



Under argon, to a solution of (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 373.2** – 1.21 mmol, 324 mg) in 10 ml of DCM were successively added 1.03 ml of acetic acid, acetaldehyde (6.03 mmol, 337 µl) and sodium triacetoxyborohydride (2.17 mmol, 460 mg). The mixture was stirred at rt for 18h then diluted with 20 ml of dichloromethane and 20 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 3x50 ml of DCM and 2x50 ml of a mixture of DCM/isopropanol: 90/10. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a yellow foam (300 mg, 84% yield).

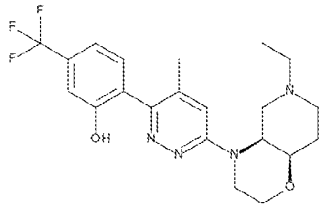
LCMS (**Method V**): Rt = 0.35; $[M+H]^+$ = 297

2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol (Example 435)

Under Ar, to a solution of 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.51 mmol, 118 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.34 mmol, 100 mg) in 4 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (0.91 mmol, 455 µl) and tetrakis(triphenylphosphine)palladium(0) (0.017 mmol, 19 mg). The mixture was stirred at 100°C for 1h. After cooling down, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over

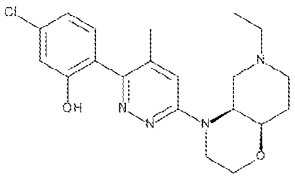
Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) to give the title compound as a white solid (62 mg, 50% yield).

Example 436: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol



Under Ar, to a solution of [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (0.51 mmol, 104 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 435.1** - 0.34 mmol, 100 mg) in 4 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (0.91 mmol, 455 µl) and tetrakis(triphenylphosphine)palladium(0) (0.017 mmol, 19 mg). The mixture was stirred at 100°C for 1 h. After cooling down, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) to give the title compound as a white solid (43 mg, 30% yield).

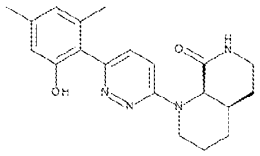
Example 437: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol



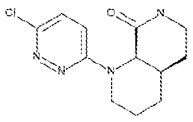
Under Ar, to a solution of (4-chloro-2-hydroxy-phenyl)boronic acid (0.51 mmol, 87 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido [4,3-b][1,4]oxazine (**Int 435.1** - 0.34 mmol, 100 mg) in 4 ml of 1,4-dioxane were

added a 2N sodium carbonate aqueous solution (0.91 mmol, 455 µl) and tetrakis(triphenylphosphine)palladium(0) (0.017 mmol, 19 mg). The mixture was stirred at 100°C for 1h. After cooling down, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) and the obtained solid was triturated in 2 ml of acetonitrile to give the title compound as a white solid (15 mg, 11% yield).

Example 300: rac-(4aR,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridin-8-one



Int 300.1: rac-(4aR,8aR)-1-(6-chloropyridazin-3-yl)-2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridin-8-one



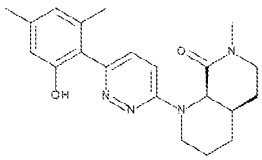
A solution of 2,3,4,4a,5,6,7,8a-octahydro-1H-1,7-naphthyridin-8-one (5.19 mmol, 800 mg), 3,6-dichloropyridazine (6.22 mmol, 927 mg) and triethylamine (72.6 mmol, 10.1 ml) in 30 ml of 1-butanol was stirred at reflux for 6h, then for 1h while removing 1-butanol and triethylamine under a stream of argon. The neat mixture was cooled down to 50°C. Another 4.5 ml of triethylamine and 20 ml of 1-butanol were added, and the mixture was stirred at 160°C for another 2h while removing 1-butanol and triethylamine under a stream of argon. The operation was re-iterated twice. The neat mixture was cooled down to rt and triturated with 20 ml of DCM and filtered. The cake was rinsed with 10 ml of DCM and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of cyclohexane/EtOAc/MeOH (from 100/0/0 to 0/85/15) to give the title compound (414 mg, 30% yield) as a beige solid.

LCMS (**Method V**): Rt = 0.50; MS m/z $[M+H]^+$ = 267

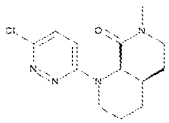
rac-(4aR,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridin-8-one (Example 300)

Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.5 mmol, 249 mg) and rac-(4aR,8aR)-1-(6-chloropyridazin-3-yl)-2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridin-8-one (0.75 mmol, 200 mg) in 10 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (2.02 mmol, 1 ml) and tetrakis(triphenylphosphine)palladium(0) (0.037 mmol, 43 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in DCM to give, after trituration in diethylether, the title compound as a yellow solid (43 mg, 16% yield).

Example 290: rac-(4aR,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridin-8-one



Int 290.1: rac-(4aR,8aR)-1-(6-chloropyridazin-3-yl)-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridin-8-one



Under argon, at 0°C, to a solution of rac-(4aR,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,6,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-5-one (**Int 300.1** – 0.80 mmol, 214 mg) in 6 ml of anhydrous N,N-dimethylformamide was added a 60% oil dispersion of sodium hydride (1.2 mmol, 48 mg) and the mixture was stirred at rt for 2h. Iodomethane (0.88 mmol, 55 µl) was added and the mixture was stirred for 2h at rt then diluted with 50

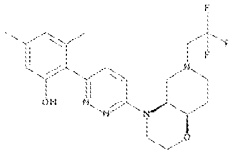
ml of EtOAc, 50 ml of diethylether and 50 ml of water. The organic layer was washed with 2x30 ml of water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in DCM to give the title compound as a yellow oil (225 mg, 100% yield).

LCMS (**Method V**): Rt = 0.57; MS m/z $[M+H]^+$ = 281

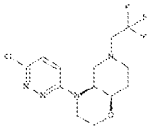
rac-(4aR,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridin-8-one (Example 290)

Following procedure of **Example 300**, rac-(4aR,8aR)-1-(6-chloropyridazin-3-yl)-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridin-8-one (0.8 mmol, 225 mg) gave the title compound as a white solid (59 mg, 20% yield).

Example 355: 2-[6-[(4aS,8aR)-6-(2,2,2-trifluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 355.1: **(4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-(2,2,2-trifluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine**



Under argon, at 0°C, to a solution of 1-[(4aS,8aR)-4-(6-chloropyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]-2,2,2-trifluoro-ethanone (**Int 347.1** – 1.43 mmol, 500 mg) in 20 ml of anhydrous THF was added dropwise a 1N borane tetrahydrofurane complex THF solution (2.85 mmol, 2.85 ml). The mixture was stirred for 4h at reflux then cooled down to rt. 1.43 ml (1.43 mmol) of 1N borane tetrahydrofurane complex THF solution was then added, and the mixture was stirred for another 4 h at reflux, cooled down to rt and quenched with 10 ml of a 4N HCl dioxane solution under stirring for 1h. The mixture was then diluted with 100 ml of diethylether and 200 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 2x100 ml of

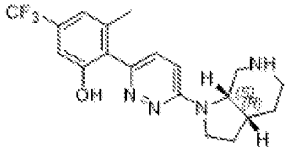
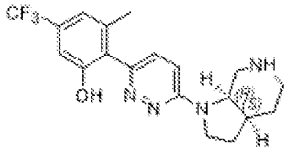
diethylether and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound as a yellow oil (187 mg, 38% yield).

LCMS (**Method V**): Rt = 0.97; MS m/z $[M+H]^+$ = 337

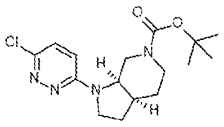
2-[6-[(4aS,8aR)-6-(2,2,2-trifluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 355)

Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.83 mmol, 138 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-(2,2,2-trifluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.56 mmol, 187 mg) in 8 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.5 mmol, 750 µl) and tetrakis(triphenylphosphine)palladium(0) (0.028 mmol, 32 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) then repurified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N/ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (18 mg, 8% yield).

Example 393 and Example 407: 2-[6-[(3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(3aS,7aR)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

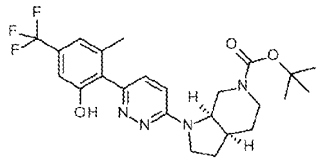
Int 393.1: tert-butyl (3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate



In a microwave vial, a mixture tert-butyl 1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (900 mg, 3.98 mmol), 3,6-dichloropyridazine (592 mg, 3.98 m mol) and K_3PO_4 (1.69 g, 7.95 mmol) in 13 ml of DMSO was heated at 80°C for 2h under microwave irradiations. After cooling down to rt, the mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound (776 mg, 57% yield).

LCMS (**Method S**): Rt = 1.22; MS m/z [M+H]+ = 339

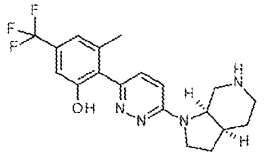
Int 393.2: tert-butyl (3aR,7aR)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate



In a sealed tube, a mixture of tert-butyl 1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (100 mg, 0.295 mmol), K_2CO_3 (81.6 mg, 0.590 mmol) and 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) phenol (0.134 g, 0.000443 mol) in 2 ml of 1,4-dioxane and 0.5 ml of water was purged with N_2. XPhos Pd G2 (11.6 mg, 0.0148 mmol) and XPhos (7.03 mg, 0.0148 mmol) were added, the mixture was purged again with N_2 then heated at 90°C for 3h. After cooling down to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound (90.8 mg, 64% yield).

LCMS (**Method R**): Rt = 1.50; MS m/z [M+H]+ = 479.5

Int 393.3: 2-[6-[rac-(3aS,7aR)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



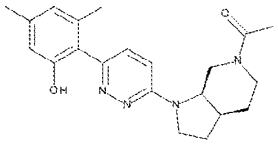
In a round bottom flask, a stirred solution of tert-butyl (3aR,7aR)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (81.0 mg, 0.169 mmol) in 2 ml of 1,4-dioxane was cooled down to 0 °C. Then HCl (4 M in dioxane) (4.00 mol/L, 0.212 mL, 0.846 mmol) was added dropwise to the mixture. The mixture was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure. The residue was triturated in a mixture of DIPE/ACN. The precipitate was filtered off and dried under reduced pressure. This residue was solubilized in MeOH, then concentrated under reduced pressure before being triturated in diethyl ether. The precipitate was filtered off and dried under reduced pressure. This precipitate was purified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 50/50 to 70/30) to afford a white solid. The solid was then purified by preparative achiral SFC (Stationary phase: Viridis 2-EP 20x250 mm, Mobile phase: CO_2/(MeOH + 0,3%iPrNH_2) 85/15) to give 32 mg of a greyish oil (46 %). The oil was triturated in DIPE. The precipitate was filtered and dried under reduced pressure to give a grey solid. This solid was purified by normal phase preparative LC (regular SiOH, 50 µm, 4 g biotage, dry loading (celite®), mobile phase gradient: from DCM/(MeOH/NH_4OH(10 %)) 100/0 to 75/25 over 20 CV) to give the title compound as a white solid (23.9 mg, 34 %).
LCMS (**Method E**): Rt = 2.47; [M+H]+ = 379.5

2-[6-[(3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol and 2-[6-[(3aS,7aR)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl) phenol (Example 393 and Example 407)

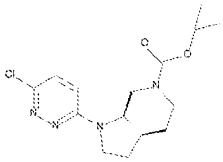
2-[6-[rac-(3aS,7aR)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (23.9 mg, 0.0576 mmol) was purified by preparative chiral SFC (Stationary phase: Chiralpak® IC 20x250 mm, Mobile phase: CO_2/(MeOH + 0,3%iPrNH_2) 50/50). The fractions containing each enantiomer were separately combined

and concentrated under reduced pressure to give a first fraction (14 mg, 22 %) as a colorless oil and a second fraction (10 mg, 16 %) as a colourless oil. The first fraction was taken-up with MeCN (1 mL), extended with water (3 mL) then lyophilized overnight to give 14 mg (22%) of a first enantiomer as a white solid. The second fraction was purified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 25/75 to 65/35) to give, after lyophilization, 6 mg (9%) of a second enantiomer as a white solid. The absolute configurations cannot be assigned at this stage.

Example 394: 1-[rac-(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone



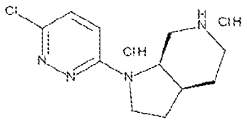
Int 394.1: tert-butyl rac-(3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate



Under Ar, a solution of tert-butyl 1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (19 mmol, 4.2 g - as a mixture of *cis* and *trans* racemates), 3,6-dichloropyridazine (28 mmol, 4.1 g) and N,N-diisopropylethylamine (74 mmol, 13 ml) in 30 ml of 1-butanol was stirred at reflux for 8h. The mixture was cooled down to rt, then diluted with 100 ml of EtOAc and 100 ml of diethylether and filtered. The cake was rinsed with 50 ml of diethylether and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of EtOAc in cyclohexane to give the title compound (2.77 g, 43% yield) as a white foam.

LCMS (**Method V**): Rt = 0.77; MS m/z $[M+H]^+$ = 339

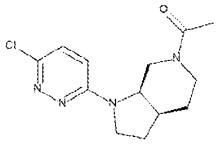
Int 394.2: rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo [2,3-c]pyridine;dihydrochloride



To a solution of tert-butyl rac-(3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (5.9 mmol, 2g) in 20 ml of dichloromethane and 10 ml of MeOH was added 14.8 ml of a 4N hydrochloric acid solution in 1,4-dioxane and the mixture was stirred at rt for 18 h then concentrated under reduced pressure. The residue was triturated in 50 ml of diethylether, filtered off, and the cake rinsed with 50 ml of diethylether, dried under reduced pressure to give the title compound (1.86 g, 100% yield) as a light brown solid.

LCMS (**Method L**): Rt = 0.39; MS m/z $[M+H]^+$ = 239

Int 394.3: 1-[rac-(3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone



Under Ar, to a suspension of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine:dihydrochloride (2.89 mmol, 903 mg) in 30 ml of DCM were added DIPEA (8.96 mmol, 1.24 ml), acetic anhydride (4.34 mmol, 907 µl) and DMAP (0.14 mmol, 18 mg). The mixture was stirred at rt for 18h then diluted with 100 ml of dichloromethane and washed with 100 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (680 mg, 84% yield) as a yellow solid.

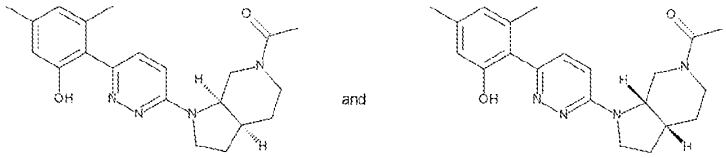
LCMS (**Method V**): Rt = 0.64; MS m/z $[M+H]^+$ = 281

1-[rac-(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone (Example 394)

Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (2.42 mmol, 402 mg) and 1-[rac-(3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-6-yl]ethanone (1.21 mmol, 340 mg) in 15 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (3.27 mmol, 1.63 ml) then tetrakis(triphenylphosphine) palladium(0) (0.061 mmol, 70 mg). The mixture was stirred at 100°C for 2h. After cooling down, the mixture was diluted with 100 ml of EtOAc and 100 ml of diethylether. The organic layer was washed successively with 2x100 ml of a saturated aqueous sodium bicarbonate solution and 105 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) to give the title compound as a yellow solid (85 mg, 19% yield).

Compound Example 395 was synthetized analogously to Example 394

Example 413 and 414: 1-[(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone and 1-[(3aS,7aS)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo [2,3-c] pyridin-6-yl]ethanone

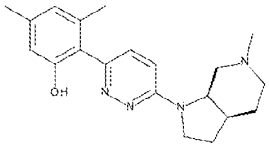


Both enantiomers of 1-[rac-(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone (**Example 394** - 71 mg) were separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD, 300×50 mm I.D., 20 µm particle size; Mobile phase: CO_2/Methanol (+0.1% Triethylamine) 40%; flow rate: 220 mL/min; outlet pressure: 100 bar; 3 injections; UV detection: 265 nm) to provide 1-[(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone, first enantiomer eluting at Rt = 7.47 min (27 mg, **Example 413**, Enantiomer 1), as a white solid, and 1-[(3aS,7aS)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl] ethanone, second enantiomer

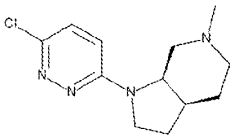
eluting at Rt = 12.06 min (26 mg, **Example 414**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Compounds Examples 369 and 370 were separated analogously to Examples 413 and 414 using a chiral column Daicel Chiralpak® AS.

Example 342: 3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



Int 342.1: **rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine**



To a suspension of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;dihydrochloride (**Int 394.2** – 1.93 mmol, 600 mg) in 20 ml of dichloromethane were added successively triethylamine (4.81 mmol, 691 µl), a 37% weight formaldehyde aqueous solution (4.81 mmol, 376 µl) and sodium triacetoxyborohydride (7.7 mmol, 1.63 g) portion wise. The mixture was stirred at rt for 8 h then diluted with 100 ml of dichloromethane and 100 ml of a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in DCM to give the title compound as a beige solid (449 mg, 92% yield).

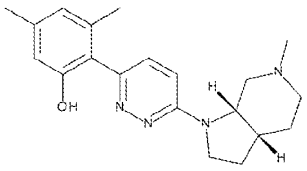
LCMS (**Method L**): Rt = 0.42; MS m/z $[M+H]^+$ = 253

3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (Example 342)

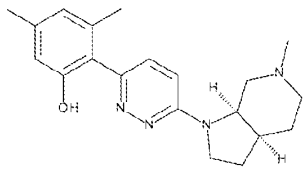
Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.87 mmol, 144 mg) and rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.44 mmol, 110 mg) in 4 ml of 1,4-dioxane and 800 µl of water, was added cesium carbonate (1.31 mmol, 425 mg). The mixture was degased by argon bubbling for 5 min then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0) (0.044 mmol, 32 mg) was added and the mixture was stirred at 90°C for 4h. After cooling down, the mixture was diluted with 50 ml of DCM and the organic layer was washed with 50 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 20 ml of DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 80/9.8/9.8/0.4) to give the title compound as a brown solid (100 mg, 68% yield).

Compound Examples 364, 371 and 378 were synthesized analogously to Example 342

Example 383 and 384: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



and

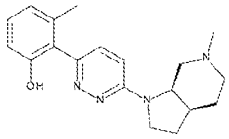


Both enantiomers of 3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (**Example 342** - 160 mg) were separated by chiral preparative HPLC (Column: Daicel Chiralpak® AY, 230×100 mm I.D., 20 µm particle size; Mobile phase: Heptane/Ethanol (+0.1% Triethylamine) 20%; flow rate: 400 mL/min; 1 injection; UV detection: 265 nm) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, first enantiomer eluting at Rt = 12.9 min (62 mg, **Example 383**, Enantiomer 1), as a white solid, and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, second enantiomer eluting at Rt = 18.8

min (61 mg, **Example 384**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

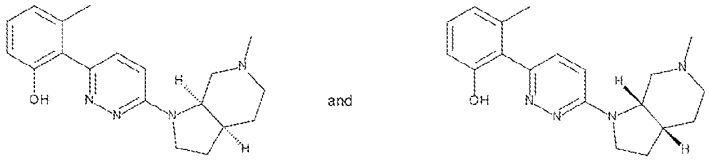
Compounds Examples 391; 392 and 406; 429 were synthesized separated to Example 383/384 using a chiral column Daicel Chiralpak® AD.

Example 385: 3-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



Under Ar, to a solution of (2-hydroxy-6-methyl-phenyl)boronic acid (**Int 354.1** - 0.65 mmol, 98 mg) and rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 342.1** - 0.40 mmol, 102 mg) in 4 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.09 mmol, 545 µl) and TETRAKIS(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg). The mixture was stirred at 100°C for 3h30 then cooled down to rt and diluted with 50 ml of EtOAc. The organic layer was washed with 20 ml of water and the aqueous layer extracted with 20 ml of EtOAc. The combined organic layers were washed with 10 ml of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2) to give the title compound as a white solid (70 mg, 53% yield).

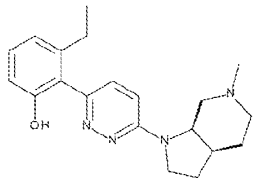
Examples 415 and 416: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol



Both enantiomers of 3-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (**Example 385** - 65 mg) were separated by

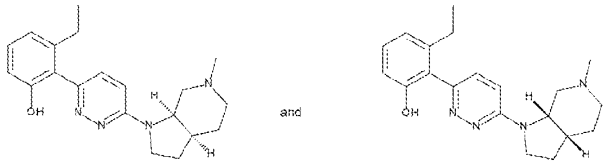
Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AY-H, 350x30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 40%; flow rate: 120 mL/min; outlet pressure: 100 bar; 3 injections; UV detection : 265 nm) to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl] pyridazin-3-yl]-3-methyl-phenol, first enantiomer eluting at Rt = 3.17 min (23 mg, **Example 415**, Enantiomer 1), as a white solid, and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol, second enantiomer eluting at Rt = 4.79 min (22 mg, **Example 415**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 388: 3-ethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



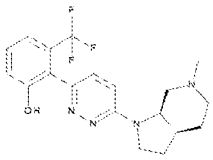
Under Ar, to a solution of (2-ethyl-6-hydroxy-phenyl)boronic acid (**Int 358.2** - 0.66 mmol, 109 mg) and rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 342.1** - 0.41 mmol, 104 mg) in 4 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.11 mmol, 555 µl) and tetrakis(triphenylphosphine)palladium(0) (0.021 mmol, 24 mg). The mixture was stirred at 100°C for 3h30 then cooled down to rt and diluted with 50 ml of EtOAc. The organic layer was washed with 20 ml of water and the aqueous layer extracted with 20 ml of EtOAc. The combined organic layers were washed with 10 ml of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2) to give the title compound as a white solid (81 mg, 58% yield).

Examples 422 and 423: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol



Both enantiomers of 3-ethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (**Example 388** - 75 mg)) were separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AY-H, 350×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 40%; flow rate: 120 mL/min; outlet pressure: 100 bar; 3 injections; UV detection: 265 nm) to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol, first enantiomer eluting at Rt = 2.64 min (29 mg, **Example 422**, Enantiomer 1), as a white solid, and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol, second enantiomer eluting at Rt = 4.50 min (31 mg, **Example 423**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

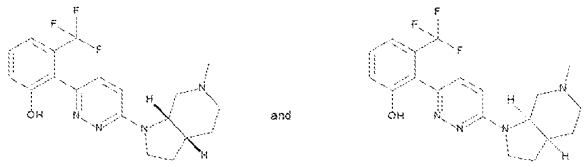
Example 389: 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol



Under Ar, to a solution of [2-hydroxy-6-(trifluoromethyl)phenyl]boronic acid (0.63 mmol, 130 mg) and rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 342.1** - 0.40 mmol, 100 mg) in 4 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.07 mmol, 534 µl) and tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg). The mixture was stirred at 100°C for 3h then cooled down to rt and diluted with 50 ml of EtOAc. The organic layer was washed with 20 ml of water and the aqueous layer extracted with 20 ml of EtOAc. The combined organic layers were washed with 10 ml of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on

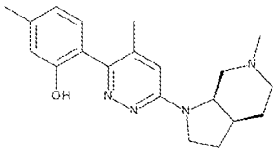
silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 90/4.9/4.9/0.2) to give the title compound as a white solid (119 mg, 79% yield).

Example 426 and 427: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl) phenol

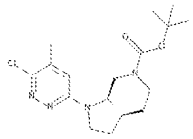


Both enantiomers of 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol (**Example 389** - 112 mg) were separated by chiral preparative HPLC (Column: LUX AMYLOSE-1, 250×30 mm I.D., 5 µm particle size; Mobile phase: Heptane/Ethanol (+0.1% Triethylamine) 30%; flow rate: 45 mL/min; 5 injection; UV detection: 265 nm) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl) phenol, first enantiomer eluting at Rt = 6.2 min (40 mg, **Example 426**, Enantiomer 1), as a white solid, and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol, second enantiomer eluting at Rt = 12.3 min (38 mg, **Example 427**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 341: 5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



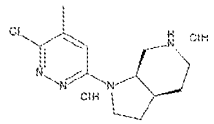
Int 341.1: tert-butyl rac-(3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate



Under Ar, a solution of tert-butyl 1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (12.27 mmol, 2.78 g - as a mixture of *cis* and *trans* racemates), 3,6-dichloro-4-methyl-pyridazine (12.27 mmol, 2 g) and N,N-diisopropylethylamine (49.1 mmol, 8.55 ml) in 20 ml of 1-butanol was stirred at reflux for 25h. The mixture was cooled down to rt, concentrated under reduced pressure and the residue solubilized in 200 ml of EtOAc. The organic layer was washed with 2x50 ml of water then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of cyclohexane/EtOAc/MeOH (from 100/0/0 to 0/98/2) to give the title compound as a brown solid (1.14 g, 26% yield).

LCMS (**Method L**): Rt = 0.76; MS m/z $[M+H]^+$ = 353

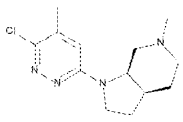
Int 341.2: rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;dihydrochloride



Following procedure of **Int 394.2**, tert-butyl rac-(3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (3.22 mmol, 1.14 g) gave the title compound (1.05 g, 100% yield) as a colourless oil.

LCMS (**Method L**): Rt = 0.40; MS m/z $[M+H]^+$ = 253

Int 341.3: rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



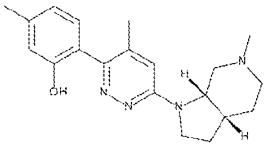
Following procedure of **Int 342.1**, rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;dihydrochloride (3.22 mmol, 1.05 g) gave the title compound (820 mg, 95% yield) as a colourless oil.

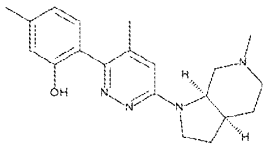
LCMS (**Method V**): Rt = 0.65; MS m/z $[M+H]^+$ = 267

5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo [2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (Example 341)

Under Ar, to a solution of (2-hydroxy-4-methyl-phenyl)boronic acid (1.41 mmol, 214 mg) and rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.94 mmol, 250 mg) in 6 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (2.53 mmol, 1.27 ml) and Tetrakis(triphenylphosphine)palladium(0) (0.047 mmol, 54 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 100 ml of EtOAc and 100 ml of diethylether, and the organic layer was washed successively with 2x50 ml of a saturated aqueous sodium bicarbonate solution and 50 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (203 mg, 64% yield).

Example 374 and 375: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol

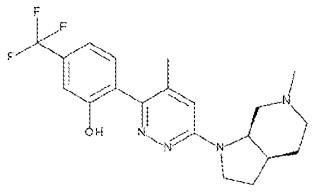


and


Both enantiomers of 5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (**Example 341** - 193 mg) were separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AY, 250×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine)

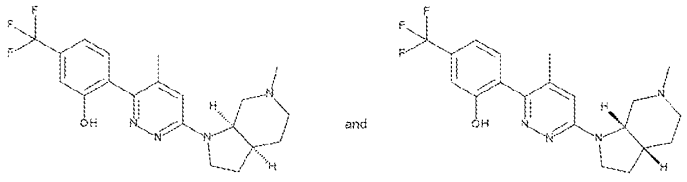
30%; flow rate: 120 mL/min; outlet pressure: 100 bar; 40 injections; UV detection : 265 nm) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol, first enantiomer eluting at Rt = 4.9 min (70 mg, **Example 374**, Enantiomer 1), as a white solid, and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol, second enantiomer eluting at Rt = 6.7 min (77 mg, **Example 375**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 340: 2-[4-methyl-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol



Following procedure of **Example 341**, rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 341.3** – 0.94 mmol, 250 mg) gave the title compound (101 mg, 27% yield) as a white solid.

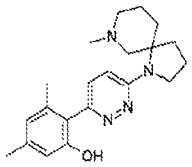
Example 366 and 367: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol



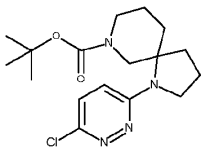
Both enantiomers of 2-[4-methyl-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (**Example 340** - 86 mg) were separated by Supercritical Fluidic Chromatography (SFC - Column: Daicel Chiralpak® AD-H, 250×30 mm I.D., 5 µm particle size; Mobile phase: CO_2/Ethanol (+0.1% Triethylamine) 30%; flow rate: 120 mL/min; outlet pressure: 100 bar; 10 injections; UV

detection: 265 nm) to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol, first enantiomer eluting at Rt = 2.20 min (32 mg, **Example 366**, Enantiomer 1), as a white solid, and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol, second enantiomer eluting at Rt = 2.88 min (36 mg, **Example 367**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 428: 3,5-dimethyl-2-[6-(9-methyl-1,9-diazaspiro[4.5]decan-1-yl)pyridazin-3-yl]phenol



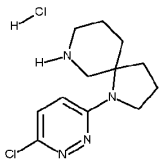
Int 428.1: tert-butyl 1-(6-chloropyridazin-3-yl)-1,9-diazaspiro[4.5]decane-9-carboxylate



In a microwave vial, under Ar, to a solution of 3,6-dichloropyridazine (1.530 mmol, 240 mg) in 10 ml of 1-butanol was added tert-butyl 1,7-diazaspiro[4.5]decane-7-carboxylate (1.530 mmol, 379 mg) and DIPEA (3.36 mmol, 0.592 mL). The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 3h. After cooling down to rt, the mixture was concentrated under reduced pressure to give a mixture of the title compound and 1-(6-chloropyridazin-3-yl)-1,9-diazaspiro[4.5]decane, as an oil (529 mg), which was used in the next step without further purification.

LCMS (**Method H**): Rt = 1.09; MS m/z [M+H]+ = 353

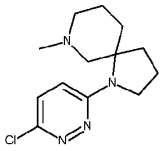
Int 428.2: 1-(6-chloropyridazin-3-yl)-1,9-diazaspiro[4.5]decane;hydrochloride



To a solution of tert-butyl 1-(6-chloropyridazin-3-yl)-1,9-diazaspiro[4.5]decane-9-carboxylate (1.53 mmol, 540 mg) in 3 ml of dichloromethane was added hydrochloric acid (4M/dioxane) (7.65 mmol, 1.91 mL). The mixture was stirred for 2h30 at rt. The mixture was concentrated under reduced pressure, taken up in methanol (3x2 mL), and concentrated under reduced pressure to dryness to give the titled product as a solid (554 mg), which was used without further purification in the next step.

LCMS (**Method H**): Rt = 0.29; MS m/z [M+H]+ = 253

Int 428.3: 1-(6-chloropyridazin-3-yl)-9-methyl-1,9-diazaspiro[4.5]decane



To a solution of 1-(6-chloropyridazin-3-yl)-1,9-diazaspiro[4.5]decane (0;474 mmol, 120 mg) in 2 ml of methanol was added acetic acid (1.9 mmol, 0.113 mL) and formaldehyde 37wt. % in water (0.588 mmol, 0.055 mL). The mixture was stirred for 20 min at rt. Sodium cyanoborohydride (0.946 mmol, 74.6 mg) was added and the mixture was stirred for 4h at rt. Dichloromethane was added, then NaOH 1N until pH 10. The aqueous layer was extracted with AcOEt (3 times), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the titled compound as a solid (181 mg, 100% yield).

LCMS (**Method L**): Rt = 0.29; [M+H]+ = 267

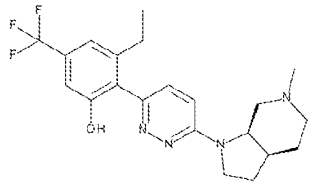
3,5-dimethyl-2-[6-(9-methyl-1,9-diazaspiro[4.5]decan-1-yl)pyridazin-3-yl]phenol (Example 428)

In a microwave vial, under Ar, to a solution of (2-hydroxy-4,6-dimethylphenyl)boronic acid (0.618 mmol, 108 mg) and 1-(6-chloropyridazin-3-yl)-9-methyl-1,9-diazaspiro[4.5]decane (0.475 mmol, 127 mg) in 3 ml of dioxane were added sodium carbonate (1.43 mmol, 118

mg) and 0.74 ml of water. The solution was purged with Ar for 10 min, then $Pd(PPh_3)_4$ (23.8 µmol, 28 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling down to rt, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, then diluted with DCM and washed with water (3 times). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2), then suspended in dichloromethane (1 mL) and stirred 10 min at room temperature. The suspension was filtered off and dried under reduced pressure to give the title compound as a white solid (13,9 mg, 8% yield).

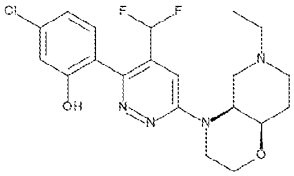
Compounds Examples 440, 441, 444, 445, 446, 449, 450, 451 and 455 were synthesized analogously to Example 428. Chiral separation of Examples 445/446 and 450/451 were realized using Chiralpak® OD-I column.

Example 452: 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol

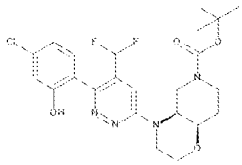


In a microwave vial under Ar, to a mixture of 3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (**Int 380.3** - 67.5 mg, 0.214 mmol), K_2CO_3 (49.2 mg, 0.356 mmol) and (3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 342.1** - 45.0 mg, 0.178 mmol) in 1 ml of 1,4-dioxane and 0.2 ml of water were added XPhos (4.24 mg, 0.00890 mmol) and XPhos Pd G2 (7.00 mg, 0.0890 mmol). The mixture was heated at 90 °C for 3h. After cooling down to rt, the mixture was filtrated over celite® and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/(MeOH/NH_4OH (10%)) from 100/0 to 80/20). The residue obtained was purified by reverse preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 30/70 to 65/35), to give after lyophilization the title compound (6 mg, 8% yield).

Example 456: 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol

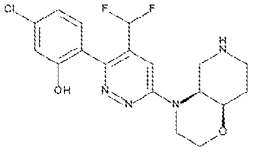


Int 456.1: **tert-butyl (4aS,8aR)-4-[6-(4-chloro-2-hydroxy-phenyl)-5-(difluoromethyl) pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate**



Under Ar, to a solution of (4-chloro-2-hydroxy-phenyl)boronic acid (1.11 mmol, 192 mg) and tert-butyl (4aS,8aR)-4-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 298.4** – 0.62 mmol, 250 mg) in 10 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.67 mmol, 834 µl), then tetrakis(triphenylphosphine)palladium(0) (0.031 mmol, 36 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 60% of EtOAc in cyclohexane to give the title compound (306 mg, 99% yield) as a yellow solid.
LCMS (**Method V**): Rt = 1.12; MS m/z $[M+H]^+$ = 497

Int 456.2: **2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol**



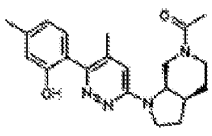
To a solution of tert-butyl (4aS,8aR)-4-[6-(4-chloro-2-hydroxy-phenyl)-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (0.616 mmol, 306 mg) in 9 ml of dichloromethane was added 1 ml of trifluoroacetic acid and the mixture was stirred for 2 h at rt, then concentrated under reduced pressure. The residue was diluted with 50 ml of dichloromethane and washed with 2x50 ml of a saturated aqueous sodium bicarbonate solution and 10 ml of water then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (244 mg, 100% yield) as a yellow solid.

LCMS (**Method V**): Rt = 0.53; MS m/z $[M+H]^+$ = 397

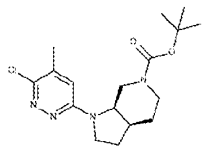
2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol (Example 456)

To a solution of 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol (0.61 mmol, 244 mg) and acetaldehyde (3.07 mmol, 135 mg) in 10 ml of DCM was added 0.528 ml of acetic acid and the mixture was stirred for 10 min at rt. Then was added sodium triacetoxyborohydride (1.11 mmol, 235 mg) and the mixture was stirred 18 h at rt. The reaction mixture was diluted with 50 ml of DCM and washed with 50 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 3X15 ml of dichloromethane and 2x15 ml of a mixture of dichloromethane/isopropanol: 90 / 10. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10), then repurified by prep-HPLC (column: Sunfire prep C18 OBD ; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (84 mg, 32% yield).

Example 457: 1-[(3aR,7aR)-1-[6-(2-hydroxy-4-methyl-phenyl)-5-methyl-pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone



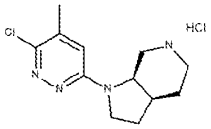
Int 457.1: **tert-butyl (3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate**



In a microwave vial, under Ar, a solution of 3,6-dichloro-4-methyl-pyridazine (3.82 mmol, 635 mg), tert-butyl (3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (2.94 mmol, 700 mg) and potassium phosphate tribasic (5.88 mmol, 1.25 g) in 20 ml of DMSO was heated at 100°C under microwave irradiation for 2.5h. After cooling down to rt, the reaction mixture was diluted with EtOAc and water. The organic layer was washed twice with water, with brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of heptane/EtOAc (60/40) to give the title compound as a white solid (237 mg, 23% yield).

LCMS (**Method L**): Rt = 0.94; MS m/z $[M+H]^+$ = 353

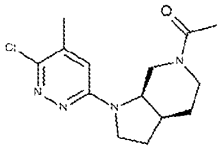
Int 457.2: (3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride



To a solution of tert-butyl (3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (0.67 mmol, 237 mg) in 5 ml of dichloromethane was added 1.68 ml of a 4N hydrochloric acid solution in 1,4-dioxane and the mixture was stirred at rt for 2h, then concentrated under reduced pressure to give the title compound (193 mg) as an orange solid, which was used without further purification in the next step.

LCMS (**Method L**): Rt = 0.29; [M+H]+ = 253

Int 457.3: **1-[(3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone**



Under Ar, to a suspension of (3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride (0.67 mmol, 193 mg) in 15 ml of DCM were added Et3N (2.0 mmol, 280 µl), acetic anhydride (1.0 mmol, 95 µl) and DMAP (33 µmol, 4.2 mg). The mixture was stirred at rt for 3h, then diluted with dichloromethane and washed with a saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (95/2.5/2.5) to give the title compound as a white solid (75 mg, 38% yield).

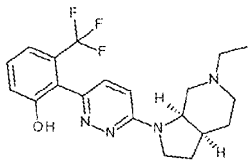
LCMS (**Method L**): Rt = 0.55; MS m/z [M+H]+ = 295

1-[(3aR,7aR)-1-[6-(2-hydroxy-4-methyl-phenyl)-5-methyl-pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone (Example 457)

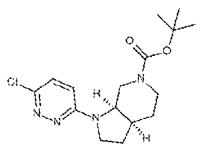
In a microwave vial, under Ar, to a solution of 1-[(3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone (0.122 mmol, 36 mg) and 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol (0.158 mmol, 38 mg) in 0.6 ml of 1,4-dioxane were added sodium carbonate (0.31 mmol, 33 mg) and 0.15 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (6.1 µmol, 7 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling down to rt, the reaction was concentrated under reduced pressure. To the residue was added DCM and the organic layer was washed successively with a saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (95/2.5/2.5) to give the title compound as a white solid (22 mg, 63% yield).

Compound Example 514 was synthetized analogously to Example 457.

Example 458: 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol



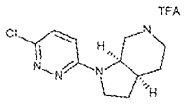
Int 458.1: tert-butyl (3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate



In a microwave vial, a mixture of tert-butyl (3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (900 mg, 3.98 mmol), 3,6-dichloropyridazine (592 mg, 3.98 mmol) and K_3PO_4 (1.69 g,7.95 mmol) in 13 ml of DMSO was heated at 80°C using one single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2h. After cooling down to rt, the reaction mixture was filtered, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH from 100/0 to 95/5, to give the title compound (776 mg, 57%).

LCMS (**Method S**) Rt = 1.22; MS m/z [M+H]+ = 339.2

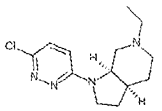
Int 458.2: (3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo [2,3-c]pyridine;2,2,2-trifluoroacetic acid



At 0°C, to a stirred solution of tert-butyl (3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (650 mg, 1.92 mmol) in 6 ml of dichloromethane was added TFA (1.42 mL, 19.2 mmol) and the reaction mixture was stirred at rt for 18h. The reaction mixture was concentrated under reduced pressure to give the title compound (1.20 g), which was used without further purification in the next step.

1H NMR (400 MHz, DMSO-d6) δ (ppm): 8.45 (m, 1H), 7.57 (d, J = 9.5 Hz, 1H), 7.05 (d, J = 9.5 Hz, 1H), 4.56 – 4.17 (m, 1H), 3.72 – 3.46 (m, 2H), 3.46 – 3.26 (m, 1H), 3.24 – 3.07 (m, 1H), 3.00 – 2.81 (m, 2H), 2.50 (m, 1H), 2.27 – 2.10 (m, 1H), 2.09 – 1.93 (m, 2H), 1.89 – 1.81 (m, 1H).

Int 458.3: (3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



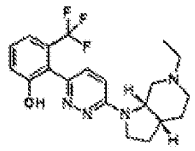
In sealed tube, to a stirred solution of (3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid (300 mg, 0.643 mmol) in 5 ml of ethanol were added acetaldehyde 5 M in THF (0.386 mL, 1.93 mmol), acetic acid (0.0368 mL, 0.643 mmol) and $NaBH_3CN$ (80.8 mg, 1.29 mmol). The reaction mixture was stirred at rt for 1h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using a gradient of DCM/(MeOH/NH_4OH (10%)) from 100% to 90/10, to give the title compound (135 mg, 80%).

LCMS (**Method R**): Rt = 0.92; MS m/z [M+H]+ = 267.3

2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol (Example 458)

Under Ar, in a microwave vial, to a mixture of [[2-hydroxy-6-(trifluoromethyl)phenyl]boronic acid (74.1 mg, 0.360 mmol), K_2CO_3 (82.9 mg, 00.600 mmol), (3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (80.0 mg, 0.300 mmol) in 2 ml of 1,4-dioxane and 0.5 ml of water were added XPhos (7.15 mg, 0.00150 mmol) and XPhos Pd G2 (11.8 mg, 0.00150 mmol). The mixture was purged again with Ar, then heated at 90°C for 3h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using a gradient of DCM/(MeOH/NH_4OH 90/10) 100/0 to 80/20, to give the title compound a white solid (80.8 mg, 68%).

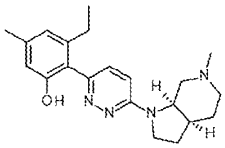
Example 473: 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol



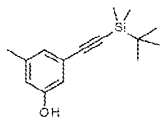
Both enantiomers of 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol (Example 458 - 70 mg) were separated by Supercritical Fluidic Chromatography (SFC - Chiralpak® IC-3 4.6x100 mm, Mobile phase: CO_2/(MeOH + 0,3% iPrNH2) 70/30)) to provide 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl) phenol, first enantiomer eluting at Rt = 1.53 min (18 mg, **Example 473**, Enantiomer 1), as a white solid, and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol, second enantiomer eluting at Rt = 2.05 min.

The absolute configurations cannot be assigned at this stage.

Example 459: 3-ethyl-5-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



Int 459.1: 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-5-methyl-phenol

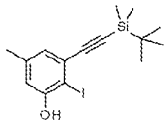


To a solution of 3-bromo-5-methyl-phenol (2.00 g, 0.0107 mol) and tert-butyl-ethynyl-dimethyl-silane (5.99 mL 0.0321 mol) in 20 ml of DMF was added 4.5 ml of NEt_3 (4.5 mL, 32 mmol). The mixture was purged with N_2, then $PdCl_2$(dppf) (873 mg, 1.07 mol) and CuI (204 mg, 1.07 mmol) were added. The mixture was purged again with N_2 and stirred at 80°C for 3h. After cooling down to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of

heptane/EtOAc (100/0 to 80/20, then isocratic 80/20) to give the title compound as a dark orange residue (1.73 g, 66%).

1H NMR (400 MHz, DMSO) δ (ppm): 9.55 (s, 1H), 6.73 – 6.67 (m, 1H), 6.63 – 6.61 (m, 1H), 6.61 – 6.58 (m, 1H), 2.19 (s, 3H), 0.95 (s, 9H), 0.14 (s, 6H).

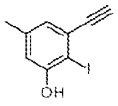
Int 459.2: 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-5-methyl-phenol



At 0°C, to a solution of 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-5-methyl-phenol (1.73 g, 0.00702 mol) in 70 ml of toluene) was added NaH (60% in mineral oil) (60.0 %, 0.562 g, 0.0140 mol). The mixture was stirred for 10 min, then I_2 (1.78 g, 0.00702 mol) was added. The reaction mixture was allowed to warm to rt and stirred for 18 h. The mixture was diluted with EtOAc, then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was separated and extracted again with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of heptane/EtOAc (100/0 to 80/20, then isocratic 80/20), then purified by preparative chiral SFC (Stationary phase: Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2/MeOH 90/10) to give the title compound as a yellow oil (173 mg, 7%).

1H NMR (400 MHz, DMSO) δ (ppm): 10.37 (s, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.56 (d, J = 1.9 Hz, 1H), 2.18 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

Int 459.3: 3-ethynyl-2-iodo-5-methyl-phenol

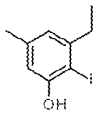


To a solution of 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-5-methyl-phenol (1.02 g, 0.00274 mol) in 27 ml of THF was added TBAF 1M in THF (4.11 mL, 0.00411 mol). The solution was stirred at rt for 5h. EtOAc and water were added. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel using a DCM to give the title compound as a pale pink oil which crystallized (0.585 g, 83 %).

1H NMR (400 MHz, DMSO) δ (ppm): 10.28 (s, 1H), 6.65 (d, J = 1.9 Hz, 1H), 6.52 (d, J = 1.9 Hz, 1H), 4.24 (s, 1H), 2.00 (s, 3H).

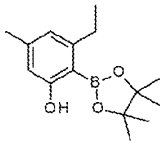
Int 459.4: 3-ethyl-2-iodo-5-methyl-phenol



To a solution of 3-ethynyl-2-iodo-5-methyl-phenol (0.585 g, 0.00227 mol) in 25 ml of methanol was added Pd/C 10% activated on wood carbon, unreduced, 50% water wet paste (5.00 %, 0.241 g, 0.000113 mol). The reaction was stirred under H_2 atmosphere (10 Bar) at rt for 5h. The reaction mixture was filtered on a pad of Celite®, and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of heptane/DCM (90/10 to 50/50) to give the title compound as a colorless oil (0.319 g, 54 %).

1H NMR (400 MHz, DMSO) δ (ppm): 9.91 (s, 1H), 6.40 (d, J = 1.9 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 2.45 (q, J = 7.5 Hz, 2H), 2.00 (s, 3H), 0.92 (t, J = 7.5 Hz, 3H).

Int 459.5: 3-ethyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



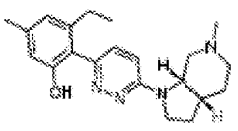
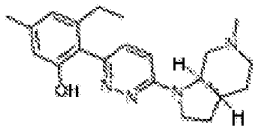
In a sealed tube, to a solution of 3-ethyl-2-iodo-5-methyl-phenol 2 (180 mg, 0.687 mol) and HBpin (0.50 mL, 3.44 mmol) in 8 ml of 1,4-dioxane was slowly added NEt_3 (0.670 mL, 4.81 mmol). After 1 min, the solution was purged with N_2. $Pd(OAc)_2$ (18.5 mg, 0.0824 mmol) and CyJohnPhos (53.0 mg, 0.151 mmol) were added. The mixture was purged again with N_2 then heated at 80°C for 18h. After cooling down to rt, water was added. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of heptane/EtOAc (100/0 to 90/10) to give the title compound (93.4 mg, 51%).

1H NMR (500 MHz, DMSO-d6) δ (ppm): 8.81 (s, 1H), 6.44 (s, 1H), 6.40 – 6.35 (m, 1H), 2.59 – 2.50 (m, 2H), 2.17 (s, 3H), 1.29 (s, 12H), 1.08 (t, J = 7.5 Hz, 3H)

3-ethyl-5-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo [2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (Example 459)

In a microwave vial, under N_2, to a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 342.1** - 100 mg, 0.396 mmol) and 3-ethyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (131 mg, 0.475 mmol) in 3 ml of 1,4-dioxane and 0.75 ml of water was added K_2CO_3 (109 mg, 0.000791 mol). The solution was degazed under N_2 flow. XPhos (9.43 mg, 1.98e-5 mol) and XPhos Pd G2 (15.6 mg, 1.98e-5 mol) were added. The reaction mixture was stirred at 90°C for 4h. After cooling down to rt, the mixture was filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient DCM/ (MeOH/NH_4OH: 90/10) 100/0 to 80/20 to give the title compound as a white solid (74 mg, 53%).

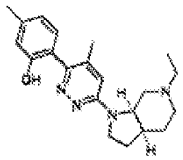
Examples 476 and 477: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol


and


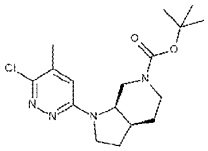
Both enantiomers of 3-ethyl-5-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (Example 459 - 74 mg)) were separated by Supercritical Fluidic Chromatography (SFC - Column: Chiralpak® AD-H 20x250 mm, Mobile phase: CO_2/(MeOH + 0,3%$iPrNH_2$) 70/30) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol, first enantiomer eluting at Rt = 1.29 min (38 mg, **Example 476**, Enantiomer 1), as a white solid after lyophilization, and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol, second enantiomer eluting at Rt = 1.92 min (33 mg, **Example 477**, Enantiomer 2),

as a white solid after lyophilization. The absolute configurations cannot be assigned at this stage.

Example 460: 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol



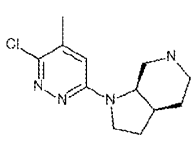
Int 460.1: tert-butyl rac-(3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate



In a microwave vial, a mixture of tert-butyl rac-(3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (1.00 g, 4.42 mmol), 3,6-dichloro-4-methyl-pyridazine (720 mg, 4.42 mmol) and DIPEA (1.51 mL, 8.84 mmol) in 14 ml of butan-1-ol was heated at 130°C for 10h. After cooling down to tr, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH from 100/0 to 95/5, then repurified by preparative achiral SFC (Stationary phase: Cyano 20x250 mm, Mobile phase: CO_2/MeOH 95/5) to give tert-butyl rac-(3aR,7aR)-1-(6-chloro-4-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridine-6-carboxylate as a pale-yellow solid (105 mg) and the title compound as a pale-yellow solid (433 mg, 28 %).

LCMS (**Method R**): Rt = 1.35; MS m/z [M+H]+ = 353.3

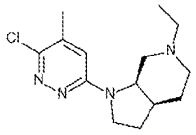
Int 460.2: rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2- trifluoroacetic acid



At 0 °C, to a stirred solution of tert-butyl rac-(3aR,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (433 mg, 0.00123 mol) in 7 ml of dichloromethane was added TFA (0.912 mL, 12.3 mmol). The reaction mixture was then stirred at rt for 18h. The reaction mixture was concentrated under reduced pressure to afford the title compound as a brown oil (1.04 g) which was used without further purification in next step.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 8.39 (s, 1H), 7.00 (s, 1H), 4.40 – 4.32 (m, 1H), 3.56 – 3.49 (m, 2H), 3.36 (q, J = 8.8 Hz, 1H), 3.19 – 3.11 (m, 1H), 3.09 – 3.01 (m, 1H), 2.99 – 2.90 (m, 1H), 2.58 – 2.52 (m, 1H), 2.28 (s, 3H), 2.22 – 2.11 (m, 1H), 2.09 – 1.93 (m, 2H), 1.89 – 1.81 (m, 1H), proton hidden under DMSO peak.

Int 460.3: rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



To a stirred solution of rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2- trifluoroacetic acid (520 mg, 1.08 mmol) in 12 ml of acetonitrile at rt were added K_2CO_3 (299 mg, 2.16 mmol) and iodoethane (0.0870 mL, 108 mmol). The reaction mixture was stirred at 50°C for 5h. After cooling down to rt, the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/(MeOH/NH4OH: 90/10) from 100/0 to 95/5, to give the title compound as a pale-yellow oil (123 mg, 35 %).

LCMS (**Method T**): Rt = 5.25; MS m/z [M+H]+ = 281.2

2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol (Example 460)

Under Ar, in a sealed tube, to a solution of rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (118 mg, 0.420 mmol), K_2CO_3 (174 mg, 1.26 mmol) and (2-hydroxy-4-methyl-phenyl)boronic acid (95.8 mg, 0.630 mmol) in 2 ml of 1,4-dioxane and 0.5 ml of water were added XPhos Pd G2 (16.5 mg, 0.0210

mmol) and XPhos (10.0 mg, 0.0210 mmol). The mixture was purged again with Ar, then heated at 90°C for 3.5h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/(MeOH/NH_4OH: 90/10) from 100/0 to 95/5, then repurified by reverse phase preparative LC (Column YMC –Actus Triart Prep C18-S 150*30mm 5µm Flow rate 50ml/min-Focused gradient MeCN-MeOH [50/50] /aq. NH_4HCO_3 0.2% pH=10 Focused gradient from 50/50 to 70/30 15CV) to give a pale yellow solid (56 mg, 38 %). 9 mg were lyophilized to give the title compound as a white solid (9 mg).

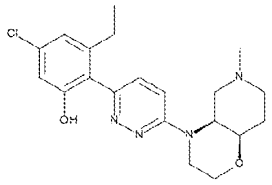
Example 468 and 469: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol

In a microwave vial, under Ar, to a suspension of 4-chloro-2-hydroxyphenylboronic acid (487 µmol, 87 mg) and rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (375 µmol, 100 mg) in 1,9 ml of 1,4-dioxane and 0.5 ml of water was added sodium carbonate (937 µmol, 99 mg). The solution was purged with Ar for 5 min, then $Pd(PPh_3)_4$ (19 µmol, 22 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling down to rt, the reacting mixture was concentrated under reduced pressure. The residue was taken up with CH_2Cl_2, the organic layer was washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/ACN/MeOH (90/5/5) + 1% NH_3 7N in MeOH, then repurified by SFC (Column: Column Lux Amylose-1 5µm, 250x30mm, Flow rate 45ml/min, eluent (Heptane/EtOH 80/20 +0.1% TEA) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol, first enantiomer eluting at Rt = 9.7 min (44 mg, **Example 468**, Enantiomer 1), as a white solid, and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol, second enantiomer eluting at Rt = 15.5 min (39 mg, **Example 469**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 474 and 475: 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol

Both enantiomers of 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol (**Example 460** - 47 mg) were separated by Supercritical Fluidic Chromatography (SFC - Chiralpak® IC-3 4.6x100 mm, Mobile phase: CO_2 / (MeOH + 0,3%$iPrNH_2$) 50/50) to provide 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl -phenol, first enantiomer eluting at Rt = 2.07 min (22 mg, **Example 474**, Enantiomer 1), as a white solid, and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol, second enantiomer eluting at Rt = 2.68 min (20 mg, **Example 475**, Enantiomer 2), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 461: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol

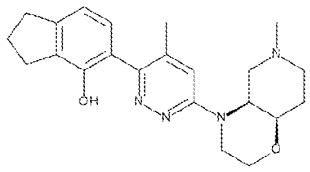


Under Ar, to a solution of 5-chloro-3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**Int 381.3** 0.67 mmol, 189 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** - 0.37 mmol, 100 mg) in 6 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1 mmol, 500 µl), then tetrakis(triphenylphosphine)palladium(0) (0.019 mmol, 21 mg). The mixture was stirred at 100°C for 1h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN

(from 100/0/0 to 85/7.5/7.5) to give, after trituration in acetonitrile, the title compound as a white solid (48 mg, 33% yield).

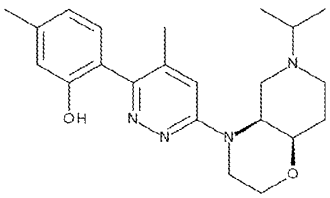
Compound Example 526 was synthesized analogously to Example 461

Example 471: 5-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]indan-4-ol

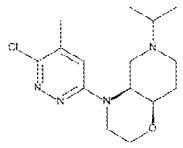


Under Ar, to a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indan-4-ol (**Int 324.2** – 1.99 mmol, 519 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 373.3** – 0.84 mmol, 238 mg) in 8 ml of 1,4-dioxane and 1.5 ml of water was added a 2N sodium carbonate aqueous solution (2.53 mmol, 1.26 ml), then tetrakis(triphenylphosphine)palladium(0) (0.084 mmol, 97 mg). The mixture was stirred at 100°C for 1.5h. After cooling down to rt, the mixture was diluted with 50 ml of DCM and washed successively with 20 ml of a 2N aqueous sodium carbonate solution and 20 ml of a saturated aqueous sodium bicarbonate solution. The pooled aqueous layers were extracted with 20 ml of DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 89/5/5/1 to give the title compound as a pale yellow solid (196 mg, 61% yield).

Example 472: 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol



Int 472.1: **(4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine**



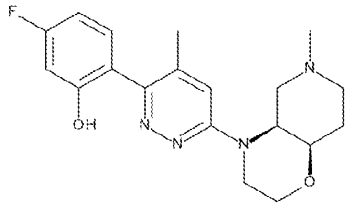
To a solution of tert-butyl (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carboxylate (**Int 373.1** – 0.76 mmol, 280 mg) in 8 ml of dichloromethane was added 2 ml of trifluoroacetic acid and the mixture was stirred at RT for 4 h, then concentrated under reduced pressure. To the residue solubilized in 15 ml of dichloromethane were added successively acetone (19 mmol, 1.4 ml), and sodium triacetoxyborohydride (1.37 mmol, 290 mg) and the mixture was stirred at rt for 2h. Then were added successively triethylamine (4.55 mmol, 635 µl), acetic acid (3.8 mmol, 217 µl), 1 ml of MeOH and another sodium triacetoxyborohydride (1.52 mmol, 322 mg) and the mixture was stirred again at rt for 1 h30. The reaction mixture was then diluted with 10 ml of dichloromethane and 5 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 10 ml of dichloromethane and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. To the residue solubilized in 15 ml of dichloromethane and 2 ml of MeOH were added 440 µl of acetic acid, acetone (19 mmol, 1.4 ml) and sodium triacetoxyborohydride (4.56 mmol, 1.68 g). The reaction mixture was stirred at rt for 1h15 then was added another sodium triacetoxyborohydride (4.56 mmol, 1.68 g) and the mixture was stirred at rt for 1 h. The reaction mixture was then diluted with 20 ml of dichloromethane, 10 ml of a 2N aqueous sodium carbonate and 10 ml of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 10 ml of dichloromethane and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 89/5/5/1 to give the title compound as a pale yellow foam (131 mg, 56% yield).

LCMS (**Method L**): Rt = 0.53; MS m/z $[M+H]^+$ = 311

2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol (Example 472)

Under Ar, to a solution of 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.84 mmol, 196 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (0.42 mmol, 130 mg) in 6 ml of 1,4-dioxane and 0.5 ml of water was added a 2N sodium carbonate aqueous solution (1.25 mmol, 627 µl), then tetrakis(triphenylphosphine)palladium(0) (0.042 mmol, 48 mg). The mixture was stirred at 100°C for 3h. After cooling down to rt, the mixture was diluted with 50 ml of DCM and washed successively with 10 ml of a 2N aqueous sodium carbonate solution and 20 ml of a saturated aqueous sodium bicarbonate solution. The pooled aqueous layers were extracted with 20 ml of DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN/NH_3 7N sol. in MeOH (from 100/0/0/0 to 89/5/5/1 to give the title compound as a pale yellow solid (105 mg, 66% yield).

Example 480: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-fluoro-phenol

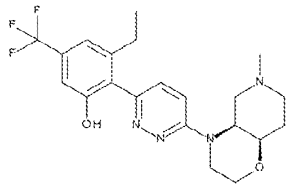


Under Ar, to a solution of 5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.94 mmol, 225 mg) and (4aS,8aR)-4-(6-chloro-5-methyl-pyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 373.3** – 0.63 mmol, 178 mg) in 6 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1.70 mmol, 850 µl), then TETRAKIS(triphenylphosphine)palladium(0) (0.0315 mmol, 36 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5), then repurified by prep-HPLC (column: Sunfire prep C18

OBD; 250 * 50 mm * 10 µm; mobile phase: [aqueous TFA 10^{-2} N / ACN] from 10% to 100% ACN in 35 min. at 50 ml/min) to give the title compound as a white solid (52 mg, 22% yield).

Compound Example 479 was synthesized analogously to Example 480 starting from Int435.1.

Example 481: 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol



Under Ar, to a solution of 3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (**Int 380.3** - 0.59 mmol, 176 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine (**Int 321.3** - 0.37 mmol, 100 mg) in 6 ml of 1,4-dioxane was added a 2N sodium carbonate aqueous solution (1 mmol, 500 µl), then tetrakis(triphenylphosphine)palladium(0) (0.019 mmol, 21 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 20 ml of a saturated aqueous sodium bicarbonate solution (twice) and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 85/7.5/7.5) to give, after trituration in acetonitrile, the title compound as a white solid (57 mg, 36% yield).

Examples 482 and 483: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol

Int 482.1: 2-[4-(difluoromethyl)-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol

In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridine (**Int 506.3**; 0.51 mmol, 155 mg) 2-hydroxy-4-(trifluoromethyl)phenyl boronic acid (0.77 mmol, 158 mg) in 3.2 ml of 1,2-dimethoxyethane were added sodium carbonate (1.28 mmol, 136 mg) and 0.7 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.04 mmol, 42 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc, filtered and concentrated under reduce pressure. The residue was diluted with CH_2Cl_2, filtered and concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a pale yellow solid (75 mg, 34% yield).

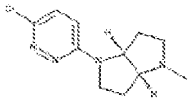
LCMS (**Method U**): Rt = 1.06; MS m/z $[M+H]^+$ = 429

2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol (Examples 482 et 483)

Both enantiomers of 2-[4-(difluoromethyl)-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (74 mg) were separated by chiral preparative HPLC (Column Chiralpak® AD 5µm, 300x50mm, Flow rate 230ml/min, eluent (CO_2/ethanol+0.1% TEA 85/15), to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl) pyridazin-3-yl]-5-(trifluoromethyl)phenol, first enantiomer eluting Rt = 7.0 min (29 mg, **Example 482**), as a white solid and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol, second enantiomer eluting at Rt = 10.25 min (27 mg, **Example 483**), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 484: 3-methyl-2-[6-[rac-(3aS,6aS)-1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo [3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Int 484.1: rac-(3aS,6aS)-4-(6-chloropyridazin-3-yl)-1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrole



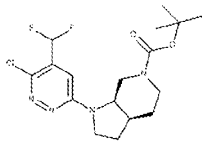
Under vigorous stirring, at rt, to a solution of rac-(3aS,6aS)-4-(6-chloropyridazin-3-yl)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrole;dihydrochloride (**Int 377.2**; 270 mg, 0.9072 mmol) and Formalin (184 mg, 2.2681 mmol, 37 mass%) in 15 ml of DCM was added by fractions sodium triacetoxyborohydride (769 mg, 3.6289 mmol). The reaction was stirred at rt overnight. The reaction mixture was diluted with DCM, washed with an aqueous saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure to give the title compound as a solid (133 mg, 61% yield).
LCMS (**Method L**): Rt = 0.23 min; MS m/z [M+H]+ = 239

3-methyl-2-[6-[rac-(3aS,6aS)-1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol (Example 484)

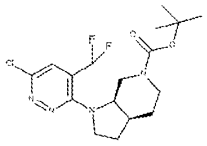
In a microwave vial, under Ar, to a solution of rac-(3aS,6aS)-4-(6-chloropyridazin-3-yl)-1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrole (133 mg, 0.5571 mmol) and aqueous solution of sodium carbonate (2 mol/l ; 0.750 ml, 1.5043 mmol) in 4 ml of 1,4-dioxane were added 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (253 mg, 0.8357 mmol) and tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.0557 mmol). The mixture was heated at 100°C under microwave irradiation for 2h. After cooling down to rt, the reaction mixture was diluted with AcOEt, extracted with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/ [DCM80 /CH_3CN 10/MeOH 10/Et_3N 0.1] (from 100/0 to 0/100), then repurified by chiral phase LC (Column WHELK 0®1 SS 5 µm, 30x250 mm, Flow rate 45 ml/min, eluent n-heptane/ethanol (70/30) + 0,1% TEA, detection 265 nm) to give the title compound as a white solid (58 mg, 25% yield).

Examples 487 and 488: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol

Int 487.1 and Int 487.1bis: tert-butyl rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (Int 487.1) and tert-butyl rac-(3aR,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (Int 487.1bis)



and



Int 487 .1 Int 487.1bis

In a microwave vial, a solution of 3,6-dichloro-4-(difluoromethyl)pyridazine (0.100 g, 0.000503 mol), tert-butyl rac-(3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (0.114 g, 0.000503 mol) and K_3PO_4 (0.213 g, 0.00101 mol) in 1 ml of DMSO was heated at 80 °C using a single mode microwave (Biotage Initiator EXP 60) with a power output ranging from 0 to 400 W for 2h. After cooling down to rt, the mixture was filtered. The solid was rinsed with DCM and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient heptane/ EtOAc (90/10 to 70/30, then isocratic) to give **Int 487.1bis** as a yellow solid (67.6 mg, 35%) and Int 487.1 as a yellow solid (0.106 g, 54%).

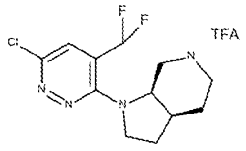
Int 487.1:

1H NMR (400 MHz, DMSO) δ (ppm): 7.13 (t, J = 53.3 Hz, 1H), 7.12 (s, 1H), 4.28 – 3.69 (m, 2H), 3.66 – 3.38 (m, 3H), 3.29 – 2.70 (m, 2H), 2.31 – 1.91 (m, 2H), 1.81 (s, 1H), 1.63 (s, 1H), 1.51 – 1.21 (m, 10H).

Int 487.1bis:

1H NMR (400 MHz, DMSO) δ (ppm): 7.84 (s, 1H), 7.26 (t, J = 53.2 Hz, 1H), 4.44 (d, J = 14.6 Hz, 1H), 4.29 – 4.02 (m, 1H), 3.92 – 3.71 (m, 2H), 3.41 (t, J = 8.9 Hz, 1H), 3.13 (d, J = 14.8 Hz, 1H), 2.78 (t, J = 12.2 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.08 – 1.88 (m, 1H), 1.79 – 1.56 (m, 2H), 1.51 – 1.27 (m, 4H), 1.01 (s, 6H)

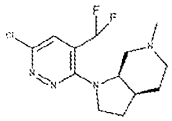
Int 487.2: rac-(3aS,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid



To a solution of tert-butyl rac-(3aR,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (**Int 487.1bis** - 200 mg, 0.000514 mol) in 3.5 ml of DCM was added TFA (0.586 g, 0.00514 mol) and the solution was stirred at rt for 4h. The mixture was concentrated under reduced pressure to give the title compound as a brown oil (241 mg) which was used without further purification in the next step.

LCMS (**Method S**): MS m/z [M+H]+ = 289; Rt = 0.85

Int 487.3: rac-(3aS,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



To a solution of rac-(3aS,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid (200 mg, 0.000387 mol) in 1.5 ml of methanol and 1.5 ml of tetrahydrofuran were added formaldehyde (37% in water, 0.157 g, 0.00194 mol) and $NaBH_3CN$ (1 eq., 0.0243 g, 0.000387 mol). After stirring at rt for 2 h, the resulting solution was under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient DCM/MeOH (100/0 to 80/20) to give the title compound as a yellow oil (110 mg, 77%).

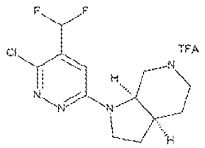
1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (d, J = 1.6 Hz, 1H), 7.11 (t, J = 53.3 Hz, 1H), 4.67 (dt, J = 5.9, 3.0 Hz, 1H), 3.93 (td, J = 9.9, 6.6 Hz, 1H), 3.75 – 3.37 (m, 3H), 2.84 (dd, J = 13.4, 3.4 Hz, 1H), 2.71 – 2.42 (m, 5H), 2.16 – 2.01 (m, 2H), 2.01 – 1.90 (m, 1H), 1.90 – 1.82 (m, 1H).

2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol (Examples 487 and 488)

To rac-(3aS,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (90.0 mg, 0.000297 mol), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.0740 g, 0.000446 mol) were added potassium carbonate (0.123 g, 0.000892 mol), XPhos Pd G2 (0.0117 g, 1.49e-5 mol) and XPhos (0.00709 g, 1.49e-5 mol). The resulting mixture was purged under vacuum and backfilled with nitrogen 3 times, then 1.8 ml of 1,4-dioxane and 0.5 ml of water were added, and the resulting mixture was stirred at 90°C for 18h. After cooling down to rt, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient DCM/MeOH (100/0 to 30/70) then repurified by reverse phase preparative LC (spherical C18 25 µm, 12 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient 0.2% aq. NH_4+HCO_3-/MeCN from 75:25 to 40:60) to give 26 mg of a white solid. This solid was purified by SFC (Stationary phase: Chiralpak® IG 20x250 mm, Mobile phase: CO_2 / (MeOH + 0,3%iPrNH2) 65/35) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol, first enantiomer eluting Rt = 1.05 min (9 mg, **Example 487**), as a white solid and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol, second enantiomer eluting at Rt = 2.26 min (14 mg, **Example 488**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 489 and 490: 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl) pyridazin-3-yl]-5-methyl-phenol

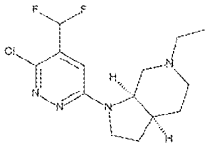
Int 489.1: rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid



At 0°C, to a solution of tert-butyl rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (**Int 506.1** – 0.67 mmol, 260 mg) in 5 ml of dichloromethane was added TFA (6.7 mmol, 0.762 g). The reaction mixture was stirred at rt for 18h, then concentrated under reduced pressure to give the title compound (330 mg) as a brown oil, which was used without further purification in the next step.

LCMS (**Method S**): Rt = 0.84; MS m/z $[M+H]^+$ = 289

Int 489.2: rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



To a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid (0.621 mmol, 250 mg) in 4 ml of acetonitrile were added K_2CO_3 (2.48 mmol, 0.343 g) followed by iodoethane (0.621 mmol, 0.097 g). The mixture was stirred at 50°C for 3h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH (from 100/0 to 90/10) to give the title compound as a yellow oil (260 mg, 94%)

LCMS (**Method S**): Rt = 1.00; MS m/z $[M+H]^+$ = 317

2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol (Examples 489 and 490)

Under N_2, to a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.316 mmol, 100 mg) and (2-

hydroxy-4-methyl-phenyl)boronic acid (0.474 mmol, 0.0720 g) in 2.5 ml of 1,4-dioxane and 0.5 ml of water were added K_2CO_3 (0.947 mmol, 0.131 g), XPhos (0.00752 g, 1.58e-5 mol) and XPhos Pd G2 (0.0124 g, 1.58e-5 mol). The mixture was purged again with N_2 and stirred at 90°C for 2h. After cooling down to rt, the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH (from 100/0 to 90/10), then repurified by reverse phase preparative LC (spherical C18 25 µm, 12 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient 0.2% aq. NH_4+HCO_3-/MeCN from 75:25 to 40:60) to give 26 mg of a white solid. This solid was purified by SFC (Stationary phase: Chiralpak® IG-3 4.6x100 mm, Mobile phase: CO_2/(iPrOH + 0,3%$iPrNH_2$) 75/25) to provide 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol, first enantiomer eluting Rt 2.66 min (17 mg, **Example 489**), as a white solid and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol, second enantiomer eluting at Rt = 3.25 min (15 mg, **Example 490**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 485 and 486: 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol

Under N_2, to a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 489.2** - 0.316 mmol, 100 mg) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.474 mmol, 0.136 g) in 2.5 ml of 1,4-dioxane and 0.5 ml of water were added K_2CO_3 (0.947 mmol, 0.131 g), XPhos (0.00752 g, 1.58e-5 mol) and XPhos Pd G2 (0.0124 g, 1.58e-5 mol). The mixture was purged again with N_2 and stirred at 90°C for 2h. After cooling down to rt, the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH (from 100/0 to 90/10), then repurified by reverse phase preparative LC (spherical C18 25 µm, 12 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient 0.2% aq. NH_4+HCO_3-/MeCN from 75:25 to 40:60) to give 30 mg of a white solid. This solid was purified by SFC (Stationary phase:

Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2 / (EtOH + 0,3%iPrNH2) 90/10) to provide 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol, first enantiomer eluting Rt 1.63 min (14 mg, example 485), as a white solid and 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol, second enantiomer eluting at Rt = 2.36 min (14 mg, **Example 486**), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 491 and 492: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol

Int 491.1: 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol (Example 452)

In a microwave vial under Ar, to a mixture of 3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (**Int 380.3** - 188 mg, 0.593 mmol), K_2CO_3 (164 mg, 1.2 mmol) and rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 342.1** - 100 mg, 0.396 mmol) in 2 ml of 1,4-dioxane and 0.4 ml of water were added XPhos (9.43 mg, 0.019 mmol) and XPhos Pd G2 (15.6 mg, 0.019 mmol). The mixture was purged again with Ar, then heated at 90°C for 3h. After cooling down to rt, the mixture was filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/(MeOH/NH4OH (10%)) from 100/0 to 80/20) to give the title compound as a yellow oil (123 mg, 76%).

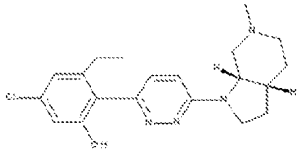
2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol (Examples 491 and 492)

Both enantiomers of 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol (Int 491.1-120 mg)) were separated by Supercritical Fluidic Chromatography (SFC - Column

Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2 / (iPrOH + 0,3%$iPrNH_2$) 80/20) to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol, first enantiomer eluting at Rt = 1.87 min (39 mg, **Example 491**, Enantiomer 1), as a white solid after lyophilization, and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol, second enantiomer eluting at Rt = 2.70 min (38 mg, **Example 492**, Enantiomer 2), as a white solid after lyophilization. The absolute configurations cannot be assigned at this stage.

Examples 493 and 494: 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol

Int 493.1: 2-[6-[rac-(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol



In a microwave, under Ar, to a solution of 5-chloro-3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol ((Int 381.3 – 55.3 mg, 0.196 mmol), K_2CO_3 (54.1 mg, 0.392 mmol) and rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (Int 342.1 - 33.0 mg, 0.131 mol) in 1.2 ml of 1,4-dioxane and 0.3 ml of water were added XPhos (3.11 mg, 0.00653 mmol) and XPhos Pd G2 (5.14 mg, 0.00653 mmol). The mixture was purged again with Ar, then was heated at 90°C for 3h. After cooling down to rt, the mixture was filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/ (MeOH/NH_4OH (10%)) from 100/0 to 80/20 to give the title compound as a yellow oil (37 mg, 79% yield).

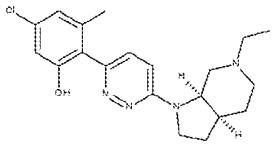
LCMS (**Method S**): Rt = 1.11; MS m/z $[M+H]^+$ = 373.3

2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol (Examples 493 and 494)

Both enantiomers of 2-[6-[rac-(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol (35 mg) were separated by chiral preparative HPLC (Column Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2/ (EtOH + 0,3% $iPrNH_2$) 70/30), to provide 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol, first enantiomer eluting at Rt = 1.62 min (15 mg, **Example 493**), as a white solid and 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol, second enantiomer eluting at Rt = 2.91 min (14 mg, **Example 494**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 496 and 497: 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol

Int 496.1: 5-chloro-3-methyl-2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (**Int 504.1**; 0.58 mmol, 155 mg) and (4-chloro-2-hydroxy-6-methylphenyl)boronic acid (0.87 mmol, 145 mg) in 3.2 ml of 1,2-dimethoxyethane are added sodium carbonate (1.45 mmol, 154 mg) and 0.7 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.04 mmol, 47 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc then filtered and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using

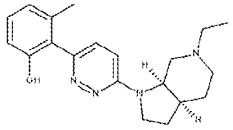
DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a brown solid (130 mg, 63% yield).
LCMS (**Method U**): Rt = 0.87; MS m/z $[M+H]^+$ = 373

2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl] pyridazin-3-yl]-5-chloro-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol (Examples 496 and 497)

Both enantiomers of 5-chloro-3-methyl-2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (126 mg) were separated by chiral preparative HPLC (Column Chiralpak® IG 5µm, 250x30mm, Flow rate 45ml/min, eluent (n-heptane/ethanol 85/15) + 0,1% TEA), to provide 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, first enantiomer eluting at Rt= 20.7 min (28 mg, **Example 496**), as a white solid and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, second enantiomer eluting at Rt = 24.5 min (30 mg, **Example 497**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 498 and 499: 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol

Int 498.1: 3-methyl-2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (Int 504.1 ; 0.56 mmol, 151 mg) and (2-hydroxy-6-methylphenyl)boronic acid (0.85 mmol, 129 mg) in 3.2 ml of 1,2-dimethoxyethane were added sodium carbonate (1.42 mmol, 150 mg) and 0.7 ml of water. The solution was purged with Ar for 3 min, then $Pd(PPh_3)_4$ (0.04 mmol, 46 mg) was added.

The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc, filtered on hydrophobic column and concentrated under reduce pressure. The residue was diluted with CH_2Cl_2, filtered and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a brown solid (110 mg, 57% yield).

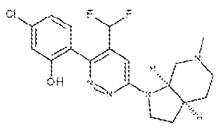
LCMS (**Method U**): Rt = 0.78; MS m/z $[M+H]^+$ = 353

2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol (Examples 498 and 499)

Both enantiomers of 3-methyl-2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (108 mg) were separated by chiral preparative HPLC (Column Chiralpak® IG 5µm, 250x30mm, Flow rate 115ml/min, eluent (CO_2/EtOH+0.1% TEA 65/35), to provide 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol, first enantiomer eluting at Rt = 8.9 min (36 mg, **Example 498**), as a white solid and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol, second enantiomer eluting at Rt = 11.1 min (32 mg, **Example 499**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 500 and 501: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol

Int 500.1: 5-chloro-2-[4-(difluoromethyl)-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol



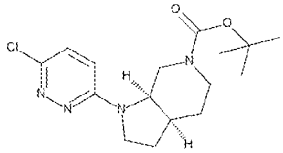
In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridine (**Int 506.3**; 0.27 mmol, 82 mg) and (4-chloro-2-hydroxy-phenyl)boronic acid (0.41 mmol, 70 mg) in 1.3 ml of 1,2-dimethoxyethane were added sodium carbonate (0.68 mmol, 72 mg) and 0.35 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.02 mmol, 22 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc, filtered and concentrated under reduce pressure. The residue was diluted with CH_2Cl_2, filtered and concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 84/8/8) to give the title compound as a pale yellow solid (65 mg, 61% yield).
LCMS (**Method U**): Rt = 0.99; MS m/z $[M+H]^+$ = 395

2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol (Examples 500 et 501)

Both enantiomers of 5-chloro-2-[4-(difluoromethyl)-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (63 mg) were separated by chiral preparative HPLC (Column Chiralpak® AD-H 5µm, 250x30mm, Flow rate 100ml/min, eluent (CO_2/ethanol + 0,1% TEA 80/20), to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl) pyridazin-3-yl]-5-chloro-phenol, first enantiomer eluting Rt = 4.7 min (23 mg, **Example 500**), as a white solid and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol, second enantiomer eluting at Rt = 7.2 min (20 mg, **Example 501**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 502 and 503: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol

Int 502.1: tert-butyl rac-(3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate

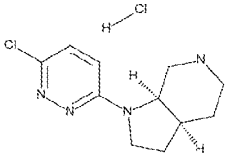


In a microwave vial, under Ar, to a suspension of tert-butyl rac-(3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (0.98 mmol, 222 mg) and 3,6-dichloropyridazine (0.89 mmol, 133 mg) in 2.66 ml of n-butanol was added triethylamine (1.96 mmol, 0.27 ml). The reaction mixture was heated at 130°C under microwave irradiation for 3h30. In another microwave vial, under Ar, to a suspension of tert-butyl rac-(3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (5.25 mmol, 1.19 g) and 3,6-dichloropyridazine (4.77 mmol, 711 mg) in 14.2 ml of n-butanol was added triethylamine (10.50 mmol, 1.46 ml). The reaction mixture was heated at 130°C under microwave irradiation for 3h30.

The reaction mixtures were combined and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with water (3 times), dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 95/2.5/2.5) to give the title compound as a beige solid (1.35 g, 71% yield).

LCMS (**Method U**): Rt = 1.54; MS m/z $[M+H]^+$ = 339

Int 502.2: rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride

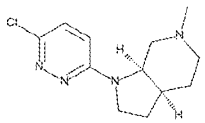


To a solution of tert-butyl rac-(3aR,7aR)-1-(6-chloropyridazin-3-yl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (3.98 mmol, 1.35 g) in 8 ml of dichloromethane was added 4N hydrochloric acid in dioxan (59.8 mmol, 14.9 ml). The

reaction mixture was stirred at rt overnight, then concentrated under reduced pressure. MeOH was added and the mixture was concentrated under reduced pressure to give the title compound (1.5 g) as a brown solid, which was used without further purification in the next step.

LCMS (**Method U**): Rt = 0.19 and 0.29; MS m/z $[M+H]^+$ = 239

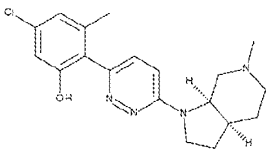
Int 502.3: **rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine**



To a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride (0.73 mmol, 200 mg) in 7 ml of DCM and 1.6 ml of MeOH was added 37% aqueous solution of formaldehyde (1.82 mmol, 135 µl). The reaction mixture was stirred at room temperature for 10 minutes, then sodium triacetoxyborohydride (2.91 mmol, 616 mg) was added. The reaction mixture was stirred at room temperature for 1h. 2 ml of a saturated aqueous sodium bicarbonate solution were added, and the organic layer was concentrated under reduced pressure. The aqueous layer was extracted 3 times with DCM and the combined organic layers were filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a pale yellow solid (176 mg, 96% yield).

LCMS (**Method U**): Rt = 0.17 and 0.29; MS m/z $[M+H]^+$ = 253

Int 502.4: **5-chloro-3-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol**



In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.69 mmol, 174 mg) and (4-

chloro-2-hydroxy-6-methylphenyl)boronic acid (1.03 mmol, 192 mg) in 3.2 ml of 1,2-dimethoxyethane were added sodium carbonate (1.72 mmol, 182 mg) and 0.7 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.04 mmol, 48 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc then filtered and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a pale yellow solid (146 mg, 59% yield).

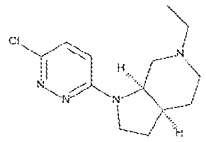
LCMS (**Method U**): Rt = 0.85; MS m/z $[M+H]^+$ = 359

2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol (Examples 502 and 503)

Both enantiomers of 5-chloro-3-methyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (144 mg) were separated by chiral preparative HPLC (Column: chiral phase LC (Column Chiralpak® AD-H 20µm, 350x76.5mm, Flow rate 400ml/min, eluent (n-heptane+0.1% TEA/ethanol+0.1% TEA 90/10 to 50/50), to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, first enantiomer eluting at Rt= 33.4 min (30 mg, example 502), as a white solid and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol, second enantiomer eluting at Rt = 40.3 min (30 mg, **Example 503**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 504 and 505: 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

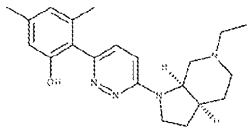
Int 504.1: **rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine**



At 0°C, to a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride (**Int 502.2** ; 2.19 mmol, 604 mg) in 16 ml of MeOH was added acetaldehyde (110 mmol, 6.16 ml) previously cooled at 0°C. After stirring 1 min at 0°C, the reaction mixture was stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (8.78 mmol, 1.86 g) was then added and the reaction mixture was stirred at room temperature for 1h. 13.5 ml of a saturated aqueous sodium bicarbonate solution was added, and the organic layer was concentrated under reduced pressure. The aqueous layer was extracted 3 times with DCM and the combined organic layers were filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a beige solid (512 mg, 87% yield).

LCMS (**Method U**): Rt = 0.72; MS m/z $[M+H]^+$ = 267

Int 504.2: **3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol**



In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-(6-chloropyridazin-3-yl)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.58 mmol, 155 mg) and (2-hydroxy-4,6-dimethylphenyl)boronic acid (0.87 mmol, 145 mg) in 3.2 ml of 1,2-dimethoxyethane were added sodium carbonate (1.45 mmol, 154 mg) and 0.7 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.04 mmol, 47 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc then filtered and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, filtered and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 80/10/10) to give the title compound as a brown solid (130 mg, 63% yield).

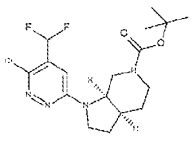
LCMS (**Method U**): Rt = 0.77; MS m/z $[M+H]^+$ = 267

2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Examples 504 et 505)

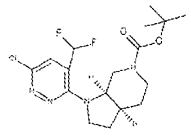
Both enantiomers of 3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (125 mg) were separated by chiral preparative HPLC (Column Chiralpak® AY-H 5µm, 250x30mm, Flow rate 100ml/min, eluent (CO_2/EtOH+ 0,1% TEA 75/25), to provide 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, first enantiomer eluting at Rt = 15 min (42 mg, **Example 504**), as a white solid and 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, second enantiomer eluting at Rt = 19.1 min (39 mg, **Example 505**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 506 and 507: 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol.

Int 506.1 and 506.1bis: tert-butyl rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (Int 506.1) and tert-butyl rac-(3aR,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (Int 506.1bis)



and

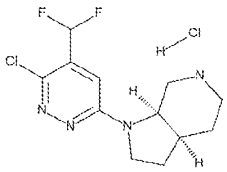


In a microwave vial, under Ar, to a solution of tert-butyl rac-(3aR,7aR)-1,2,3,3a,4,5,7,7a-octahydropyrrolo[2,3-c]pyridine-6-carboxylate (2.65 mmol, 600 mg) and 3,6-dichloro-4-(difluoromethyl)pyridazine (3.45 mmol, 686 mg) in 20 ml of DMSO was added potassium phosphate tribasic (6.63 mmol, 1.48 g) and the reaction was heated at 90°C under microwave irradiation for 2h. The reaction mixture was taken up in 400 ml of diethyl ether. The organic layer was washed twice with water, dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 80/20) to give tert-butyl rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (**Int 506.1**) as a pale yellow solid (363 mg, 35% yield) and tert-butyl rac-(3aR,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (**Int 506.1bis**) as a pale yellow solid (206 mg, 20% yield).

Int 506.1 - LCMS: (**Method U**): Rt = 1.72; MS m/z $[M+H]^+$ = 389

Int 506.1bis - LCMS: (**Method U**): Rt = 1.73; MS m/z $[M+H]^+$ = 389

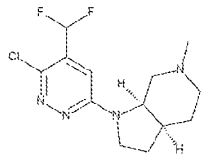
Int 506.2: rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride



To a solution of tert-butyl rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (1.03 mmol, 402 mg) in 3 ml of dichloromethane was added 4N hydrochloric acid in dioxan (15.51 mmol, 3.88 ml). The reaction mixture was stirred at rt for 40h, then concentrated under reduced pressure. MeOH and toluene were added, and the mixture was concentrated under reduced pressure to give the title compound (492 mg) as a brown oil, which was used without further purification in the next step.

LCMS (**Method U**): Rt = 0.67; MS m/z $[M+H]^+$ = 289

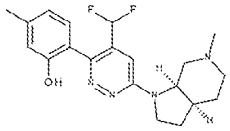
Int 506.3: rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



To a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;hydrochloride (1.03 mmol, 336 mg) in 12 ml of DCM and 1 ml of MeOH was added 37% aqueous solution of formaldehyde (2.58 mmol, 192 µl). The reaction mixture was stirred at room temperature for 10 minutes, then sodium triacetoxyborohydride (4.13 mmol, 876 mg) was added. The reaction mixture was stirred at room temperature for 1h. 3 ml of a saturated aqueous sodium bicarbonate solution was added, and the reaction mixture was diluted with CH_2Cl_2. The aqueous layer was extracted twice with DCM, and the combined organic layers were filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 86/7/7) to give the title compound as a pale yellow solid (331 mg, quantitative yield).

LCMS (**Method U**): Rt = 0.69; MS m/z $[M+H]^+$ = 303

Int 506.4: 2-[4-(difluoromethyl)-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-methyl-phenol



In a microwave vial, under Ar, to a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.27 mmol, 81 mg) and 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.40 mmol, 94 mg) in 1.3 ml of 1,2-dimethoxyethane were added sodium carbonate (0.67 mmol, 71 mg) and 0.35 ml of water. The solution was purged with Ar for 3 min, then $Pd(PPh_3)_4$ (0.02 mmol, 22 mg) was added. The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was diluted with EtOAc, filtered and concentrated under reduce pressure. The residue was diluted with

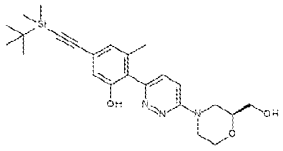
CH_2Cl_2, filtered on hydrophobic column and concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 84/8/8) to give the title compound as a pale yellow solid (76 mg, 76% yield).
LCMS (**Method U**): Rt = 0.94; MS m/z $[M+H]^+$ = 375

2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol (Examples 506 and 507)

Both enantiomers of 2-[4-(difluoromethyl)-6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-methyl-phenol (74 mg) were separated by chiral preparative HPLC (Column Chiralpak® AD-H 5µm, 250x30mm, Flow rate 105ml/min, eluent (CO_2/EtOH+0,1% TEA 85/15), to provide 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol, first enantiomer eluting Rt = 8.15 min (29 mg, **Example 506**), as a white solid and 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol, second enantiomer eluting at Rt =11.9 min (28 mg, **Example 507**), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 508: 5-ethynyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol

Int 508.4: 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-[6-[(2S)-2-(hydroxymethyl) morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol



At 0°C, under N_2, In a sealed tube, XPhos Pd G2 (6.87 mg, 8.73e-6 mol) and XPhos (4.16 mg, 8.73e-6 mol) were added to a solution of 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**Int 508.3** - 65.0 mg, 0.175 mmol), [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (**Int 8.1** - 40.1 mg, 0.175

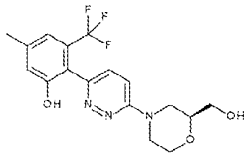
mmol) and K_2CO_3 (48.2 mg, 0.349 mmol) in 1 ml of 1,4-dioxane and 0.25 ml of water. The mixture was stirred at 95°C for 2h. After cooling down to rt, the mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (from 100/0 to 97/3, then isocratic) to give the title compound as a white solid (44 mg, 60% pure, 40% yield).

LCMS (**Method R**): Rt = 1.53; MS m/z [M+H]+ = 440

5-ethynyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol (Example 508)

To a solution of 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-[6-[(2S)-2-(hydroxymethyl) morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol (60.0 %, 44.0 mg, 6.01e-5 mol) in 0.8 ml of THF was added TBAF 1 M in THF (1.00 mol/L, 90.1 mL, 9.01e-5 mol). The solution was stirred at rt for 1h. The mixture was diluted with EtOAc and water was added. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Heptane/EtOA (from 90/10 to 20/80, then isocratic), the repurified by reverse phase preparative LC (spherical C18 25 µm, 25 g YMC-ODS-25, dry loading (Celite®), mobile phase gradient 0.2% aq. $NH_4^+HCO_3^-$/MeCN from 90/10 to 50/50) to give the title compound as a white solid (15 mg, 77%).

Example 509: 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol

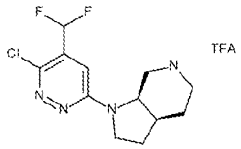


In a microwave vial, under N_2, a solution of 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenol (**Int 509.2** - 0.200 g, 0.666 mmol), [(2S)-4-(6-chloropyridazin-3-yl)morpholin-2-yl]methanol (**Int 8.1** - 0.102 g, 0.444 mol) and K_2CO_3 (0.123 g, 0.888 mmol) in 2.7 ml of 1,4-dioxane and 0.65 ml of water, were added XPhos Pd G2 (0.0175 g, 2.22e-5 mol) and XPhos (0.0106 g, 2.22e-5 mol). The mixture was stirred at 95°C for 2h. After cooling down to rt, the mixture was filtered and concentrated under

reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (from 100/0 to 95/5 then 90/10), then was purified again by flash chromatography on silica gel (column Spherical SiOH 15 µm) using DCM/MeOH (from 100/0 to 95/5 then 90/10), to give the title compound as a white solid (25 mg, 39%).

Example 510 and 511: 1-[(3aS,7aS)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone and 1-[(3aR,7aR)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone

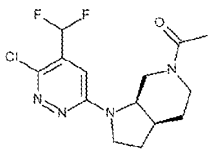
Int 510.1: rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid



At 0°C, to a solution of tert-butyl rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine-6-carboxylate (**Int 487.1** - 260 mg, 0.000669 mol) in 5 ml of DCM was added TFA (0.762 g, 0.00669 mol) and the solution was stirred at rt for 18h. The mixture was concentrated under reduced pressure to give the title compound as a brown oil (330 mg) which was used without further purification in the next step.

LCMS (**Method S**): Rt = 0.84; [M+H]+ = 289

Int 510.2: 1-[rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone



At 0°C, to a solution of rac-(3aS,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid (100 mg,

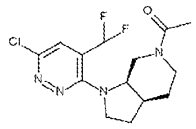
0.000248 mol) and DIPEA (0.128 g, 0.000993 mol) in 2 ml of DCM was added acetyl chloride (0.0390 g, 0.000497 mol) and the resulting mixture was stirred at rt for 18h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient DCM/MeOH (100/0 to 90/10) to give the title compound as a brown solid (91 mg, 90%).
LCMS (**Method S**): Rt = 1.04; MS m/z [M+H]+ = 331

1-[(3aS,7aS)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone and 1-[(3aR,7aR)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone (Examples 510 and 511)

Under N_2, to a solution of 1-[rac-(3aR,7aR)-1-[6-chloro-5-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone (190 mg, 0.000574 mol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (0.248 g, 0.000862 mol) in 5 ml of 1,4-dioxane and 1 ml of water were added potassium carbonate (0.238 g, 0.00172 mol), XPhos Pd G2 (0.0226 g, 2.87e-5 mol) and XPhos (0.0137 g, 2.87e-5 mol). The resulting mixture was purged again with N_2, then stirred at 90°C for 3h. After cooling down to rt, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient DCM/MeOH (100/0 to 90/10) then repurified by reverse phase chromatography (Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 35/65 to 75/25) to give 53 ml of a solid. This latter was purified by SFC (Stationary phase: Chiralpak® IH 20x250 mm, Mobile phase: CO_2/iPrOH 75/25) to provide 1-[(3aS,7aS)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-6-yl]ethenone, first enantiomer eluting Rt = 0.65 min (30 mg, **Example 510**), as a white solid and 1-[(3aR,7aR)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c] pyridin-6-yl]ethenone, second enantiomer eluting at Rt = 1.03 min (28 mg, **Example 511**), as a white solid. The absolute configurations cannot be assigned at this stage.

Example 512 and 513: 1-[(3aS,7aS)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone and 1-[(3aR,7aR)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone

Int 512.1: 1-[rac-(3aR,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone



To a solution of rac-(3aS,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2-trifluoroacetic acid (**Int 487.2** - 300 mg, 0.000528 mol) and DIPEA (0.273 g, 0.00211 mol) in 4 ml of DCM was added acetyl chloride (0.0539 g, 0.000687 mol) and the resulting mixture was stirred at rt for 2 h. The mixture was diluted with ethyl acetate, washed with a solution of sodium bicarbonate, water and brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient heptane/ethyl acetate (100/0 to 0/100), then ethyl acetate/methanol (100/0 to 90/10) to give the title compound as an orange solid (109 mg, 50%).

LCMS (**Method S**): Rt = 1.04; MS m/z [M+H]+ = 331

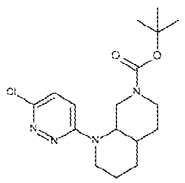
1-[(3aS,7aS)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone and 1-[(3aR,7aR)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone (Examples 512 and 513)

Under N_2, to a solution of 1-[rac-(3aR,7aR)-1-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone (80.0 mg, 0.000189 mol), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (0.251 g, 0.00151 mol) in 1 ml of 1,4-dioxane and 0.2 ml of water were added potassium carbonate (0.156 g, 0.00113 mol), XPhos Pd G2 (0.0297 g, 3.77e-5 mol) and XPhos (0.0180 g, 3.77e-5 mol). The resulting mixture was purged again with N_2, then stirred at 80 °C for 18 h. After cooling down to rt, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (spherical C18 25 µm, 12 g YMC-ODS-25, dry loading

(Celite®), mobile phase gradient 0.2% aq. NH_4+HCO_3-/MeCN from 75:25 to 50:50) to give 36 ml of a white solid. This solid was purified by SFC (Stationary phase Chiralpak® IH 20x250 mm, Mobile phase: CO_2/iPrOH 70/30) to provide 1-[(3aS,7aS)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone, first enantiomer eluting Rt = 0.67 min (15 mg, **Example 512**), as a white solid and 1-[(3aR,7aR)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethenone, second enantiomer eluting at Rt = 1.21 min (12 mg, **Example 513**), as a white solid. The absolute configurations cannot be assigned at this stage.

Examples 517; 518; 519 and 520 : 2-[6-[(4aR,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol ; 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(4aS,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

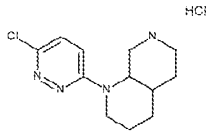
Int 517.1: tert-butyl 1-(6-chloropyridazin-3-yl)-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridine-7-carboxylate



Under Ar, in a vial, to a solution of tert-butyl 2,3,4,4a,5,6,8,8a-octahydro-1H-1,7-naphthyridine-7-carboxylate (807 mg, 3.3562 mmol) in 1 ml of Triethylamine was added 3,6-dichloropyridazine (500 mg, 3.3562 mmol). The vial was sealed and heated at 130°C for 1h. The vial was open, and the triethylamine was evaporated under a flux of Ar. Then the heating was continued for 5h. After cooling down to rt, the mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/ [DCM90 /CH_3CN 2.5/MeOH 2.5] (from 100/0 to 0/100) to give the title compound as a yellow oil (320mg, 27% yield).

LCMS (**Method L**): Rt = 1.10; MS m/z $[M+H]^+$ = 353

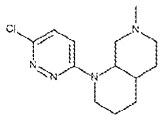
Int 517.2: 1-(6-chloropyridazin-3-yl)-3,4,4a,5,6,7,8,8a-octahydro-2H-1,7-naphthyridine;hydrochloride



To a solution of tert-butyl 1-(6-chloropyridazin-3-yl)-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridine-7-carboxylate (170 mg, 0.4818 mmol, 100 mass%) in 2.4 ml of DCM was added HCl 4N in dioxane (2.4 ml, 9.6356 mmol). The mixture was stirred overnight at rt. The reaction mixture was concentrated under reduced pressure to give the title compound as a cream solid (144 mg, 91 % yield).

LCMS (**Method L**): Rt = 0.33; MS m/z $[M+H]^+$ = 253

Int 517.3: 1-(6-chloropyridazin-3-yl)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridine



To a vigorously stirred mixture of 1-(6-chloropyridazin-3-yl)-3,4,4a,5,6,7,8,8a-octahydro-2H-1,7-naphthyridine;hydrochloride (253 mg, 0.7769 mmol) and Formalin (0.152ml, 1.9422 mmol, 37 mass%) wad added by fractions sodium triacetoxyborohydride (659mg, 3.1075 mmol). The reaction mixture was stirred for 2h at rt. Formalin (40µl, 0.080 mmol) and Sodium triacetoxyborohydride (180 mg, 0.850 mmol) were added and the mixture was stirred for 1h. The reaction mixture was diluted with DCM, washed with an aqueous saturated solution of $NaHCO_3$, brine, dried over Mg_2SO_4, filtered, and concentrated under reduce pressure to give the title compound as a cream solid (173mg), which was used without further purification in the next step.

LCMS (**Method L**): Rt = 0.33; MS m/z $[M+H]^+$ = 267

2-[6-[(4aR,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl] pyridazine-3-yl]-3,5-dimethyl-phenol; 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-

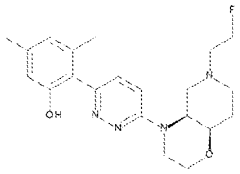
octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(4aS,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Examples 517; 518; 519 and 520)

In a microwave vial, under Ar, to a solution of 1-(6-chloropyridazin-3-yl)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridine (80 mg, 0,2999 mmol), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (75 mg, 0,4498 mmol) and sodium carbonate (80 mg, 0,7497 mmol) in 2 ml of 1,4-dioxane and 0.5 ml of water was added tetrakis(triphenylphosphine)palladium(0) (17mg, 0,015 mmol). The mixture was heated at 110°C under microwave irradiation for 1h. Additional Sodium carbonate (40 mg, 0.375 mmol), (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (40 mg, 0.240 mmol) et tetrakis(triphenylphosphine)palladium(0) 10 mg, 0.009 mmol) were added and the mixture was stirred for 1h at 110°C under microwave irradiations. After cooling down to rt, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/ [DCM80/CH_3CN 10/MeOH 10/Et3n 0.1] (from 80/20 to 0/100) to give, after crystallization, a white solid (50 mg). From this latter, the 4 isomers of compound 3,5-dimethyl-2-[6-(7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl)pyridazin-3-yl]phenol were separated by SFC chiral phase LC (Column Chiralpak® IG 5µm 250x30mm, Flow rate 115ml/min, eluent (CO_2 70%/ EtOH+0.1%TEA 30%) and after 23 min (CO_2 60%/ EtOH+0.1%TEA 40%), detection 265 nm) to provide successively first TRANS enantiomer, 2-[6-[(4aR,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol eluting at rt =14 min (2.8 mg, **Example 517**) as a white solid, then first CIS enantiomer, 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, Rt =18.5 min (12.9 mg, **Example 518**) as a white solid, then second CIS enantiomer, 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, Rt = 22.5 min (12.8 mg, **Example 519**) as a white solid and second Trans enantiomer, 2-[6-[(4aS,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, Rt = 32 min (3.1 mg, **Example 520**) as a white solid. The absolute configurations cannot be assigned at this stage.

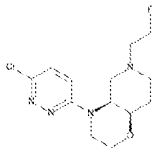
Examples 523 and 524 were synthesized analogously to examples 518-519, using a ChiralpaK® AD-H column.

Examples 515 and 516 were synthesized analogously to examples 518-519, using a ChiralpaK® AY-H column.

Example 521: 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol



Int 521.1: (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine



To a solution of (4aS,8aR)-4-(6-chloropyridazin-3-yl)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (**Int 321.2** – 0.98 mmol, 250 mg) in 10 ml of acetonitrile were added potassium carbonate (1.96 mmol, 274 mg) and 1-fluoro-2-iodo-ethane (0.98 mmol, 80 µl). The mixture was stirred at 60°C for 3h then cooled down to rt, diluted with 50 ml of diethylether, 50 ml of EtOAc and 100 ml of water. The organic layer was washed with 100 ml of water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound (173 mg, 59% yield) as a yellow oil.
LCMS (**Method V**): Rt = 0.59; MS m/z $[M+H]^+$ = 301

2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4] oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 521)

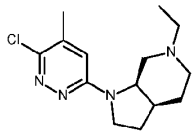
Under Ar, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (1.04 mmol, 172 mg) and (4aS,8aR)-4-(6-chloropyridazin-3-yl)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-

2H-pyrido[4,3-b][1,4]oxazine (0.58 mmol, 173 mg) in 8 ml of 1,4-dioxane were added a 2N sodium carbonate aqueous solution (1.55 mmol, 780 µl), then tetrakis(triphenylphosphine)palladium(0) (0.03 mmol, 33 mg). The mixture was stirred at 100°C for 2h. After cooling down to rt, the mixture was diluted with 50 ml of EtOAc and 50 ml of diethylether and the organic layer was washed successively with 2x20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give the title compound as a white solid (44 mg, 20% yield).

Examples 522, 525 and 527 were synthesized analogously to Example 521.

Example 528: 5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-isopropyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol

Int 528.1: rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-isopropyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine



To a stirred solution of rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridine;2,2,2- trifluoroacetic acid (**Int 460.2** - 420 mg, 0.874 mmol) in 8 ml of acetonitrile at rt were added K_2CO_3 (241 mg, 1.75 mmol) and 2-iodopropane (0.087 mL, 0.874 mmol). The reaction mixture was stirred at 50 °C for 5h. After cooling down to rt, the reaction mixture was poured into water. The aqueous layer was extracted with twice DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH from 98/2 to 85/15, to give the title compound as a pale-yellow oil (50 mg, 17 %).

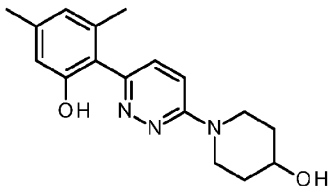
LCMS (**Method T**): Rt = 5.46; MS m/z [M+H]+ = 295.1

5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-isopropyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo [2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol (Example 528)

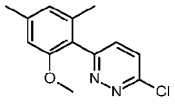
Under Ar, in a sealed tube, to a solution of rac-(3aS,7aR)-1-(6-chloro-5-methyl-pyridazin-3-yl)-6-isopropyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridine (0.0500 g, 0.000170 mol), K_2CO_3 (0.0313 g, 0.000226 mol) and 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.0596 g, 0.000254 mol) in 3.5 ml of 1,4-dioxane and 0.8 ml of water were added XPhos Pd G2 (0.00445 g, 5.65e-6 mol) and XPhos (0.00269 g, 5.65e-6 mol). The mixture was purged again with Ar, then heated at 90 °C for 16h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of DCM/MeOH (100/0 to 90/10), then repurified by flash chromatography on silica gel using a gradient of DCM/MeOH (100/0 to 80/20) to give after lyophilization the title compound as a white solid (5 mg, 5%).

Synthesis of examples according to reaction scheme 2

Example 1: 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-4-ol



Int 1.1: 3-chloro-6-(2-methoxy-4,6-dimethyl-phenyl)pyridazine



Under N_2, to a solution of (2-methoxy-4,6-dimethyl-phenyl)boronic acid (5.56 mmol, 1 g) and 3,6-dichloropyridazine (6.67 mmol, 990 mg) in 20 ml of 1,4-dioxane and 5 ml of water was added cesium carbonate (6.67 mmol, 2.2 g). The solution was purged with Ar, degassed by Ar bubbling, then was added [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.55 mmol, 405 g) and the mixture was stirred at reflux for 1h. After cooling down to rt, NH_4Cl saturated aqueous solution was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using cyclohexane/EtOAc (from 10/0 to 60/40) to give the title compound (900 mg, 65% yield).

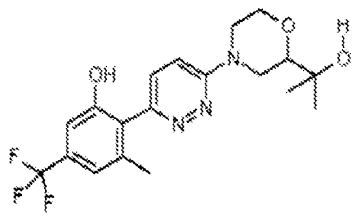
LCMS (Method I): Rt = 1,47 min; MS m/z [M+H]+ 249,2

1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-4-ol (Example 1)

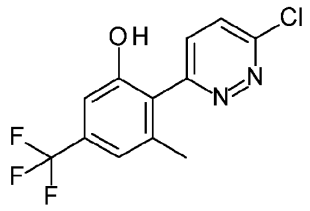
In a vial, piperidin-4-ol (2.4 mmol, 245 mg) and Et_3N (1.22 mmol, 0.18 ml) were added to a solution of 3-chloro-6-(2-methoxy-4,6-dimethyl-phenyl)pyridazine (0.8 mmol, 200 mg) in 4 ml of n-BuOH. The vial was sealed, and the mixture was heated at 150°C for 3 h. After cooling down, EtOAc and water are added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using cyclohexane/EtOAc (from 10/0 to 0/10). 5 ml of DCM are added, and the solution was cooling down to 0°C. Then, a 1M solution of Tribromoboron (2.0 mmol, 2.0 ml) was slowly added and the mixture was stirred at rt for 1,5h. After cooling down to 0°C, MeOH was added, and the resulting mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Sunfire prep C18 OBD; 100 * 30 mm * 10 µm; mobile phase: [water (TFA 10^{-2} N)-ACN]; B%: 0%-30% in 14 min. at 50 ml/min) to give the title compound as a white solid (76 mg, 32% yield).

Compounds Examples 2 and 3 were synthesized analogously to Example 1.

Example 26: 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol



Int 26.2: 2-(6-chloropyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol



In a microwave vial, under Ar, to a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (6.62 mmol, 2 g) and 3,6-dichloropyridazine (9.3 mmol, 1.4 g) in 41 ml of DMF was added a solution of sodium carbonate (14.6 mmol, 1.2 g) in 10 ml of water. The solution was purged with Ar for 10 min, then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.23 mmol, 165 mg) was added. The vial was sealed, and the mixture was heated at 110°C under microwave irradiation for 1h. After cooling down to rt and concentration under reduced pressure, EtOAc was added, and the resulting mixture was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Heptane/EtOAc (8/2). The fractions containing the product were pooled, concentrated under reduced pressure, DCM was added, and the mixture was stirred for 10 min. The suspension was filtered off and dried under reduced pressure to give the title compound as a white solid (598 mg, 31% yield).
LCMS (**Method G**): Rt = 2,51 min; MS m/z $[M+H]^+$ 289

2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 26)

In a microwave vial, under Ar, 2-(morpholin-2-yl)propan-2-ol hydrochloride (0.38 mmol, 73 mg) and DIPEA (0.76 mmol, 0.14 ml) were added to a solution of 2-(6-chloropyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (0.38 mmol, 110 mg) in 1.1 ml of NMP. The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 2h. After cooling down the solution, EtOAc was added, and the solution was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 90/5/5) to give the title compound as a yellow solid (29 mg, 19% yield).

Compounds Examples 27, 28, 29 and 266 were synthesized analogously to Example 26.

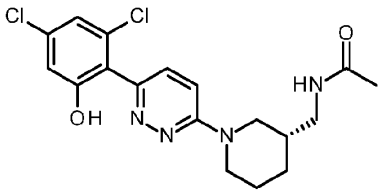
Examples 52 and 53: separation of enantiomers of 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

The 2 enantiomers of compound 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (Example 26, 21 mg) were separated by chiral phase LC (Column Amylose 3, 250*4.6mm 5µm, Flow rate 5ml/min, eluent n-heptane/ethanol (85/15) + 0,1% TEA), to give both enantiomers, first eluting Rt = 17 min, **Example 52** (6.1mg) and second eluting Rt = 21 min, **Example 53** (8.3 mg). The absolute configurations cannot be assigned at this stage.

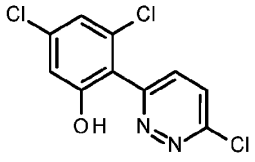
Compounds Examples 59 and 60 were separated enantiomerically from Example 24, analogously to Examples 52 and 53 using a Chiralpak® AD column.

Compounds Examples 94 and 95 were separated enantiomerically from Example 84, analogously to Examples 52 and 53 using a Chiralpak® IC column.

Example 58: N-[[(3S)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide



Int 58.5: 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol



To a solution of (2,4-dichloro-6-hydroxy-phenyl)boronic acid (22.7 mmol) and 3,6-dichloropyridazine (45.4 mmol, 6.76g) in 140 ml of 1,4-dioxane was added 2N sodium

carbonate aqueous solution (61 mmol, 32 ml). The solution was purged with Ar, degassed by Ar bubbling, then was added Tetrakis(triphenylphosphine)palladium(0) (0.907 mmol, 1.05 g) and the mixture was stirred at 75°C for 3.5 h. The reaction was then cooled down and diluted with 300 ml of EtOAc. The organic layer was successively washed with a 5% aqueous citric acid solution and water, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in diethylether, filtered off and the solid washed with diethylether, dried under reduced pressure to give the title compound as a light pink solid (4.27g, 68% yield)

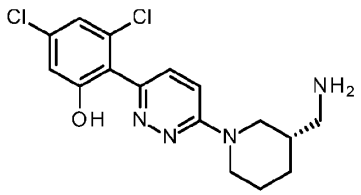
LCMS (**Method I**): Rt = 1.67 min; MS m/z $[M+H]^+$ 275

N-[[(3S)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl]methyl] acetamide (Example 58)

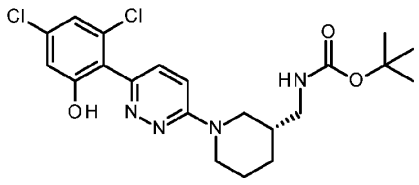
A solution of 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol (0.544 mmol, 150 mg), N-[[(3R)-3-piperidyl]methyl]acetamide;2,2,2-trifluoroacetic acid (1.52 mmol, 586 mg) and Et_3N (2.18 mmol, 0.304 ml) in 3 ml of NMP was stirred at 130°C for 30h. The mixture was cooled down, diluted with AcOEt and diethylether, and washed with water (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 30% of EtOAc in cyclohexane to give the title compound as a yellow solid (82 mg, 38% yield).

Compounds Examples 57, 64 and 66 were synthesized analogously to Example 58.

Example 18: 2-[6-[(3S)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol



Int 18.1: tert-butyl N-[[(3S)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]carbamate



A solution of 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol (0.544 mmol, 150 mg), tert-butyl N-[[(3R)-3-piperidyl]methyl]carbamate (1.14 mmol, 245 mg) in 2.5 ml of NMP was stirred at 130°C for 2h. The mixture was cooled down, diluted with AcOEt and diethylether, then washed with water (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 20% of EtOAc in cyclohexane to give the title compound as a yellow solid (222 mg, 90% yield).

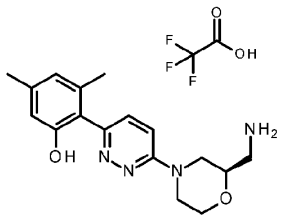
LCMS (**Method O**): Rt = 1.47 min; MS m/z $[M+H]^+$ 453

2-[6-[(3S)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol (Example 18)

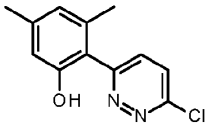
A solution of tert-butyl N-[[(3S)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]carbamate (0.49 mmol, 222 mg) in 18 ml of DCM and 2 ml of TFA was stirred at rt for 3h. The solution was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Sunfire prep C18 OBD; 250 * 50 mm * 10 µm; mobile phase: [water (TFA 10^{-2} N)-ACN]; B%: 10%-100%, 25 min. (50 ml/min). The pure fractions were extracted in DCM / $NaHCO_3$ sat and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a white solid (106 mg, 61% yield).

Compounds Examples 17, 19, 21, 22, 23, 25, 32 to 43, 46, 47, 49, 50, 51, and 55 were synthesized analogously to Example 18.

Example 89: 2-[6-[(3R)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol; 2,2,2-trifluoroacetic acid



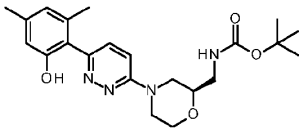
Int 89.1: 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol



In a microwave vial, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (4.15 mmol, 690 mg) and 3,6-dichloropyridazine (3.20 mmol, 500 mg) in 20 ml of 1,4-dioxane and 5 ml of water was added sodium carbonate (9.6 mmol, 790 mg). The solution was purged with Ar, degassed by Ar bubbling, then was added tetrakis(triphenylphosphine)palladium(0) (0.16 mmol, 180 mg). The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. After cooling down, the solution was concentrated under reduced pressure, then 25 ml of DCM was added. The organic layer was washed with water (3 times), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in pentane, filtered off and the solid washed with pentane, dried under reduced pressure to give the title compound as a light brown solid (440 mg, 58% yield).

LCMS (Method G): Rt = 1.54 min; MS m/z $[M+H]^+$ 235

Int 89.2: tert-butyl N-[[(2R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]carbamate



In a microwave vial, under Ar, (S)-tert-butyl(morpholin-2-ylmethyl)carbamate (0.56 mmol, 126 mg) and Et_3N (1.22 mmol, 0,18 ml) were added to a solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (0.56 mmol, 130 mg) in 5 ml of n-BuOH. The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 4h. After cooling down, the solution was concentrated under vacuum. 15 ml of EtOAc was added and the

solution was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 94/3/3) to give the title compound as a yellow solid (48 mg, 21% yield).

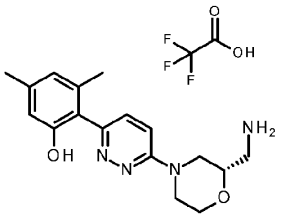
LCMS (Method G): Rt = 1.38 min; MS m/z $[M+H]^+$ 415

2-[6-[(3R)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol ; 2,2,2-trifluoroacetic acid (Example 89)

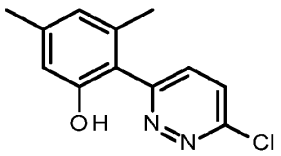
A solution of tert-butyl N-[[(3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]carbamate (0.12 mmol, 49 mg) in 1 ml of DCM and 0.1 ml of TFA was stirred at rt for 16 h. The solution was concentrated under reduced pressure. 1 ml of MeOH was added and the solution was concentrated under reduced pressure (3 times). The residue was triturated in 2 ml of pentane, filtered off and dried under reduced pressure at 40°C for 4h to give the titled compound a light pink solid (27 mg, 53% yield).

Compound Example 107 was synthesized analogously to Example 89.

Example 87: 2-[6-[(2S)-2-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol ; 2,2,2-trifluoroacetic acid



Int 87.1: 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol

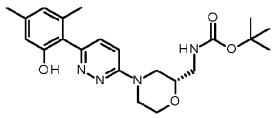


In a microwave vial, to a solution of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (4.15 mmol, 690 mg) and 3,6-dichloropyridazine (3.20 mmol, 500 mg) in 20 ml of 1,4-dioxane

and 5 ml of water was added sodium carbonate (9.6 mmol, 790 mg). The solution was purged with Ar, degassed by Ar bubbling, then was added Tetrakis(triphenylphosphine)palladium(0) (0.16 mmol, 180 mg). The vial was sealed, and the mixture was heated at 100°C under microwave irradiation for 1h. After cooling down, the solution was concentrated under reduced pressure, then 25 ml of DCM was added. The organic layer was washed with water (3 times), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in pentane, filtered off and the solid washed with pentane, dried under reduced pressure to give the title compound as a light brown solid (440 mg, 58% yield).

LCMS (**Method G**): Rt = 1.54 min; MS m/z $[M+H]^+$ 235

Int 87.2: tert-butyl N-[[(2S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]carbamate



In a microwave vial, under Ar, (R)-tert-butyl (morpholin-2-ylmethyl) carbamate (0.51 mmol, 116 mg) and Et_3N (1.12 mmol, 0.16 ml) were added to a solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (0.51 mmol, 116 mg) in 5 ml of n-BuOH. The vial was sealed, and the mixture was heated at 180°C under microwave irradiation for 3h. After cooling down, the solution was concentrated under vacuum. 15 ml of EtOAc was added and the solution was washed with water (3 times) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a yellow solid (63 mg, 29% yield).

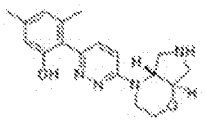
LCMS (**Method G**): Rt = 1.36 min; MS m/z $[M+H]^+$ = 415

2-[6-[(2S)-2-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; 2,2,2-trifluoroacetic acid (Example 87)

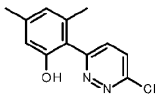
To a solution of tert-butyl N-[[(2S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]carbamate (0.152 mmol, 63 mg) in 1 ml of dichloromethane, 0.12 ml of TFA was added dropwise. The resulting solution was stirred at room temperature for

16h. After completion of reaction, the solution was concentrated under reduced pressure, 1 ml of MeOH was added and the solution was concentrated under reduced pressure (3 times). The residue was suspended in 2 ml of diethyl ether and stirred overnight at room temperature. The suspension was filtered off and dried under reduced pressure to give the titled compound as a light pink solid (34 mg, 52% yield).

Example 190: 2-[6-[rac-(4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol



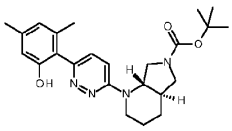
Int 190.1: 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol



In a microwave vial under Ar, to a mixture of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (429 mg, 2.58 mmol) in 8 ml of 1,4-dioxane was added 3-bromo-6-chloro-pyridazine (500 mg, 2.58 mmol) and K_3PO_4 (1.65 g, 7.75 mmol) in 2 ml of water. The mixture was purged with N_2. Then Pd^{118} (185 mg, 0.284 mmol) was added and purged again with N_2. The mixture was then heated at 90°C for 18h. After cooling to rt, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 30/70) to give the title compound as an orange solid (120 mg, 19 % yield)

LCMS (**Method S**): Rt = 1.12 min; MS m/z $[M+H]^+$ = 235.1

Int 190.2: **tert-butyl rac-(4aR,7aS)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-6-carboxylate**



Under Ar, to a stirred solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (154 mg, 0.657 mmol) in 5 ml of tetrahydrofuran at rt were added tert-butyl (4aR,7aR)-3,4,4a,5,7,7a-

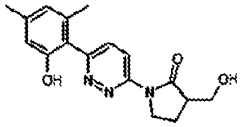
hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxylate (150 mg, 0.657 mmol), LiHMDS (1M in THF) (3.55 mL, 0.3.55 mmol) and BrettPhos Pd G3 (0.0298 g, 0.0329 mmol). The reaction mixture was stirred at 100 °C for 18h. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give the title compound as an orange solid (30 mg, 10 % yield)

LCMS (**Method S**): Rt = 1.34 min; MS m/z $[M+H]^+$ = 427.4

2-[6-[rac-(4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl] pyridazin-3-yl]-3,5-dimethylphenol (Example 190)

At 0°C, to a stirred solution of tert-butyl rac-(4aR,7aR)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazine-6-carboxylate (30.0 mg, 0.007 mmol) in 1 ml of DCM was added TFA (0.0052 mL, 0.703 mmol). The reaction mixture was stirred at 30°C for 18h. After cooling to rt, the mixture was concentrated under reduced pressure. The residue was then taken up in water and basified with an aqueous solution of K_2CO_3 10 %. The mixture was extracted with DCM/MeOH (80/20), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 50ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 15/85 to 45/55, to give after lyophilisation the title compound as a white powder (3 mg, 11 % yield).

Example 122: 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl) pyrrolidin-2-one



In a microwave vial, under Ar, a mixture of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (0.89 mmol, 210 mg), 3-(hydroxymethyl)pyrrolidin-2-one (1.34 mmol, 155 mg), potassium phosphate tribasic (1.79 mmol, 380 mg), 1,1'bis(diphenylphosphino)ferrocene (0.16 mmol, 89 mg) and palladium acetate (0.05 mmol, 12 mg) in 3 ml of 1,4-dioxane was heated at 110°C under microwave irradiation for 2h. After cooling to rt, the reaction mixture was

diluted with EtOAc and filtered. The solid was washed with EtOAc, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 94/3/3) to give the title compound as a brown solid (83 mg, 30% yield).

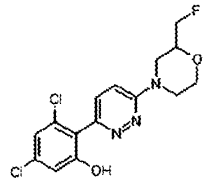
Compounds Examples 131, 132, 235, 250, 264 and 269 were synthesized analogously to Example 122.

Examples 137 and 138: (4R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl)pyrrolidin-2-one (Compound 137) and (4S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl)pyrrolidin-2-one (compound 138) were separated from racemic compound 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl)pyrrolidin-2-one which was synthesized analogously to ex 122 using 4-(hydroxymethyl)pyrrolidin-2-one. The 2 enantiomers of compound 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl)pyrrolidin-2-one (70 mg) were separated by preparative chiral phase LC (Column Chiralcel® OD 5µm, 350x30mm, Flow rate 45ml/min, eluent (n-heptane/ethanol 20/80) + 0,1% TEA, to give both enantiomers, first eluting Rt = 6.0 min, **Example 137** (15 mg) and second eluting Rt = 13 min, **Example 138** (15.5 mg). The absolute configurations cannot be assigned at this stage.

Examples 139 and 140: separation of enantiomers of 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl)pyrrolidin-2-one, namely (3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl)pyrrolidin-2-one (Example 139) and (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl) pyrrolidin-2-one (Example 140)

The 2 enantiomers of compound 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl)pyrrolidin-2-one (**Example 122**, 75 mg) were separated by preparative chiral phase LC (Column Chiralcel® OJ-H 5µm, 350x30mm, Flow rate 45ml/min, eluent (n-heptane/ethanol 60/40) + 0,1% TEA, to give both enantiomers, first eluting Rt = 8.6 min, **Example 139** (20mg) and second eluting Rt = 12.7 min, **Example 140** (28.5 mg). The absolute configurations cannot be assigned at this stage.

Example 161: 3,5-dichloro-2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol



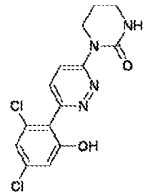
In a microwave vial, under Ar, a suspension of 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol (0.18 mmol, 50 mg), 2-(fluoromethyl)morpholine hydrochloride (0.27 mmol, 42 mg) and diisopropylethylamine (0.40 mmol, 0.07 ml) in 0.5 ml of n-butanol was heated at 160°C under microwave irradiation for 1h. In another microwave vial, under Ar, a suspension of 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol (0.18 mmol, 50 mg), 2-(fluoromethyl)morpholine hydrochloride (0.27 mmol, 42 mg) and diisopropylethylamine (0.40 mmol, 0.07 ml) in 0.5 ml of acetonitrile was heated at 160°C under microwave irradiation for 1h. The reaction mixtures were combined, diluted with CH2Cl2 and the organic layer was washed with 45 ml of water, filtered on hydrophobic column and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (from 100/0/0 to 96/2/2) to give the title compound as a white solid (84 mg, 65% yield).

Examples 237 and 238: separation of enantiomers of 3,5-dichloro-2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol, namely 3,5-dichloro-2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol (example 237) and 3,5-dichloro-2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol (example 238).

The 2 enantiomers of compound 3,5-dichloro-2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol (example 161, 60 mg) were separated by preparative chiral phase LC (Column Chiralpak® AY-H 5µm, 250x30mm, Flow rate 40ml/min, eluent (n-heptane/ethanol 90/10) + 0,1% TEA to give both enantiomers, first eluting Rt = 21.5 min, Example 237 (22.1 mg) and second eluting Rt = 24.8 min, Example 238 (25.4 mg). The absolute configurations cannot be assigned at this stage.

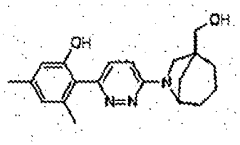
Compounds examples 219 and 220 were separated enantiomerically from example174, analogously to examples 237 and 238 using a Chiralpak® IB-N column.

Example 239: 1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]hexahydropyrimidin-2-one



In a microwave vial, under Ar, a suspension of tetrahydro-2(1H)-pyrimidinone (3.63 mmol, 363 mg), 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol (1.81 mmol, 500 mg), cesium carbonate (3.63 mmol, 1.18 g), $Pd_2(dba)_3$ (0.18 mmol, 166 mg) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.36 mmol, 210 mg) in 10 ml of 1,4-dioxane was heated at 110°C under microwave irradiation for 2h. After cooling to rt, the reaction mixture was diluted with EtOAc, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 0/100). The solid obtained after filtration was also purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 0/100). Fractions from both purifications containing expected compound were combined and concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel using DCM/EtOAc (from 100/0 to 0/100) to give the title compound as a brown solid (46 mg, 7% yield).

Example 114: 2-[6-[1-(hydroxymethyl)-6-azabicyclo[3.2.1]octan-6-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

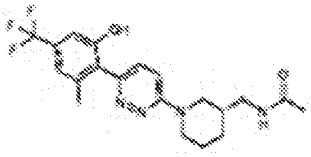


A solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (100 mg, 0.4261 mmol), 6-azabicyclo[3.2.1]octan-1-ylmethanol;hydrochloride (98 mg, 0.5539 mmol) and Triethylamine (198 µl, 1.4062mmol) in 2.5 ml of 1-Butanol was heated at 150°C by microwave irradiation for 2h. 6-azabicyclo[3.2.1]octan-1-ylmethanol;hydrochloride (30 mg) was added and the mixture was heated for 1h at 150°C. After cooling to rt, the reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed

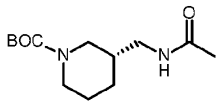
with brine, dry over Mg_2SO_4, filtered, and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel using DCM/ MeOH (100/0 to 95/05) to give after crystallization in diethyl ether, the title compound as a beige solid (20 mg, 13% yield).

Compounds Examples 115, 117, 120, 174, 206 and 207 were synthesized analogously to Example 114.

Example 164: N-[[(3S)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3-piperidyl]methyl]acetamide



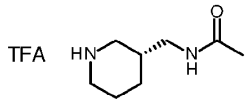
Int 164.1: tert-butyl (3S)-3-(acetamidomethyl)piperidine-1-carboxylate



To a solution of tert-butyl (3S)-3-(aminomethyl)piperidine-1-carboxylate (1 g, 4.6663 mmol) was solubilized in 20 ml of DCM id added triethylamine (656 µl, 4.6663 mmol) and N,N-dimethylpyridin-4-amine (29 mg, 0.2333 mmol). Acetic anhydride (916 µl, 6.9994 mmol) was slowly added to the solution and the mixture was stirred overnight. The reaction mixture was diluted with DCM, washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried on $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (from 100/0 to 95/5) to give the title compound as a colorless oil (1.10 g, 91% yield).

1H NMR (400 MHz, $CDCl_3$, 30°C) δ ppm 1.15 - 1.27 (m, 1 H), 1.29 - 1.38 (m, 1 H), 1.39 (s, 9 H), 1.50 - 1.78 (m, 3 H), 1.92 (s, 3 H), 2.74 - 3.34 (m, 4 H), 3.44 - 3.70 (m, 2 H), 5.50 - 6.04 (m, 1 H)

Int 164.2: **N-[[(3R)-3-piperidyl]methyl]acetamide;2,2,2-trifluoroacetic acid**



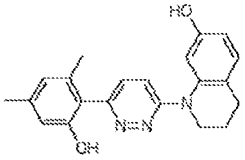
tert-butyl (3S)-3-(acetamidomethyl)piperidine-1-carboxylate (300 mg, 1.1703 mmol) was solubilized in 15 ml of DCM. The mixture was cooled to 0°C and 1.5 ml of TFA was slowly added. After 3h stirring at room temperature, the reaction mixture was concentrated under reduce pressure to give the title compound as a colourless oil (460mg, yield >th), which was used without further purification in the next step.

N-[[(3S)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3-piperidyl]methyl]acetamide (Example 164)

In a microwave vial, under Ar, to a solution of 2-(6-chloropyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (130 mg, 0.4504 mmol) in 2.5 ml of 1-Butanol were added N-[[(3R)-3-piperidyl]methyl]acetamide;2,2,2-trifluoroacetic acid (304 mg, 1.1259 mmol) and triethylamine (314 µl, 2.2518 mmol). The mixture was heated at 160°C under microwave irradiation for 2h. After cooling to rt, the reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give the title compound as a white solid (101 mg, 55% yield).

Compound Example 167 was synthesized analogously to Example 164.

Example 217: 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-7-ol

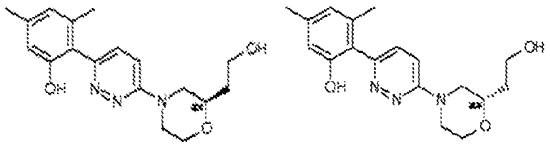


In a microwave vial under Ar, 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (130mg, 0.5539 mmol) and 1,2,3,4-tetrahydroquinolin-7-ol (207 mg, 1,3849 mmol) in 2.5 ml of 1-Butanol were heated at 160°C under microwave irradiation for 2h. After cooling to rt, the reaction mixture was diluted with AcOEt, the organic layer was washed with water and

brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 97/3) to give the title compound as a white solid (23 mg, 12% yield).

Compounds Examples 230, 231, 232, 236, 240, 241, 242, 253, 254 and 272 were synthesized analogously to Example 217.

Examples 233 and 234: 2-[6-[(2R)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol and 2-[6-[(2S)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol

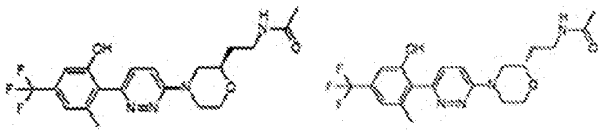


In a microwave vial, under Ar, to a solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (300 mg, 1.2783 mmol) in 6 ml of 1-Butanol were added 2-morpholin-2-ylethanol (419 mg, 3.1958 mmol) and Et_3N (445 µl, 3.1958 mmol). The mixture was heated at 160°C under microwave irradiation for 2h. After cooling to rt, the reaction mixture was diluted with AcOEt, the organic layer was washed with water and brine, dried over and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give 2-[6-[2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (180mg, 43% yield).

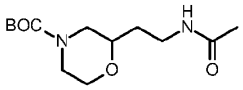
The 2 enantiomers of 2-[6-[2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol were separated by chiral phase LC (Column Cellulose 4, 350x76.5mm, Flow rate 400ml/min, eluent n-heptane/ethanol (75/25) + 0,1% TEA), to give both enantiomers, first eluting Rt = 18.5 min, **Example 233** (81 mg) and second eluting Rt = 25.7 min, **Example 234** (83 mg). Absolute configuration was unknown for the two compounds.

Examples 277 and 278: N-[2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide and N-[2-[(2S)-4-

[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl] acetamide



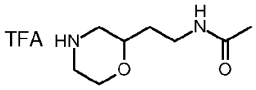
Int 277.1: tert-butyl 2-(2-acetamidoethyl)morpholine-4-carboxylate



To a solution of tert-butyl 2-(2-aminoethyl)morpholine-4-carboxylate (1 g, 4.3421 mmol) in 20 ml of DCM was added Et_3N (610 µl, 4.3421 mmol) and N,N-dimethylpyridin-4-amine (27 mg, 0.2171 mmol). Acetic anhydride (664 mg, 6.5131 mmol) was slowly added, and the mixture was stirred overnight at rt. The reaction mixture was diluted with DCM, the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/5) to give the title compound as colorless oil (1.09 g, 92% yield).

1H NMR (400 MHz, $CDCl_3$, 30°C) δ ppm 1.39 (s, 9 H), 1.46 - 1.57 (m, 1 H), 1.58 - 1.71 (m, 1 H), 1.89 (s, 3 H), 2.55 (br t, J=11.3 Hz, 1 H), 2.84 (br t, J=11.3 Hz, 1 H), 3.14 - 3.24 (m, 1 H), 3.31 - 3.54 (m, 3 H), 3.77 - 3.85 (m, 3 H), 5.89 (br s, 1 H)

Int 277.2: N-(2-morpholin-2-ylethyl)acetamide;2,2,2-trifluoroacetic acid



Tert-butyl 2-(2-acetamidoethyl)morpholine-4-carboxylate (350 mg, 1.2852 mmol) was solubilized in 15 ml of DCM. The solution was cooled to 0°C and TFA (1.5 ml) was added. After 2h stirring at room temperature, the reaction mixture was concentrated under reduce pressure to give the title compound as a colourless oil (631 mg), which was used without further purification in the next step.

1H NMR (400 MHz, DMSO-d6, 30°C) δ ppm 1.45 - 1.67 (m, 2 H), 1.79 (s, 3 H), 2.65 - 2.81 (m, 1 H), 2.89 - 3.10 (m, 2 H), 3.11 - 3.25 (m, 3 H), 3.55 - 3.72 (m, 2 H), 3.95 (dd, J=12.6, 3.5 Hz, 1 H), 7.89 (br t, J=5.5 Hz, 1 H), 8.77 - 9.21 (m, 2 H)

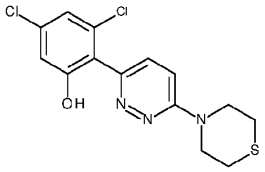
2-[6-[(2R)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 277) and 2-[6-[(2S)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol (Example 278)

In a microwave vial, under Ar, to a solution of 2-(6-chloropyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (150 mg, 0.5197 mmol) in 6 ml of 1-Butanol were added N-(2-morpholin-2-ylethyl)acetamide;2,2,2-trifluoroacetic acid (520 mg 1.2991 mmol) and Et_3N (362 µl, 2.5983 mmol). The mixture was heated at 160°C under microwave irradiation for 2h. After cooling to rt, the reaction mixture was diluted with AcOEt, the organic layer was washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (100/0 to 95/6) to give 140mg of N-[2-[4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide.

The 2 enantiomers of N-[2-[4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide were separated by chiral phase LC (Column CHIRALPAK® IC 20µm, 76.5 x 400 mm, Flow rate 400 ml/min, eluent n-heptane/ethanol (75/25) + 0,1% TEA), to give both enantiomers, first eluting Rt = 8.9 min, **Example 277** (55 mg) and second eluting Rt = 11.9 min, **Example 278** (53 mg).

The absolute configuration was unknown for the two compounds.

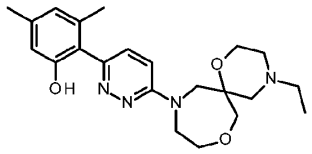
Example 203: 3,5-dichloro-2-(6-thiomorpholinopyridazin-3-yl)phenol



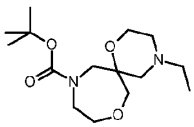
A solution of 3,5-dichloro-2-(6-chloropyridazin-3-yl)phenol (**Int 58.5** – 0.911 mmol, 251 mg), thiomorpholine (1.37 mmol, 141 mg) and triethylamine (1.09 mmol, 152 µl) in 9 ml of n-butanol was stirred at 120°C for 18h. The mixture was cooled down, concentrated under reduced pressure and the residue was diluted with 50 ml of dichloromethane then washed successively with 5 ml of a saturated aqueous sodium bicarbonate solution and 5 ml of brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of EtOAc in toluene to give the title compound (115 mg, 37% yield) as a white solid.

Example 317: 2-[6-(4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecan-8-yl)pyridazin-3-yl]-3,5-dimethyl-phenol



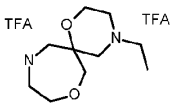
Int 317.1: tert-butyl 4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecane-8-carboxylate



To a stirred solution of tert-butyl 1,11-dioxa-4,8-diazaspiro[5.6]dodecane-8-carboxylate (150 mg, 5.51 mmol) in 5 ml of acetonitrile were added K_2CO_3 (152 mg, 1.10 mmol) and iodoethane (0.0576 mL, 0.716 mmol). The reaction mixture was stirred at rt for 18h. The reaction was quenched with water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (130 mg, 79%) which was used without further purification in the next step.

1H NMR (400 MHz, DMSO-d6) δ (ppm): 3.78 – 3.37 (m, 11H), 2.40 – 2.06 (m, 5H), 1.40 (s, 9H), 0.98 (t, J = 7.1 Hz, 3H).

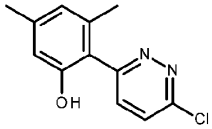
Int 317.2: 4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecane;2,2,2-trifluoroacetic acid



At 0°C, to a stirred solution of tert-butyl 4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecane-8-carboxylate (80 mg, 0.600 mmol) in 5 ml of dichloromethane was added TFA (0.684 g, 0.006.0 mmol). The reaction mixture was stirred at 30 °C for 4h. The reaction mixture was concentrated under reduced pressure to give the title compound (270 mg, quant. Yield: 105%), which was used without further purification in the next step.

1H NMR (500 MHz, DMSO-d6) δ (ppm): 5.59 – 5.31 (m, 1H), 3.78 – 3.60 (m, 2H), 3.62 – 3.28 (m, 4H), 3.16 – 3.04 (m, 1H), 2.98 – 2.89 (m, 1H), 2.90 – 2.71 (m, 2H), 2.37 – 2.31 (m, 1H), 2.30 – 2.21 (m, 3H), 2.22 – 2.15 (m, 1H), 2.03 (d, J = 11.4 Hz, 1H), 0.97 (t, J = 7.2 Hz, 3H).

Int 317.3: 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol



In a microwave vial, under N2, to a mixture of (2-hydroxy-4,6-dimethyl-phenyl)boronic acid (730 mg, 4.40 mmol) in 16 ml of 1,4-dioxane were added 3-bromo-6-chloro-pyridazine (1.00 g, 5.16 mmol) and K_3PO_4 (3.30 g, 15.5 mmol) in 4 ml of water. The mixture was purged with N_2. Pd118 (370 mg, 0.568 mmol) was added, and the mixture was purged again with N2. The mixture was then heated at 90 °C for 2.5h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (100/0 to 50/50, then 30/70) to give the title compound as an orange solid (180.5 mg, 15 %).

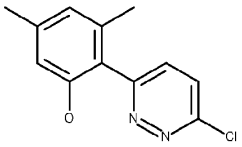
LCMS (**Method S**): Rt = 1.08; MS m/z $[M-H]^+$ = 235.1

2-[6-(4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecan-8-yl)pyridazin-3-yl]-3,5-dimethyl-phenol (Example 317)

To a stirred solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (Int 317.3 - 20.0 mg, 0.0852 mmol) in 1 ml of tetrahydrofuran were added 4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecane;2,2,2-trifluoroacetic acid (**Int 317.2** - 36.5 mg, 0.0852 mmol), LiHMDS (1M in THF) (0.460 mL, 0.460 mmol) and BrettPhos Pd G3 (3.86 mg, 0.00426 mmol) under inert atmosphere. The reaction mixture was stirred at 90°C for 2.5h. The reaction mixture was cooled down to rt, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/EtOAc (100/0 to 95/5) to give 8.5 mg of a colorless oil. This oil was purified by reverse phase Column YMC –Actus Triart Prep C18-S 150*30mm 5 µm Flow rate 40ml/min-Focused gradient MeCN/aq.NH_4HCO_3 0.2% pH=7.9 Focused gradient from 35/65 to 75/25, to give after lyophilization, the title compound (3 mg, 6%).

Examples 329 and 330: (6R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one and (6S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one

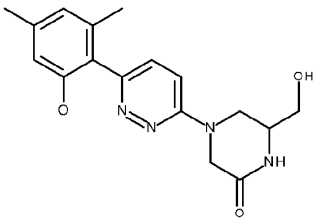
Int 329.1: 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol



Under Ar, to a solution of (2-hydroxy-4,6-dimethylphenyl)boronic acid (12.05 mmol, 2 g) and 3,6-dichloropyridazine (12.05 mmol, 1.79 g) in 32 ml of 1,2-dimethoxyethane were added sodium carbonate (30.12 mmol, 3.19 g) and 8 ml of water. The solution was purged with Ar, then $Pd(PPh_3)_4$ (0.60 mmol, 696 mg) was added. The reaction mixture was heated under reflux for 4h. After cooling down to rt, the solution was concentrated under reduced pressure. 42 ml of EtOAc was added and the resulting mixture was filtered. The solid was taken up in a EtOAc/CH_2Cl_2 mixture, to give after trituration and filtration, the title compound as a pale brown solid (866 mg). Besides, to the filtrate, EtOAc was added, and the organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in CH_2Cl_2, then filtered to afford the title compound as a pale brown solid (858 mg). Overall, the title compound was obtained as a pale brown solid (1.57 g, 56% yield).

LCMS (**Method U**): Rt = 1.36 min; MS m/z [M+H]+ = 235

Int 329.2: 4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl) piperazin-2-one



In a microwave vial, under Ar, to a suspension of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (0.43 mmol, 100 mg) in 1 ml of 1-butanol was added 6-(hydroxymethyl)piperazin-2-one hydrochloride (0.64 mmol, 106 mg), diisopropylethylamine (0.85 mmol, 0.15 ml) and the resulting mixture was heated at 150°C under microwave irradiation for 1h30. After cooling down to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (100/0/0 to 80/10/10) to give the title compound as a yellow solid (61 mg, 44% yield).
LCMS (**Method G**): Rt = 1.69; MS m/z [M+H]+ = 329

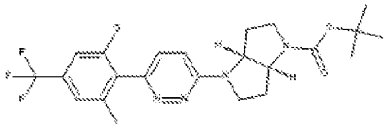
(6R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl) piperazin-2-one and (6S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one (Examples 329 and 330)

The 2 enantiomers of 4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one were separated by chiral phase LC (Column Chiralpak® IC 5µm, 250x30mm, Flow rate 40ml/min, eluent (n-heptane/ethanol 60/40) + 0,1% TEA, to give both enantiomers, first eluting Rt = 10.3 min, **Example 329** (15.8 mg, yield 26%) and second eluting Rt = 14.4 min, **Example 330** (14.5 mg, yield 24%). The absolute configurations cannot be assigned at this stage.

Chiral separation of compounds Examples 419 and 420 were realized analogously to Example 329 and 330.

Example 346: 3-methyl-2-[6-[rac-(3aS,6aS)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride

Int 346.1: tert-butyl rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl]pyridazin-3-yl]-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrole-4-carboxylate



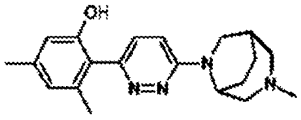
To a solution of 2-(6-chloropyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (100 mg, 0.3464 mmol) in 2 ml of 1-Butanol was added tert-butyl cis-hexahydropyrrolo[3,2-

B]pyrrole-1(2H)-carboxylate (147 mg, 0.6929 mmol) and Triethylamine (0.121 ml, 08661 mmol). The mixture was heated at 160°C for 2h under microwave irradiation. After cooling down to rt, the reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH (from 100/0 to 95/5) to give the title compound as a yellow solid (62 mg, 38% yield).
LCMS (**Method G**): Rt = 1.01; MS m/z $[M+H]^+$ = 465

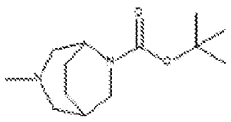
3-methyl-2-[6-[rac-(3aS,6aS)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride (Example 346)

To a solution of tert-butyl rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrole-4-carboxylate (62 mg, 0.1335 mmol) in 4 ml of DCM was added a solution of HCl 4N in dioxane (0.33ml, 1.3348 mmol) and mixture was heated at 50°C for 1h and stirred at RT overnight. Additional HCl 4N in dioxane (0.40 ml 1.6179 mmol) was added and the reaction mixture was heated at 50°C for 3h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was crystallized in acetone, filtered, and washed with acetone to give the title compound as a cream solid (36 mg, 67% yield).

Example 410: 3,5-dimethyl-2-[6-(3-methyl-3,6-diazabicyclo[3.2.2]nonan-6-yl)pyridazin-3-yl]phenol



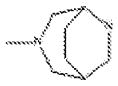
Int 410.1: tert-butyl 3-methyl-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate



To a solution of tert-butyl 3,6-diazabicyclo[3.2.2]nonane-6-carboxylate (400 mg, 1.7674 mmol) in 12 ml of THF was added by portions sodium hydride 60% (78 mg, 1.9442 mmol).

After stirring 30 min, Iodomethane (276 mg, 1.9442 mmol) was added, and the mixture was stirred at rt overnight. The mixture was concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH (100/0 to 97/3) to give the title compound as a yellow oil (450 mg), which was used without further purification in the next step.

Int 410.2: 3-methyl-3,6-diazabicyclo[3.2.2]nonane;2,2,2-trifluoroacetic acid



To a solution of tert-butyl 3-methyl-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate (450 mg, 1.8723 mmol) in 20 ml of DCM was added 2 ml of TFA. The reaction was stirred for 16h. The reaction was concentrated under reduce pressure and the residue obtained was used without further purification in the next step.

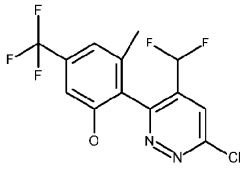
3,5-dimethyl-2-[6-(3-methyl-3,6-diazabicyclo[3.2.2]nonan-6-yl)pyridazin-3-yl]phenol (Example 410)

In a microwave vial, to a solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (100 mg, 0.4261 mmol) in 2 ml of 1-Butanol was added 3-methyl-3,6-diazabicyclo[3.2.2]nonane;2,2,2-trifluoroacetic acid (313 mg, 0.8522 mmol) and Triethylamine (0.148ml, 1.0653 mmol). The mixture was heated at 160°C under microwave irradiation for 2h. Additional 3-methyl-3,6-diazabicyclo[3.2.2]nonane;2,2,2-trifluoroacetic acid (100 mg, 0.2723 mmol) and Triethylamine (0.200 ml, 1.4396 mmol) were added and the mixture was heated for 1h30 at 160°C. After cooling down to rt, the mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of DCM/MeOH (100/0 to 90/10) to give, after crystallization in pentane, the title compound as a white solid (10 mg, 7% yield).

Compound Examples 417 was synthesized analogously to Example 410.

Example 372: (4S)-1-[5-(difluoromethyl)-6-[2-hydroxy-6-methyl-4-(trifluoromethyl) phenyl] pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one

Int 372.1: 2-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl) phenol

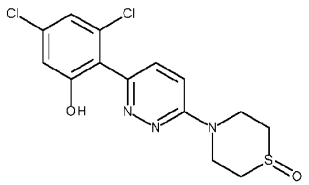


In a microwave vial, under Ar, to a solution of 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (2.48 mmol, 0.75 g) and 3,6-dichloro-4-(difluoromethyl)pyridazine (2.48 mmol, 0.49 g) in 12 ml of 1,2-dimethoxyethane were added sodium carbonate (6.20 mmol, 0.66 g), 3 ml of water and $Pd(PPh_3)_4$ (0.12 mmol, 143 mg). The reaction mixture was purged with Ar, then heated at 100°C under microwave irradiation for 1h. After cooling down to rt, EtOAc was added, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (100/0/0 to 96/2/2) to give the title compound as a brown solid (88 mg, 10% yield).
LCMS (**Method B**): Rt = 1.64; MS m/z [M+H]+ = 339

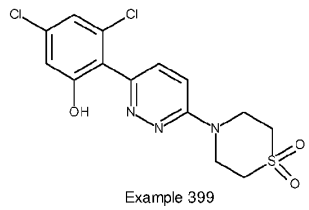
(4S)-1-[5-(difluoromethyl)-6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl] pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one (Example 372)

In a microwave vial, under Ar, a suspension of 2-[6-chloro-4-(difluoromethyl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol (0.24 mmol, 82 mg), (S)-4-hydroxy-2-pyrrolidinone (0.29 mmol, 29 mg), potassium phosphate tribasic (0.48 mmol, 103 mg), 1-1'-bis(diphenylphosphino)ferrocene (0.07 mmol, 40 mg), palladium acetate (0.02 mmol, 5 mg) in 1.2 ml of 1,4-dioxane was heated at 110°C under microwave irradiation for 2h. After cooling down to rt, EtOAc and CH_2Cl_2 were added, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH/ACN (100/0/0 to 90/5/5) to give the title compound as a brown solid (26 mg, 27% yield).

Example 399 and 400: 3,5-dichloro-2-[6-(1,1-dioxo-1,4-thiazinan-4-yl)pyridazin-3-yl]phenol and 3,5-dichloro-2-[6-(1-oxo-1,4-thiazinan-4-yl)pyridazin-3-yl]phenol

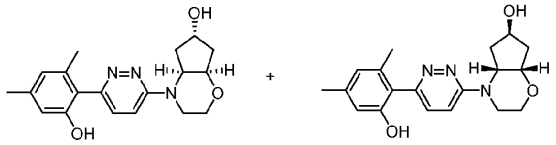

Example 400

and

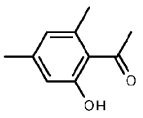

Example 399

At 0°C, to a solution of 3,5-dichloro-2-(6-thiomorpholinopyridazin-3-yl)phenol (**Example 203** - 0.14 mmol, 48 mg) in 10 ml of DCM was added 3-chloroperoxybenzoic acid (0.18 mmol, 31 mg). The mixture was stirred at 0°C for 25 min, then diluted with 20 ml of DCM. The organic layer was washed with 20 ml of a saturated aqueous sodium bicarbonate solution and 20 ml of brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give successively **Example 399** (26 mg, 49% yield) as a pale yellow solid and **Example 400** (25 mg, 50% yield) as a white solid.

Examples 466 and 467: (4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol and (4aS,6S,7aR)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol



Int 466.1: 1-(2-hydroxy-4,6-dimethyl-phenyl)ethanone

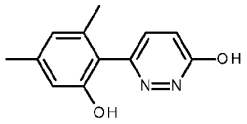


At rt, under Ar, to 3, 5-dimethylphenol (24.4 g, 200 mmol) was slowly added $TiCl_4$ (24.1 mL, 220 mmol). The reacting mixture was stirred at rt. When gas evolution ceased, acetyl chloride (23.5 g, 300 mmol) was added. The resulting mixture was stirred at room temperature for 15 minutes, then warmed to 120 °C for 1h. After cooling down to rt, the

resulting mixture was diluted with methylene chloride (250 mL) and quenched with water (150 mL). The organic layer was washed twice with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 95/5) to give the title compound as a light yellow solid (29.5 g, yield: 90%).

1H NMR (400 MHz, $CDCl_3$) δ : 12.68 (s, 1H), 6.65 (s, 1H), 6.54 (s, 1H), 2.64 (s, 3H), 2.56 (s, 3H), 2.27 (s, 3H) ppm.

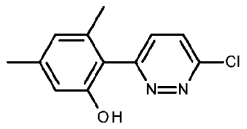
Int 466.2: 6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-ol



In an ice-bath, a solution of aqueous potassium hydroxide (20%, w/v) was added dropwise to an aqueous solution of glyoxylic acid (50%, 27.1 g, 183 mmol) till the pH reach 9. Then was added dropwise while cooling a solution of 1-(2-hydroxy-4,6-dimethyl-phenyl)ethanone (**Int 466.1**, 30 g, 183 mmol) in an aqueous potassium hydroxide solution (20% w/v, 10.3 g of KOH). The resulting mixture was stirred for 2.5h at rt, then cooled to 0°C and acidified with acetic acid to pH=8. The solution was extracted twice with dichloromethane. Acetic acid was added to the aqueous solution till pH=4. Then ammonia solution was added till pH=8. Hydrazine hydrate 85% (11.8 g, 20.1 mmol) was added, the reaction mixture was inerted under Ar, then warmed for 2.5h at 100°C. After cooling down to rt, the solid was filtered off, washed with water and dried over P_2O_5 to give the title compound as white solid (12.7 g, 32.1% yield).

LCMS (**Method Z5**): Rt = 1.56; MS m/z $[M+H]^+$ = 217

Int 466.3: 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol

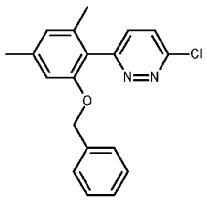


Under Ar, in an ice bath, to a solution of phosphorus oxychloride (44.7 g, 291 mmol) in 40 ml of DMF was added quickly by portions 6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-ol (**Int 466.2** - 12.6 g, 58.3 mmol). The solution was heated to 85 °C for 18h. After cooling

down to rt, the reacting mixture was poured slowly into ice-cold water and extracted twice with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 95/5) to give the title compound as a yellow solid (7.8 g, 57% yield).

1HNMR (500 MHz, DMSO-d_6) δ = 9.54 (s, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 6.63 (d, J = 4.0 Hz, 2H), 2.24 (s, 3H), 2.02 (s, 3H) ppm.

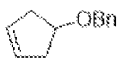
Int 466.4: 3-(2-benzyloxy-4,6-dimethyl-phenyl)-6-chloro-pyridazine



To a solution of 2-(6-chloropyridazin-3-yl)-3,5-dimethyl-phenol (Int 466.3 - 3.0 g, 12.8 mmol) in 60 ml of DMF was added bromomethylbenzene (2.62 g, 15.3 mmol) and K_2CO_3 (3.53 g, 25.6 mmol). The solution was stirred at room temperature overnight. The resulting solution was poured into water and extracted with Ethyl acetate (3 times). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as an oil (3.80 g, yield 91.5%).

LCMS (**Method Z6**): Rt = 2.15; MS m/z $[M+H]^+$ = 325

Int 466.5: cyclopent-3-en-1-yloxymethylbenzene



At 0°C, to a solution of cyclopent-3-en-1-ol (10.0 g, 0.119 mol) in 100 ml of toluene was slowly added NaH (60%, 7.13 g, 0.178 mol). The mixture was stirred at 0°C for 1h and benzyl bromide (22.4 g, 0.131 mol) was added. The reaction mixture was stirred at rt for 18h. The resulting mixture was poured into ice water (300 mL) and extracted with DCM (100 mL×3). The organic layer was washed by brine, dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether 100% to give the title compound as an oil (14.8 g, 71.5% yield).

LCMS (**Method Z4**): Rt = 2.11; MS m/z $[M+18]^+$ = 192.1

Int 466.6a and Int 466.6b: (1R,3s,5S)-3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane and (1R,3r,5S)-3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane



and

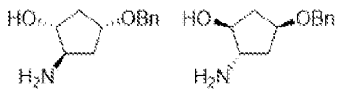
At 0°C, to a solution of cyclopent-3-en-1-yloxymethylbenzene (14.8 g, 84.9 mmol) in 200 ml of DCM was added m-CPBA (29.3 g, 170.0 mmol). The solution was stirred at rt overnight. The resulting mixture was quenched with saturated Na_2SO_3 solution and adjusted to pH = 8 ~ 9 with saturated Na_2CO_3 solution. The resulting mixture was extracted with DCM (3 times). The pooled organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give (1R,3s,5S)-3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane as an oil (6.0 g, 37.1% yield) and (1R,3r,5S)-3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane as an oil (6.7 g, 41.5% yield).

LCMS:

Int 466.6a (**Method Z4**): Rt = 1.69; MS m/z $[M+H]^+$ = 191.1

Int 466.6b (**Method Z4**): Rt = 1.55; MS m/z $[M+H]^+$ = 191.1

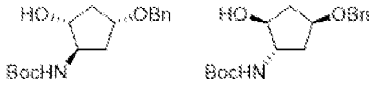
Int 466.7: rac-(1R,2R,4R)-2-amino-4-benzyloxy-cyclopentanol



In a vial, to (1R,3r,5S)-3-(benzyloxy)-6-oxabicyclo[3.1.0]hexane (Int 466.6b, 4.70 g, 24.7 mmol) was added 60 ml of $NH_3.H_2O$ (28% in water). The vial was sealed and stirred at 60°C overnight. The reaction mixture was concentrated under reduced pressure to give the title compound as a solid (5.12 g) which was used without further purification in the next step.

LCMS (**Method Z4**): Rt = 1.11; MS m/z $[M+H]^+$ = 208.1

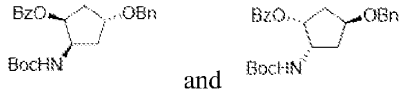
Int 466.8: tert-butyl N-[rac-(1R,2R,4R)-4-benzyloxy-2-hydroxy-cyclopentyl] carbamate



To a solution of rac-(1R,2R,4R)-2-amino-4-benzyloxy-cyclopentanol (5.12 g, 24.7 mmol) in 50 ml of methanol was added Boc_2O (8.09 g, 37.1 mmol) and TEA (5.16 mL, 37.1 mmol). The resulting mixture was stirred overnight at rt. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (4.59 g, 60.4% two steps yield).

LCMS (**Method Z5**): Rt = 1.84; MS m/z $[M+H]^+$ = 330.4

Int 466.9: [rac-(1S,2R,4R)-4-benzyloxy-2-(tert-butoxycarbonylamino)cyclopentyl] benzoate

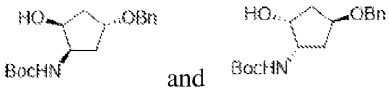


and

At 0°C, to a solution of PPh_3 (5.87 g, 22.4 mmol) in 50 ml of anhydrous THF was added DIAD (4.41 mL, 22.4 mmol). The solution was stirred at 0°C for 20 min. Then were added tert-butyl N-[rac-(1R,2R,4R)-4-benzyloxy-2-hydroxy-cyclopentyl]carbamate (**Int 466.8**; 4.59 g, 14.9 mmol) and benzoic acid (2.19 g, 17.9 mmol), and the reaction was stirred at room temperature for 16h. The reaction mixture was quenched with water, extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (5.20 g, 74.4% yield).

LCMS (**Method Z5**): Rt = 2.14; MS m/z $[M\text{-boc}]^+$ = 312.4

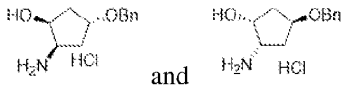
Int 466.10: tert-butyl N-[rac-(1R,2S,4R)-4-benzyloxy-2-hydroxy-cyclopentyl] carbamate



To a solution of [rac-(1S,2R,4R)-4-benzyloxy-2-(tert-butoxycarbonylamino)cyclopentyl] benzoate (5.20 g, 11.1 mmol) in 100 ml of ethanol and 50 ml of water was added K_2CO_3 (2.30 g, 16.7 mmol). The solution was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure. To the residue was added EA and water. The aqueous layer was extracted twice with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether / acetone (100/0 to 0/100) to give the title compound as a solid (3.07 g, yield 88.9 %).

LCMS (**Method Z5**): Rt = 1.87; MS m/z $[M+Na]^+$ = 330.4

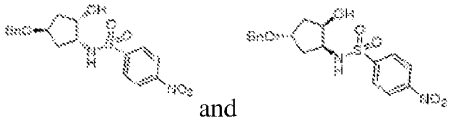
Int 466.11: rac-(1S,2R,4R)-2-amino-4-benzyloxy-cyclopentanol;hydrochloride



To a solution of tert-butyl N-[rac-(1R,2S,4R)-4-benzyloxy-2-hydroxy-cyclopentyl]carbamate (3.07 g, 9.53 mmol) in 30 ml of DCM was added 5 ml of HCl (4 M in 1,4-dioxane). The solution was stirred at rt for 2h. The reaction mixture was concentrated under reduced pressure to give the title compound as solid (2.56 g), which was used without further purification in the next step.

LCMS (**Method Z5**): Rt = 1.37; MS m/z $[M+H]^+$ = 208.4

Int 466.12: 4-nitro-N-[rac-(1R,2S,4R)-4-benzyloxy-2-hydroxy-cyclopentyl] benzenesulfonamide

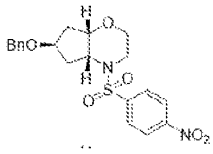


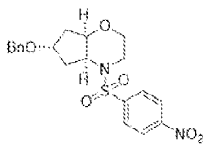
To a solution of rac-(1S,2R,4R)-2-amino-4-benzyloxy-cyclopentanol;hydrochloride (2.56 g, 10.5 mmol) in 30 ml of anhydrous DCM was added 4-nitrobenzenesulfonyl chloride (2.56 g, 11.6 mmol) and TEA (4.39 mL, 31.5 mmol). The mixture was stirred for 2h at rt. The reaction mixture was quenched with water and extracted with DCM (3 times). The combined

organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (3.07 g, two steps 78% yield).

LCMS (**Method Z5**): Rt = 1.84; MS m/z $[M+H]^+$ = 393.3

Int 466.13: rac-(4aR,6R,7aS)-6-benzyloxy-4-(4-nitrophenyl)sulfonyl-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazine

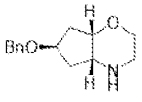


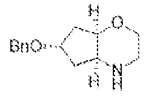
and


At 0°C, to a solution of 4-nitro-N-[rac-(1R,2S,4R)-4-benzyloxy-2-hydroxy-cyclopentyl]benzenesulfonamide (3.07 g, 6.92 mmol) in 400 ml of anhydrous DCM was added NaH (60%, 1.50 g, 37.4 mmol). After stirring for 10 minutes was added 2-bromoethyl(diphenyl)sulfonium;trifluoromethanesulfonate (8.29 g, 18.7 mmol). After stirring overnight at rt, TEA (2.51 mL) was added. The reaction was stirred at rt overnight. The reaction mixture was quenched with saturated NH_4Cl and extracted with DCM (3 times). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (1.20 g, 39.9% yield).

LCMS (**Method Z5**): Rt = 1.93; $[M+H]^+$ = 419.3

Int 466.14: rac-(4aR,6R,7aS)-6-benzyloxy-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b][1,4]oxazine



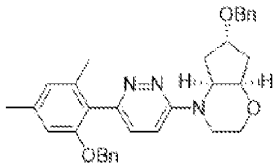
and


To a solution of rac-(4aR,6R,7aS)-6-benzyloxy-4-(4-nitrophenyl)sulfonyl-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazine (1.20 g, 2.76 mmol) in 12 ml of DMF was added 2-sulfanylacetic acid (611 mg, 6.63 mmol) and $LiOH.H_2O$ (649 mg, 15.5 mmol). The solution was stirred at rt overnight. The reaction mixture was quenched with water and

extracted with DCM (3 times). The combined organic layers were washed by saturated LiCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with DCM/(7N NH_3/MeOH) (100/0 to 0/100) to give the title compound as a solid (190 mg, 28.3% yield).

LCMS (**Method Z4**): Rt = 1.33; $[M+H]^+$ = 234.0

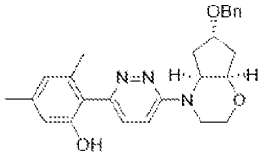
Int 466.15: rac-(4aR,6R,7aS)-6-benzyloxy-4-[6-(2-benzyloxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazine



Under Ar, to a solution of 3-(2-benzyloxy-4,6-dimethyl-phenyl)-6-chloro-pyridazine (Int 466.4, 265.0 mg, 0.814 mmol) and rac-(4aR,6R,7aS)-6-benzyloxy-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b][1,4]oxazine (Int 466.14 - 190 mg, 0.814 mmol) in 5 ml of anhydrous toluene were added Cs_2CO_3 (796 mg, 2.44 mmol), $Pd_2(dba)_3$ (47 mg, 0.081 mmol) and [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (101 mg, 0.163 mmol). The solution was purged again with Ar and stirred at 110°C overnight under argon. After cooling down to rt, the mixture was poured into water and extracted with ethyl acetate (3 times). The combined organic layers were washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (95 mg, 22.4% yield).

LCMS (**Method Z4**): Rt = 2.42; MS m/z $[M+H]^+$ = 522.0

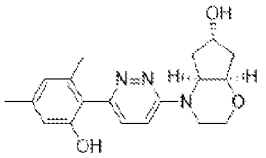
Int 466.16: 3,5-dimethyl-2-[6-[rac-(4aR,6R,7aS)-6-benzyloxy-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol



To a solution of rac-(4aR,6R,7aS)-6-benzyloxy-4-[6-(2-benzyloxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazine (95 mg, 0.128 mmol) in 5 ml of THF was added $Pd(OH)_2$ (10% wet, 50 mg). The mixture was purged with hydrogen and stirred at 40°C overnight under hydrogen. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (40 mg, yield 50.8%).

LCMS (**Method Z4**): Rt = 2.11; MS m/z $[M+H]^+$ = 432.0

Int 466.17: rac-(4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol



To the solution of 3,5-dimethyl-2-[6-[rac-(4aR,6R,7aS)-6-benzyloxy-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol (40 mg, 0.093 mmol) in 5 ml of EtOH was added Pd-C (10% wet, 20 mg) and $Pd(OH)_2$ (10% wet, 20 mg). The mixture was purged with hydrogen and stirred at 40°C overnight under hydrogen. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/EA (100/0 to 0/100) to give the title compound as a solid (18 mg, yield 56.9%).

LCMS (**Method Z4**): Rt = 1.43; MS m/z $[M+H]^+$ = 342.0

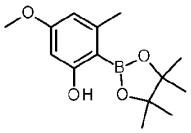
(4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol and (4aS,6S,7aR)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol (Examples 466 and 467)

Both enantiomers of rac-(4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol (18 mg) were separated by SFC (Column: IC 25*250 mm, 10 um (Daicel), Column temperature: 35 °C, Mobile phase: CO_2/MEOH[0.2%NH_3(7M in MeOH)]= 60/40, Flow rate: 120 ml/min) to provide

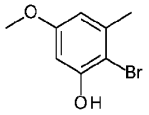
(4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol (first enantiomer eluting at Rt = 5.51 (6.10 mg, **Example 466**) as white solid and (4aS,6S,7aR)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol (second enantiomer eluting at Rt = 7.05 (6.70 mg, **Example 467**) as white solid.
The absolute configurations cannot be assigned at this stage.

Synthesis of intermediates

5-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Int 96.1: 2-bromo-5-methoxy-3-methyl-phenol



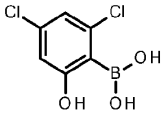
To a solution of 3-methoxy-5-methyl-phenol (43.4 mmol, 6g) in 60 ml of anhydrous DCM pre-cooled to 10°C was added N-bromosuccinimide (47.8 mmol, 8.5 g) by portions while maintaining temperature at 15°C. The mixture was stirred at 15°C for 10 min then diluted with 30 ml of petroleum ether and filtered off. The cake was rinsed with 10 ml of a 30/70 mixture of DCM/petroleum ether and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of diisopropylether in petroleum ether to give the title compound as a white solid (5.2g, 55% yield).
LCMS (**Method H**): Rt = 1.60 min; MS m/z $[M-H]^+$ 215

Int 96.2: 5-methoxy-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol
Under Ar at 0°C, to a solution of 2-bromo-5-methoxy-3-methyl-phenol (4.6 mmol, 1g) in 20 ml of anhydrous 1,4-dioxane was added Et_3N (10.6 mmol, 1.48 ml) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.9 mmol, 1.83 ml). Then, were added diacetoxypalladium (0.23 mmol, 52 mg) and dicyclohexyl-(2-phenylphenyl)phosphane (0.46 mmol, 161 mg) and the mixture was stirred at 75°C for 1.5h. After cooling down to rt, the mixture was diluted with

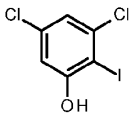
diethylether and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50% of diethylether in petroleum ether to give the title compound as a yellow solid (880 mg, 72% yield).

LCMS (**Method L**): Rt = 1.01 min; MS m/z $[M+H]^+$ 265

(2,4-dichloro-6-hydroxy-phenyl)boronic acid



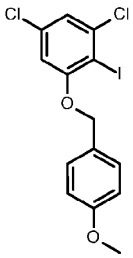
Int 58.1: 3,5-dichloro-2-iodo-phenol



To a cooled (0-5°C) suspension of NaH (60% in oil – 371 mmol, 14.8 g) in 140 ml of toluene, was slowly added a solution of 3,5-dichlorophenol (177 mmol, 30 g) in 150 ml of toluene while keeping temperature below 10°C. The mixture was stirred for 45 min at 0-5°C, then a solution of iodine (177 mmol, 44.8 g) in 330 ml of toluene was slowly added while keeping temperature below 10°C. The mixture was stirred at 0-5°C for 30 min, then quenched with 135 ml of an aqueous 2N HCl solution. The organic layer was successively washed with aqueous 10% sodium bisulfite solution and water then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a white solid (33g, 66% yield).

LCMS (**Method I**): Rt = 1.91 min; MS m/z $[M-H]^+$ 287

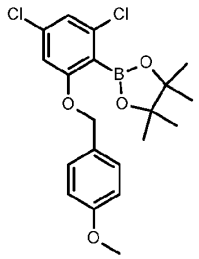
Int 58.2: 1,5-dichloro-2-iodo-3-[(4-methoxyphenyl)methoxy]benzene



A suspension of 3,5-dichloro-2-iodo-phenol (94.2 mmol, 27.2 g), 1-(chloromethyl)-4-methoxy-benzene (98.9 mmol, 15.5 g) and K_2CO_3 (113 mmol, 15.6 g) in 100 ml of DMF was stirred at 80°C for 1h. After cooling down to rt and diluted with 800 ml of diethyether and 300 ml of water, the organic layer was washed with water (3 times), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated in a mixture of pentane and diethylether (80/20), filtered off and the solid washed with pentane and dried under reduced pressure to give the title compound as a white solid (30g, 78% yield)

LCMS (**Method I**): Rt = 2.54 min; MS m/z $[M+H]^+$ 409

Int 58.3: 2-[2,4-dichloro-6-[(4-methoxyphenyl)methoxy]phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Under Ar, at 0°C, to a solution of 1,5-dichloro-2-iodo-3-[(4-methoxyphenyl)methoxy]benzene (36.7 mmol, 15g) in 160 ml of anhydrous 1,4-dioxane was added Et_3N (73.3 mmol, 10 ml), and slowly 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (73.3 mmol, 10 ml). Then, was added diacetoxypalladium (1.83 mmol, 412 mg) and dicyclohexyl-(2-phenylphenyl)phosphane (3.67 mmol, 1.29 g) and the mixture was stirred at 80°C for 1h. After cooling down, the mixture was diluted with diethylether and pentane (80/20) and washed twice with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50% of diethylether in cyclohexane to give the title compound as colorless oil (9.27g, 62% yield).

LCMS (**Method N**): Rt = 2.35 min; MS m/z $[M+Na]^+$ 431

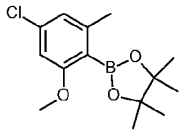
Int 58.4: (2,4-dichloro-6-hydroxy-phenyl)boronic acid

To a cooled (-10°C) solution of 2-[2,4-dichloro-6-[(4-methoxyphenyl)methoxy]phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22.7 mmol, 9.2 g) and anisole (92 mmol, 10 ml) in

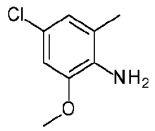
100 ml of DCM was added dropwise TFA (453 mmol, 34 ml) for 20 min. The mixture was stirred at 0°C, then quenched with 300 ml of an aqueous saturated NH_4Cl solution. 200 ml of water was added. The aqueous layer was extracted twice with DCM and the combined organic layers were dried over Na_2SO_4, filtered off and concentrated under reduced pressure. The residue was used without further purification for next step.

LCMS (**Method I**): Rt = 1.30 min; MS m/z $[M-H]^+$ 205

2-(4-chloro-2-methoxy-6-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



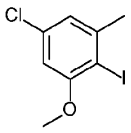
Int 63.1: 4-chloro-2-methoxy-6-methyl-aniline



To a solution of 2-bromo-4-chloro-6-methyl-aniline (104 mmol, 23 g) in 15 ml of MeOH was added a 5.4 N sodium methoxide solution in MeOH (522 mmol, 97 ml), then Copper(I) iodide (120 mmol, 22.8 g) and the mixture was stirred at reflux for 2h. After cooling to rt, 1 L of water was added and the resulting solution was extracted with EtOAc. The mixture was filtered over Dicalite® and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of EtOAc in heptane to give the title compound as a brown oil (12.6g, 70% yield).

LCMS (**Method H**): Rt = 1.53 min; MS m/z $[M+H]^+$ 172

Int 63.2: 5-chloro-2-iodo-1-methoxy-3-methyl-benzene



At 0°C, to a solution of 4-chloro-2-methoxy-6-methyl-aniline (11.65 mmol, 2g) in 40 ml of ACN and 45 ml of 4 N aqueous HCl solution was added sodium iodide (23.3 mmol, 3.5 g).

This solution was cooled to -5°C, then was added dropwise an aqueous sodium nitrite solution (12.23 mmol, 844 mg in 4 ml of water) and the mixture was stirred 1h at -5°C. After warm-up to rt, EtOAc and 10% aqueous sodium bisulfite solution were added. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of EtOAc in heptane to give the title compound as a white solid (1.08g, 33% yield).

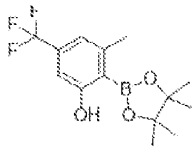
LCMS (**Method H**): Rt = 2.38 min; *No ionization*

Int 63.3: 2-(4-chloro-2-methoxy-6-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

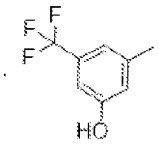
Under Ar, at 0°C, to a solution of 5-chloro-2-iodo-1-methoxy-3-methyl-benzene (3.54 mmol, 1g) in 17 ml of anhydrous 1,4-dioxane was added Et_3N (7.1 mmol, 1 ml) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7.08 mmol, 1 ml). Then, was added diacetoxypalladium (0.18 mmol, 40 mg) and dicyclohexyl-(2-phenylphenyl)phosphane (0.354 mmol, 124 mg) and the mixture was stirred at 80°C for 1.5h. After cooling down, the mixture was diluted with diethylether and pentane, and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 70% of diethylether in pentane to give the title compound as a yellow solid (880 mg, 88% yield).

LCMS (**Method I**): Rt = 2.27 min; MS m/z $[M+H]^+$ 283

3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol



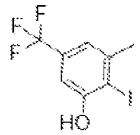
***Step 1*: 3-methyl-5-(trifluoromethyl)phenol**



To a solution of 1-bromo-3-methyl-5-(trifluoromethyl)benzene (41.8 mmol, 10 g) in 100 ml of 1,4-dioxane and 10 ml of water was added $LiOH•H_2O$ (125.5 mmol, 5.27 g), $Pd_2(dba)_3$ (837 µmol, 766 mg) and ditert-butyl-[2-(1,3,5-triphenylpyrazol-4-yl)pyrazol-3-yl]phosphane (1.67 mmol, 848 mg). The mixture was degassed and purged with N_2, and then stirred at 100 °C for 16h. After cooling to rt, the solution was filtered and washed with ethyl acetate. The filtrate was washed with 1 M HCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 70% of Ethyl acetate in Petroleum ether to give the title compound as a yellow oil (5.3 g, 72% yield).

1HNMR (400 MHz, $CDCl_3$) δ = 7.02 (s, 1H), 6.89 (s, 1H), 6.83 (s, 1H), 5.05 (d, J = 2.8 Hz, 1H), 2.37 (s, 3H).

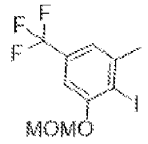
***Step 2*: 2-iodo-3-methyl-5-(trifluoromethyl)phenol**



At 0°C, under N_2, to a solution of 3-methyl-5-(trifluoromethyl)phenol (22.7 mmol, 4 g) in 80 ml of toluene was added NaH (45.4 mmol, 1.8 g, 60% purity) and the solution was stirred at 0 °C for 0.5h. Then, I_2 (22.7 mmol, 5.8 g) was slowly added, and the mixture was stirred at 0 °C for 3h. The reaction was quenched by addition of 100 ml of water at 0 °C, then adjusted pH to 5 with 2 M HCl. The solution was extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 3% of Ethyl acetate in Petroleum ether to give the title compound as a yellow oil (3.8 g, 55% yield).

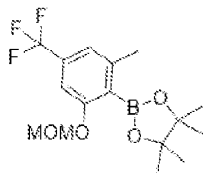
1H NMR (400 MHz, $CDCl_3$) δ = 7.07 (s, 2H), 5.66 (s, 1H), 2.52 (s, 3H).

***Step 3*: 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene**



At 0°C, under N_2, to a solution of 2-iodo-3-methyl-5-(trifluoromethyl)phenol (12.6 mmol, 3.8 g) in 80 ml of THF was added NaH (18.9 mmol, 755 mg, 60% purity) and the mixture was stirred at 0 °C for 0.5h. Then, bromo(methoxy)methane (15.1 mmol, 1.9 g) was dropwise added at 0 °C and the mixture was stirred at 25 °C for 1h. The reaction was quenched by addition of 50 ml of saturated NH_4Cl at 0 °C, then diluted with H_2O and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 1% of Ethyl acetate in Petroleum ether to give the title compound as a colorless oil (4 g, 91% yield).
1H NMR (400 MHz, $CDCl_3$) δ = 7.18 (s, 1H), 7.10 (s, 1H), 5.29 (s, 2H), 3.53 (s, 3H), 2.54 (s, 3H).

***Step 4*: 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**



Under N_2, to a solution of 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (11.7 mmol, 4.0 g) in 55 ml of 1,4-dioxane was added Et_3N (86.6 mmol, 12 ml), biphenyl-2-yl-dicyclohexylphosphane (2.81 mmol, 984 mg) and $Pd(OAc)_2$ (1.4 mmol, 315 mg). The solution was degassed and purged with N_2, then 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58.5 mmol, 7.5 g) was added and the mixture was stirred at 80 °C for 12h. After cooling down to rt, the reaction was filtered. The filtrate was washed with saturated NH_4Cl, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of Ethyl acetate in Petroleum ether to give the title compound as a yellow solid (2 g, 49% yield).

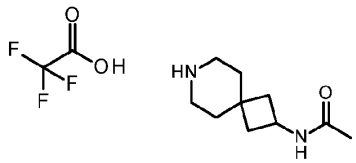
1H NMR (400 MHz, $CDCl_3$) δ = 7.06 (s, 2H), 5.17 (s, 2H), 3.48 (s, 3H), 2.40 (s, 3H), 1.40 (s, 12H).

***Step 5*: 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) phenol**

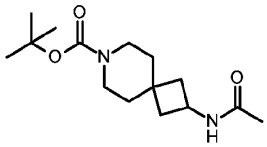
At 0°C, to a solution of 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.44 mmol, 500 mg) in 5 ml of EtOAc was added 2.5 ml of a 4N solution of HCl in EtOAc and the mixture was stirred at 0°C for 1h. Then, the reaction mixture was concentrated under reduced pressure to give 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (446 mg, crude) as a yellow oil, which was used directly for the next step.

1H NMR (400 MHz, $CDCl_3$) δ = 8.71 (s, 1H), 6.94 (d, J = 11.2 Hz, 2H), 2.54 (s, 3H), 1.39 (s, 12H).

N-(7-azaspiro[3.5]nonan-2-yl)acetamide;2,2,2-trifluoroacetic acid



Int 47.1: tert-butyl 2-acetamido-7-azaspiro[3.5]nonane-7-carboxylate



To a solution of tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate (2.08 mmol, 500 mg) in 5 ml of DCM were successively added Et_3N (2.08 mmol, 0.28 ml), N,N-dimethylpyridin-4-amine (0.104 mmol, 13 mg) and acetic anhydride (3.12 mmol, 0.3 ml) and the mixture was stirred at rt for 18h. The solution was diluted with DCM and saturated aqueous solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound as a yellow foam (600 mg, 100% yield).

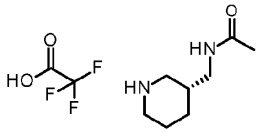
LCMS (**Method O**): Rt = 1.22 min; MS m/z $[M+H]^+$ 283

Int 47.2: N-(7-azaspiro[3.5]nonan-2-yl)acetamide;2,2,2-trifluoroacetic acid

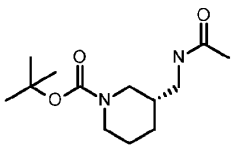
A solution of tert-butyl 2-acetamido-7-azaspiro[3.5]nonane-7-carboxylate (1.06 mmol, 300 mg) in 18 ml of DCM and 2 ml of TFA was stirred at rt for 2 h. The solution was concentrated under reduced pressure to give the title compound as a colourless oil (430 mg, 98% yield).

LCMS (**Method O**): Rt = 0.24 min; MS m/z $[M+H]^+$ 183

N-[[(3R)-3-piperidyl]methyl]acetamide;2,2,2-trifluoroacetic acid



Int 58.6: tert-butyl (3S)-3-(acetamidomethyl)piperidine-1-carboxylate



To a solution of tert-butyl (3S)-3-(aminomethyl)piperidine-1-carboxylate (4.66 mmol, 1g) in 20 ml of DCM was successively added Et_3N (4.66 mmol, 0.64 ml), DMAP (0.233 mmol, 28.5 mg) and acetic anhydride (7 mmol, 0.66 ml) and the mixture was stirred at rt for 18h. then to the solution was added DCM and saturated aq. solution of $NaHCO_3$.The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 5% of MeOH in DCM to give the title compound as a yellow oil (800 mg, 67% yield).

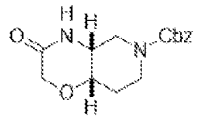
LCMS (Method O): Rt = 1.15 min; MS m/z $[M+H]^+$ 257

Int 58.7: N-[[(3R)-3-piperidyl]methyl]acetamide;2,2,2-trifluoroacetic acid

A solution of tert-butyl (3S)-3-(acetamidomethyl)piperidine-1-carboxylate (1.56 mmol, 400 mg) in 18 ml of DCM and 2 ml of TFA was stirred at rt for 2h. The solution was then concentrated under reduced pressure to give the title compound as a colourless oil (598 mg, 100% yield).

LCMS (Method O): Rt = 0.28 min; MS m/z $[M+H]^+$ 157

benzyl rac-(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate

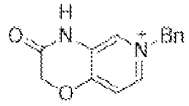


Int 10.2: 4H-pyrido[4,3-b][1,4]oxazin-3-one

To a solution of 3-aminopyridin-4-ol (227 mmol, 25 g) in 400 ml of ACN was added dropwise 2-chloroacetyl chloride (250 mmol, 19.86 ml), and the solution was stirred at 25°C for 0.5h. Then K_2CO_3 (568 mmol, 78.5 g) was added, and the mixture was stirred at 85°C for 10h. After cooling to rt, the reaction mixture was concentrated under reduced pressure and 100 ml of a solution of EtOAc/MeOH (1/1) was added. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel using DCM/MeOH (from 10/1 to 1/1) to give the title compound as a yellow solid (7 g, 20% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 5.6 Hz, 1H), 8.14 (s, 1H), 6.93 (d, *J* = 5.6 Hz, 1H), 4.74 (s, 2H).

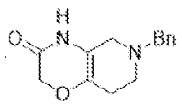
Int 10.3: 6-benzyl-4H-pyrido[4,3-b][1,4]oxazin-6-ium-3-one ; bromide



To a solution of 4H-pyrido[4,3-b][1,4]oxazin-3-one (46.6 mmol, 7 g) in 100 ml of DCM and 20 ml of MeOH was added benzylbromide (230 mmol, 162 ml), and the mixture was stirred at 25 °C for 8 h. The reaction mixture was filtered and the filter cake was dried under vacuum to give 10 g of crude 6-benzyl-3-oxo-3,4-dihydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-6-ium bromide as a white solid, which was used without further purification for next step.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.76 (br d, *J* = 6.8 Hz, 1H), 8.36 (s, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.53 - 7.33 (m, 6H), 5.75 (s, 2H), 5.00 (s, 2H)

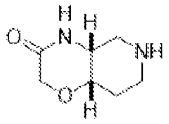
Int 10.4: 6-benzyl-4,5,7,8-tetrahydropyrido[4,3-b][1,4]oxazin-3-one



At 0 C°, to a solution of 6-benzyl-4H-pyrido[4,3-b][1,4]oxazin-6-ium-3-one ; bromide (33.2 mmol, 8 g) in 120 ml of MeOH was added $NaBH_4$ (232 mmol, 8.78 g) by batches over 2h and the mixture was then stirred at 0°C for 1h. The reaction solution was diluted with 50 ml of water and concentrated under reduced pressure. The aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 5/1 to 1/1) to give the title compound as a white solid (4.1 g, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (br s, 1H), 7.37 - 7.27 (m, 5H), 4.41 (s, 2H), 3.64 (s, 2H), 3.03 (t, *J* = 2.0 Hz, 2H), 2.66 (t, *J* = 5.6 Hz, 2H), 2.29 - 2.17 (m, 2H).

Int 10.5: rac-(4aR,8aS)-4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one



Under N_2 atmosphere, to a solution of 6-benzyl-4,5,7,8-tetrahydropyrido[4,3-b][1,4]oxazin-3-one (21 mmol, 5.1 g) in 50 ml of MeOH was added Pd/C (2.2 g). The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 8h. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to give 3.5 g of crude (4a*R*, 8a*S*)-hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one as a white solid, which was used without further purification for next step.

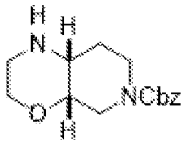
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.35 - 4.26 (m, 1H), 4.24 - 4.15 (m, 1H), 3.97 (br d, *J* = 2.4 Hz, 1H), 3.41 - 3.26 (m, 1H), 3.05 - 2.73 (m, 4H), 1.97 (br dd, *J* = 2.4, 14.4 Hz, 1H), 1.87 - 1.73 (m, 2H).

Int 10.6: benzyl rac-(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate

At 0 °C, to a solution of rac-(4aR,8aS)-4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4] oxazin-3-one (22.4 mmol, 3.5 g) in 30 ml of DCM was added Et_3N (45 mmol, 6.52 ml) and CbzCl (45 mmol, 7.65 g). The solution was then stirred at 25°C for 8h. The solution was concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 3/1 to 1/1) to give the title compound as a colorless oil (6.5 g, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 - 7.30 (m, 5H), 6.46 (br s, 1H), 5.13 (br s, 2H), 4.37 - 4.18 (m, 2H), 3.97 (br d, *J* = 2.8 Hz, 2H), 3.36 (br s, 1H), 3.09 (br s, 1H), 2.02 - 1.74 (m, 2H).

benzyl rac-(4aS,8aR)-1,2,3,4a,5,7,8,8a-octahydropyrido[3,4-b][1,4]oxazine-6-carboxylate



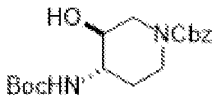
Int 4.1: benzyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate



At 0 °C, to a solution of benzyl 3,6-dihydro-2*H*-pyridine-1-carboxylate (110.5 mmol, 24 g) in 60 ml of DCM was added, *m*-CPBA (133 mmol, 27 g). The reaction was stirred for 1h at 0°C and 7h at 25°C. Then, the reaction was diluted with DCM, washed with saturated aqueous solution of $Na_2S_2O_3$, sat. aq. solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/MeOH (from 10/1 to 2/1) to give the title compound as a yellow oil (22 g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 - 7.28 (m, 5H), 5.13 (s, 2H), 4.05 - 3.88 (m, 1H), 3.85 - 3.71 (m, 1H), 3.53 (br s, 1H), 3.36 - 3.14 (m, 3H), 2.17 - 2.01 (m, 1H), 1.95 (br s, 1H).

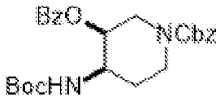
Int 4.2: benzyl rac-(3S,4S)-4-(tert-butoxycarbonylamino)-3-hydroxy-piperidine-1-carboxylate



A solution of benzyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (94.7 mmol, 22 g) in 20 ml of EtOH and 20 ml of saturated ammonium hydroxide aqueous solution was stirred at 70 °C for 5h. After cooling to rt, EtOAc and water were added to the solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. To this concentrate was added a solution of *tert*-butoxycarbonyl *tert*-butyl carbonate (104 mmol, 22.75 g) and Et_3N (94.8 mmol, 9.6 g) in 200 ml of DCM and the resulting solution was stirred for 2h. Then, 100 ml of water was added, and the solution was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 10/1 to 2/1) to give the title compound as a white solid (11 g, 33% yield).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.33 - 7.21 (m, 5H), 5.05 (s, 2H), 4.55 (br s, 1H), 4.26 (br s, 1H), 3.46 - 3.25 (m, 2H), 2.87 - 2.67 (m, 1H), 2.60 (br dd, J = 10.8, 12.4 Hz, 1H), 1.91 - 1.80 (m, 1H), 1.38 (s, 9H).

Int 4.3: benzyl rac-(3R,4S)-3-benzoyloxy-4-(tert-butoxycarbonylamino)piperidine-1-carboxylate

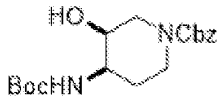


A mixture of DIAD (30.8 mmol, 6.2 g), PPh_3 (30.8 mmol, 8.1 g) in 40 ml of THF was degassed and purged with N_2 for 3 times, then stirred at 0 °C for 0.5 hr. A solution of benzyl rac-(3S,4S)-4-(tert-butoxycarbonylamino)-3-hydroxy-piperidine-1-carboxylate (25.7 mmol, 9 g) and benzoic acid (30.8 mmol, 3.8 g) in 10 ml of THF was added, and the resulting mixture was stirred for 1.5h under N_2 atmosphere. Water was added and the mixture was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried

over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 50/1 to 5/1) to give the title compound as a yellow oil (11 g, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 - 7.89 (m, 2H), 7.60 (q, *J* = 7.2 Hz, 1H), 7.46 (br t, *J* = 6.8 Hz, 2H), 7.39 - 7.27 (m, 2H), 7.24 - 7.07 (m, 2H), 7.00 (br d, *J* = 7.2 Hz, 1H), 6.47 (br s, 3H), 5.35 - 5.02 (m, 2H), 4.77 (br d, *J* = 8.0 Hz, 1H), 4.64 - 4.51 (m, 1H), 4.39 (br d, *J* = 13.6 Hz, 1H), 3.99 (br d, *J* = 3.6 Hz, 1H), 3.10 (br d, *J* = 15.2 Hz, 1H), 2.92 (br t, *J* = 10.8 Hz, 1H), 1.90 (br d, *J* = 3.6 Hz, 2H), 1.49 - 1.35 (m, 9H)

Int 4.4: benzyl rac-(3R,4S)-4-(tert-butoxycarbonylamino)-3-hydroxy-piperidine-1-carboxylate



To a solution of benzyl rac-(3R,4S)-3-benzoyloxy-4-(tert-butoxycarbonylamino) piperidine-1-carboxylate(24.2 mmol, 11.0 g) in 30 ml of EtOH and 30 ml of H_2O was added K_2CO_3 (36.3 mmol, 5.0 g) and the mixture was stirred at 70 °C for 8h. After cooling to rt, water was added, and the mixture was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 5/1 to 1/1) to give the title compound as a white solid (4,1 g, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 - 7.31 (m, 5H), 5.15 (s, 2H), 5.07 - 4.84 (m, 1H), 4.38 - 4.07 (m, 2H), 3.93 (br s, 1H), 3.79 - 3.63 (m, 1H), 3.14 - 3.00 (m, 1H), 2.98 - 2.86 (m, 1H), 1.74 (dt, *J* = 4.4, 8.8 Hz, 2H), 1.46 (s, 9H).

Int 4.5: benzyl rac-(3R,4S)-4-amino-3-hydroxy-piperidine-1-carboxylate

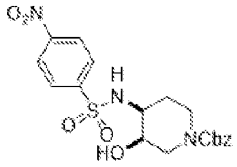


A mixture of benzyl rac-(3R,4S)-4-(tert-butoxycarbonylamino)-3-hydroxy-piperidine-1-carboxylate (11.7 mmol, 4.1 g) in 5 ml of 4M HCl/EtOAc was stirred at rt for 0.5 h. The

reaction was concentrated under reduced pressure to give 3.45 g of crude benzyl (3*S*, 4*R*)-4-amino-3-hydroxypiperidine-1-carboxylate as a white solid, which was used without further purification for next step.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.04 (br s, 2H), 7.45 - 7.26 (m, 5H), 5.62 (br s, 1H), 5.07 (s, 2H), 4.07 - 3.79 (m, 3H), 3.26 (br d, *J* = 3.2 Hz, 1H), 3.16 - 2.77 (m, 2H), 1.84 - 1.54 (m, 2H).

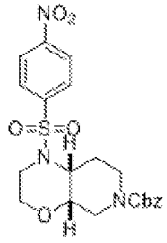
Int 4.6: benzyl rac-(3R,4S)-3-hydroxy-4-[(4-nitrophenyl)sulfonylamino]piperidine-1-carboxylate



At 0 °C, to a solution of 4-nitrobenzenesulfonyl chloride (14.9 mmol, 3.3 g) in 50 ml of DCM was added Et_3N (13.6 mmol, 1.4 g) and the mixture was stirred for 0.5 h. Then, benzyl rac-(3R,4S)-4-amino-3-hydroxy-piperidine-1-carboxylate (3.45 g, 13.78 mmol, 1.01 eq) was added at 0 °C, and the reaction was stirred at rt for another 0.5h. The reaction was diluted with water and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 50/1 to 10/1) to give the title compound as a white solid (2,6 g, 44% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.39 (br d, *J* = 8.8 Hz, 2H), 8.10 (br d, *J* = 8.8 Hz, 2H), 7.43 - 7.21 (m, 5H), 5.02 (br s, 2H), 3.78 (br d, *J* = 9.6 Hz, 2H), 3.52 (br s, 1H), 3.35 (br s, 1H), 3.08 - 2.95 (m, 1H), 2.91 - 2.74 (m, 1H), 1.75 - 1.54 (m, 1H), 1.29 - 1.16 (m, 1H).

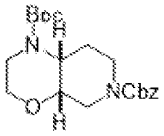
Int 4.7: benzyl rac-(4aS,8aR)-1-(4-nitrophenyl)sulfonyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate



Under N_2 athmosthere, at 0 C°, to a solution of 2-bromoethyl(diphenyl)sulfonium; trifluoromethanesulfonate (12.9 mmol, 5.7 g) in 30 ml of DCM was added NaH (26.3 mmol, 1.05 g, 60% purity). Benzyl rac-(3R,4S)-3-hydroxy-4-[(4-nitrophenyl)sulfonylamino] piperidine-1-carboxylate (4.8 mmol, 2.1 g) was added and the reaction was stirred at rt for 6h. Then Et_3N (12.4 mmol, 1.7 ml) was added, and the solution was stirred for another 6h. After that, water was added, and the solution was extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/EA (from 5/1 to 1/1) to give the title compound as a yellow solid (1,6 g, 72% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.41 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 2H), 7.48 - 7.17 (m, 5H), 5.03 (br s, 2H), 4.09 - 3.92 (m, 3H), 3.88 - 3.79 (m, 1H), 3.52 (br d, J = 11.2 Hz, 1H), 3.37 (br d, J = 6.0 Hz, 1H), 3.31 (s, 1H), 3.26 - 3.00 (m, 2H), 2.95 - 2.74 (m, 1H), 1.93 (dq, J = 4.8, 12.8 Hz, 1H), 1.33 - 1.22 (m, 1H).

Int 4.8: 6-benzyl 1-tert-butyl rac-(4aS,8aR)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-1,6-dicarboxylate



To a solution of benzyl rac-(4aS,8aR)-1-(4-nitrophenyl)sulfonyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-6-carboxylate(3.5 mmol, 1.6 g) in 15 ml DMF was added thioglycolic acid (9.0 mmol, 0.62 µl), followed by lithium hydroxide (17.4 mmol, 415 mg) and NH_3•H_2O (2.4 ml, 17.34 mmol, 28% purity) and the reaction was stirred for 6h. EtOAc and water are added. The aqueous layer was extracted with EtOAc (3 times). The combined

organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in 20 ml of DCM and then were added Et_3N (5.2 mmol, 724 µl), Boc_2O (5.20 mmol, 1.2 ml), and DMAP (520 µmol, 63 mg). After stirring for 2h, the resulting mixture was poured into water and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using Petroleum ether/Ethyl acetate (from 10/1 to 1/1) to give the title compound as a yellow oil (750 mg, 57% yield).

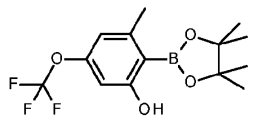
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 - 7.30 (m, 5H), 5.15 (br d, *J* = 17.6 Hz, 2H), 4.57 - 4.21 (m, 2H), 4.08 - 3.39 (m, 5H), 3.26 - 2.64 (m, 3H), 2.18 - 2.06 (m, 1H), 1.47 (s, 9H).

Int 4.9: benzyl rac-(4aS,8aR)-1,2,3,4a,5,7,8,8a-octahydropyrido[3,4-b][1,4]oxazine-6-carboxylate

A mixture of 6-benzyl 1-tert-butyl rac-(4aS,8aR)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazine-1,6-dicarboxylate(1.7 mmol, 650 mg) in 5 ml of 4M HCl/EtOAc was stirred for 0.5 h. Then the reaction was concentrated under reduced pressure to give 460 mg of crude benzyl (4*aS*, 8*aR*)-octahydro-6*H*-pyrido [3,4-*b*] [1,4] oxazine-6-carboxylate as a yellow oil, which was used without further purification for next step.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.49 - 7.23 (m, 5H), 5.05 (br s, 2H), 4.18 - 3.92 (m, 4H), 3.91 - 3.65 (m, 2H), 3.62 - 3.47 (m, 1H), 3.25 - 3.15 (m, 1H), 2.98 (br d, *J* = 14.2 Hz, 2H), 2.18 - 2.04 (m, 1H), 1.70 (br dd, *J* = 2.0, 9.2 Hz, 1H).

3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethoxy)phenol



***Step 1* Preparation of Int 121.1**

1-bromo-3-methyl-5-(trifluoromethoxy)benzene (1 eq., 1.00 g, 0.00392 mol) and lithium hydroxide hydrate (3 eq., 56.0 %, 0.881 g, 0.0118 mol) were dissolved in 1,4-dioxane (20.0 mL) and water (2.00 mL) and purged with N_2. Pd_2dba_3 (0.02 eq., 0.0451 g, 7.84e-5 mol) and BippyPhos (0.04 eq., 0.0795 g, 0.000157 mol) were added and purged another time. Then, the mixture was stirred for 18h at 100 °C. The mixture was acidified with an aqueous solution

of HCl 1M, diluted with EtOAc and washed with water. Combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The compound was purified by normal phase preparative LC (regular SiOH, 50 µm, 25 g interchim, dry loading (celite®), mobile phase gradient: from heptane/EtOAc 100/0 to 85/15 over 10 CV. The fractions containing compound were combined and evaporated in vacuo to give **Int 121.1** as a red oil (700 mg, 93%).

1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.64 – 6.50 (m, 3H), 5.01 – 4.92 (m, 1H), 2.31 (d, *J* = 0.7 Hz, 3H).

LCMS (**Method S**): Rt = 1.24 min; MS m/z $[M+H]^+$ = 191.1

Step 2 **Preparation of Int 121.2**

Int 121.1 (700 mg, 0.00364 mol, 1eq) was dissolved in toluene (20.0 mL) at 0 °C. Then, NaH (60% in mineral oil) (60.0 %, 0.291 g, 0.00729 mol, 2eq.) was added dropwise at the same temperature and stirred for 20min. I_2 (0.925 g, 0.00364 mol, 1eq.) was added at 0 °C and the mixture was stirred for 1h at 0 °C.

The mixture was acidified with an aqueous solution of HCl 1M, diluted with EtOAc and washed with water. Combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo to give a yellow oil. The compound was purified by normal phase preparative LC (regular SiOH, 50 µm, 24 g interchim, solid loading (celite®), mobile phase gradient: from heptane/EtOAc 100/0 to 80/20 over 10 CV). The fractions containing compound were combined and evaporated in vacuo to give a white solid (723 mg).

The solid was purified by normal phase preparative LC (regular SiOH, 50 µm, 24 g interchim, solid loading (celite®), mobile phase gradient: from heptane/DCM 100/0 to 50/50 over 10 CV). The fractions containing compound were combined and evaporated in vacuo to give **Int 121.2** as a colorless oil (340 mg, 29%).

1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.74 (s, 2H), 5.64 – 5.53 (m, 1H), 2.46 (s, 3H)

LCMS (**Method S**): Rt = 1.83 min; MS m/z $[M+H]^+$ = 317.0

Step 3 **Preparation of Int 121.3**

Int 121.2 (330 mg, 0.00104 mol) and K_2CO_3 (1.2 eq., 0.172 g, 0.00125 mol) were dissolved in DMF (5.00 mL) and purged with N_2. Then, chloromethyl methyl ether (1.87 eq., 0.180 mL, 0.00194 mol) was added dropwise and stirred for 18h at rt. The mixture was diluted

with EtOAc and washed with water. Organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The compound was purified by normal phase preparative LC (regular SiOH, 50 µm, 12 g interchim, solid loading (celite®), mobile phase gradient: from heptane/EtOAc 100/0 to 50/50 over 10 CV). The fractions containing compound were combined and evaporated in vacuo to give **Int 121.3** as a colourless oil (345 mg, 88%).

1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 2H), 5.28 (s, 2H), 3.76 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

LCMS (**Method S**): Rt = 1.61 min; MS m/z $[M+H]^+$ = 375.0;

Step 4 **Preparation of Int 121.4**

In a sealed flask, a mixture of Int121.3 (1 eq., 330 mg, 0.000877 mol), $Pd(OAc)_2$ (0.025 eq., 0.00492 g, 2.19e-5 mol) and CyJohnPhos (0.05 eq., 0.0154 g, 4.39e-5 mol) was purged with N_2 twice. Then 1,4-dioxane (4.00 mL) was added followed by triethylamine (3 eq., 0.266 g, 0.00263 mol) and pinacolborane (2 eq., 225 mg, 0.00175 mol), and the reaction was purged again with N_2 before being heated at 80 °C for 4h.

The reaction mixture was cooled to rt, washed with water and extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and concentrated to give a dark green solid.

The compound was purified by normal phase preparative LC (regular SiOH, 30 µm, 24 g interchim, dry loading (celite®), mobile phase gradient: from heptane/CH_2Cl_2 100/0 to 50/50 over 10 CV). The fractions containing compound were combined and evaporated in vacuo to give Int121.4 as a yellow oil (180.7 mg, 55%).

H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.74 (s, 1H), 6.66 (s, 1H), 5.17 (s, 2H), 3.71 (q, *J* = 7.0 Hz, 2H), 2.35 (s, 3H), 1.38 (s, 12H), 1.20 (t, *J* = 7.1 Hz, 3H)

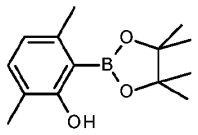
Step 5 **Preparation of Int 121.5**

Int 121.4 (1 eq., 137 mg, 0.000364 mol) was dissolved in dichloromethane (5.00 mL) and cooled to 0°C. Then, TFA (5eq., 0.208 g, 0.00182 mol) was added, the reaction mixture was stirred at 0°C for 30 min and allowed to warm up to rt and stirred for 2 h. The mixture was washed with water. Organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo to give Int 121.5 as a yellowish oil (110 mg, 95%).

1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.73 (s, 1H), 6.58 – 6.52 (m, 2H), 2.49 (s, 3H), 1.37 (s, 12H)

LCMS (**Method S**): Rt = 1.76 min; MS m/z $[M+H]^+$ = 317.2;

3,6-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Step 1 **Preparation of Int 141.1**

2,5-dimethylphenol (1 eq., 1.00 g, 8.19 mmol, 1 eq) was dissolved in DCM (50 mL) and diisopropylamine (0.1 eq., 115 µL, 0.819 mmol) was added. A suspension of NBS (1 eq., 1.46 g, 8.19 mmol) in DCM (50 mL) was then added dropwise using a dropping funnel over the course of approximately 1h; the clear mixture progressively took a deep yellow colour. The mixture was stirred for 1h afterwards at room temperature, at which point the yellow colour had disappeared and the mixture was clear again.

The mixture was washed with aqueous HCl 1M (50 mL), water (50 mL), then dried and concentrated to give a transparent oil (1.52 g). The product was purified by normal phase preparative LC (regular SiOH, 50 µm, 40 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/DCM 100/0 to 50/50 over 10 CV). The fractions containing compound were combined and evaporated in vacuo to give **Int 141.1** as a colorless oil (1.18 g, 91% purity, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.96 (d, J = 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.65 (s, 1H), 2.36 (s, 3H), 2.27 (s, 3H). Presence of di-brominated product (9% w/w).

LCMS (**Method S**): Rt = 1.32 min; MS m/z $[M+H]^+$ = 199.1/201.1

Step 2 **Preparation of Int 141.2**

Int141.1 (1 eq., 840 mg, 91% purity, 3.80 mmol), bis(pinacolato)diboron (1.4 eq., 1.35 g, 5.32 mmol) and potassium acetate (2.3 eq., 858 mg, 8.74 mmol) were suspended in dioxane (21 mL) and the vial was purged under vacuum and backfilled with nitrogen 3 times. Tetrakis(triphenylphosphine)palladium(0) (0.01 eq., 43.9 mg, 0.038 mmol) was then added, the vial was purged under vacuum and backfilled with nitrogen 3 times, and the resulting orange suspension was stirred at 100°C for at least 2h and up to 66h (the temperature probe shut down at some point over the week-end and the heating stopped).

Tetrakis(triphenylphosphine)palladium(0) (0.02 eq., 88.0 mg, 0.076 mmol) was added, the vial was purged and backfilled with nitrogen three times and the dark brown mixture was stirred at 100 °C for 18h.

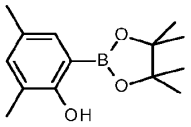
The mixture was left to cool to room temperature, then filtrated over celite® and concentrated to give a pale brown oil (2024 mg) that was purified by normal phase preparative LC (regular SiOH, 50 µm, 80 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/EtOAc 100/0 to 70/30 over 10 CV, UV detection at 254 and 301 nm) to give a white solid (564 mg).

The product was repurified by normal phase preparative LC (regular SiOH, 15 µm, 25 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/DCM 100/0 to 50/50 over 10 CV, UV detection at 254 and 301 nm) to give **Int 141.2** (373 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.65 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H), 1.28 (s, 12H)

LCMS (**Method S**): Rt = 1.74 min; MS m/z $[M+H]^+$ = 247.2 ;

2,4-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Preparation of Int 152.1:

A vial was loaded with 2-bromo-4,6-dimethyl-phenol (1 eq., 500 mg, 0.00249 mol), bis(pinacolato)diboron (1.5 eq., 0.947 g, 0.00373 mol) and potassium acetate (4 eq., 0.976 g, 0.00995 mol), purged under vacuum and backfilled with nitrogen 3 times, then dioxane (20.0 mL) was added. tetrakis(triphenylphosphine)palladium(0) (0.05 eq., 0.144 g, 0.000124 mol) was then added, the vial was purged under vacuum and backfilled with nitrogen 3 times again, and the resulting orange mixture was stirred at 100°C for 18h, at which point it had turned dark brown.

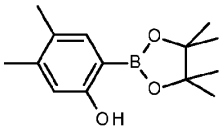
The mixture was filtrated over celite® and concentrated to give a brown oil (1365 mg) that was purified by normal phase preparative LC (regular SiOH, 50 µm, 40 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/EtOAc 100/0 to 70/30 over 10 CV, UV detection at 254 and 301 nm) to give a white solid (443 mg).

The product was repurified by normal phase preparative LC (regular SiOH, 15 µm, 12 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/DCM 100/0 to 50/50 over 10 CV, UV detection at 254 and 301 nm) to give Int152.1 as a white solid (290 mg, 47%).

1H NMR (400 MHz, CDCl3) δ (ppm): 7.82 (d, J = 0.6 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.07 – 7.04 (m, 1H), 2.23 (s, 3H), 2.21 (s, 3H), 1.36 (s, 12H).

LCMS (**Method S**): Rt = 1.66 min; MS m/z $[M+H]^+$ = 247.3

4,5-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



***Step 1* Preparation of Int 191.1**

In a 1L flask cooled by a water bath at room temperature, 3,4-dimethylphenol (1 eq., 5.00 g, 0.0409 mol) was dissolved in DCM (250 mL) then diisopropylamine (0.1 eq., 0.414 g, 0.00409 mol) was added. A solution of NBS (1 eq., 7.28 g, 0.0409 mol) in DCM (250 mL) was then added dropwise using a dropping funnel over approximately 5h (Note: this solution possibly degraded to bromine as it progressively turned from a clear suspension to a dark red mixture over several hours). The pale yellow mixture was then stirred for 18h at room temperature. The mixture was washed with a solution of HCl 1 M (200 mL), water (200 mL) and brine (200 mL), dried and concentrated to give a yellow oil, which was purified by normal phase preparative LC (regular SiOH, 50 µm, 220 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/DCM 100/0 to 50/50 over 10 CV). The fractions containing compound were combined and evaporated in vacuo to give a white solid (3896 mg). The product was repurified by preparative chiral SFC (Stationary phase: Chiralpak® IG 20x250 mm, Mobile phase: CO_2/(iPrOH + 0,3% iPrNH2) 95/5) to give Int191.1 as a brown oil (806 mg, 10%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.02 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H).

LCMS (**Method S**) Rt = 1.28 min; MS m/z $[M-H]^-$ = 199.0/201.0

***Step 2* Preparation of Int 191.2**

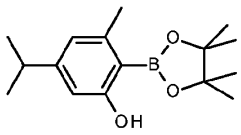
In a vial, Int191.1 (1 eq., 400 mg, 0.00199 mol), bis(pinacolato)diboron (1.5 eq., 0.758 g, 0.00298 mol) and potassium acetate (4 eq., 0.781 g, 0.00796 mol) were suspended in 1,4-dioxane (12.5 mL). The vial was purged under vacuum and backfilled with nitrogen 3 times, then tetrakis(triphenylphosphine)palladium(0) (0.05 eq., 0.115 g, 9.95e-5 mol) was added, and the vial was purged again under vacuum and backfilled with nitrogen 3 times. The resulting ochre-orange suspension was stirred at 100 °C for 18h, at which point it had turned to a dark brown mixture.

The mixture was filtrated over celite® and concentrated to give a brown oil (1365 mg) that was purified by normal phase preparative LC (regular SiOH, 50 µm, 40 g interchim, liquid loading (DCM), mobile phase gradient: from heptane/EtOAc 100/0 to 70/30 over 10 CV, UV detection at 254 and 301 nm) to give Int191.1 as a white solid (343 mg, 77% pure, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.47 (s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 2.43 (s, 3H), 2.18 (s, 3H), 1.37 (s, 12H).

LCMS (**Method S**): Rt = 1.64 min; MS m/z $[M-H]^-$ = 247.1;

5-isopropyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Int 274.2)



***Step 1* 2-iodo-5-isopropyl-3-methyl-phenol (Int 274.1)**

5-isopropyl-3-methylphenol (1000 mg, 6,657 mmol, 100 mass%)

was solubilized in toluene (60 ml) and THF (4 ml) under inert atmosphere. Sodium hydride (2.1 equiv., 13.9797 mmol, 60 mass%) were add at rt and stirred for 30 mn. The mixture was cooled at 0°C before the dropwise addition of a solution of iodine (B, 1 equiv., 6.657 mmol, 100 mass%) in toluene (44 ml). Stirring was continued for 1h30 at rt. The reaction mixture was poured into a solution of water and $NaHSO_3$ (pH=5) and extracted with AcOEt. The organic layer was wash with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluant heptane/ AcOt 15% 40mn) to obtain 200 mg of **Int 274.1** as a colorless oil, yield 11%

LCMS (**Method L**): Rt = 1.13 min; MS m/z $[M-H]^-$ = 275

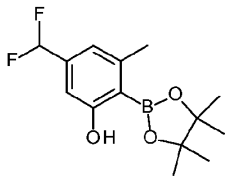
Step 2 **5-isopropyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Int 274.2)**

Int 274.1 (754 mg, 2.7308 mmol, 100 mass%) were solubilized in dioxane (14mL, 100 mass%) under Ar atmosphere and cooled down to 0°C. After addition of Triethylamine (2.30 equiv., 2.6766 mmol, 100 mass%), the mixture was stirred for 5 mn. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (D, 2.8 equiv., 7.6461 mmol, 100 mass%) were add dropwise, stirred for 5mn before the add of Palladium(II) acetate (0.0500 equiv., 0.1365 mmol, 100 mass%) and 2-(dicyclohexylphosphino)biphenyl (0.100 equiv., 0.2731 mmol, 100 mass%). The mixture was heated at 75°C for 30 mn.

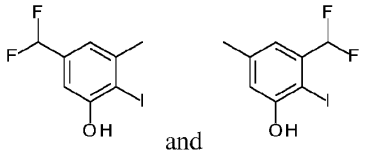
The reaction mixture was poured into water and extracted with AcOEt. The organic layer was wash with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluant heptane/ AcOt 15% 40mn) to obtain 440 mg of **Int 274.2** (5-isopropyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol) as an orange solid used without further purification for the next step.

LCMS (**Method L**): Rt = 1.44 min ; MS m/z $[M-H]^-$ = 275

5-(difluoromethyl)-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Int 134.2)



Step 1 **5-(difluoromethyl)-2-iodo-3-methyl-phenol (Int 134.1) and 3-(difluoromethyl)-2-iodo-5-methyl-phenol (Int 153.1)**

 and

To a cooled (0-5°C) suspension of NaH (60% in oil – 39.8 mmol, 1.6 g) in 80 ml of toluene, was slowly added a solution of 3-(difluoromethyl)-5-methyl-phenol (19 mmol, 3 g) in 20 ml of toluene while keeping temperature below 10°C. The mixture was stirred for 45 min at 0-5°C, then a solution of iodine (19 mmol, 4.8 g) in 80 ml of toluene was slowly added while keeping temperature at -5°C. The mixture was stirred at 0°C for 5 min, then quenched with 100 ml of an aqueous 5% citric acid solution and 100 ml of diethylether. The organic layer was successively washed with aqueous 10% sodium bisulfite solution and water then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of diethylether in petroleum ether to give successively 5-(difluoromethyl)-2-iodo-3-methyl-phenol (**Int 134.1**) as a colorless liquid (2 g, 37% yield) and 3-(difluoromethyl)-2-iodo-5-methyl-phenol (**Int 153.2**) as a white solid (1.36g, 25% yield).

LCMS (**Method L**)

Int 134.1 Rt = 1.26 min; MS m/z [M-H]+ 283

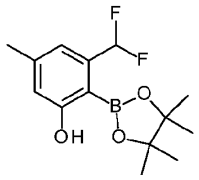
Int 153.1 Rt = 1.20 min; MS m/z [M-H]+ 283

Step 2 **5-(difluoromethyl)-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Int 134.2)**

Following procedure of **Int 96.2**, 5-(difluoromethyl)-2-iodo-3-methyl-phenol **Int 134.1** (2.46 mmol, 700 mg) gave the title compound as colourless oil (321 mg, 46% yield).

LCMS (**Method X**): Rt = 1.63 min; MS m/z $[M+H]^+$ 285

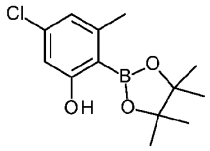
3-(difluoromethyl)-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Int 153.2)



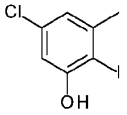
Following procedure of **Int 96.2**, 3-(difluoromethyl)-2-iodo-5-methyl-phenol (Int 153.1, 1.76 mmol, 500mg) gave the title compound as an orange oil (not isolated and used crude at the next step).

LCMS (**Method L**): Rt = 1.54 min; MS m/z $[M-H]^+$ 283.

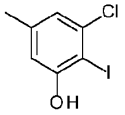
5-chloro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Step 1 **5-chloro-2-iodo-3-methyl-phenol (Int 133.1) and 3-chloro-2-iodo-5-methyl-phenol (Int 172.1).**



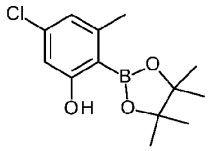
and



Int 133.1 **Int 172.1**

Following procedure of **Int 134.1 and Int 153.1**, 3-chloro-5-methyl-phenol (140 mmol, 20 g) gave the title compounds 5-chloro-2-iodo-3-methyl-phenol (**Int 133.1**) (19.08 g, 51% yield) and 3-chloro-2-iodo-5-methyl-phenol (**Int 172.1**) (4.7g, 9% yield) as white solids.
LCMS (**Method L**):
Int 133.1 Rt = 1.05 min; MS m/z [M-H]+ 267
Int 172.1 Rt = 1.00 min; MS m/z [M-H]+ 267

Step 2 **5-chloro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol**

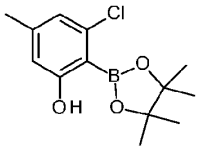


To a cooled (10-15°C) solution of 5-chloro-2-iodo-3-methyl-phenol (Int 133.1, 32.1 mmol, 8.63 g) and triethylamine (64.3 mmol, 8.77 ml) in 140 ml of anhydrous dioxanne under argon, was slowly added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70.7 mmol, 10.1 ml) while keeping temperature below 15°C (strong gas evolution). The mixture was stirred for 30 min at rt until complete solubilization, then diacetoxypalladium (1.61 mmol, 361 mg) and dicyclohexyl-(2-phenylphenyl)phosphane (3.21 mmol, 1.13 g) were added. The mixture was stirred at 50°C for 30 min, then quenched with 250 ml of diethylether, 250 ml of ethyl acetate

and 200 ml of an aqueous 5% citric acid solution. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 20% of diethylether in pentane to give the title compound as a colorless oil (7 g, 71% yield).

LCMS (**Method L**): Rt = 1.38 min; MS m/z $[M-H]^+$ 267

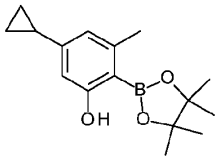
3-chloro-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



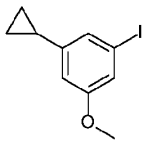
Following procedure of Int 96.2, 3-chloro-2-iodo-5-methyl-phenol (Int 172.1, 2.23 mmol, 600mg) gave the title compound an orange oil (596 mg, 99% yield).

LCMS (Method L): Rt = 1.23 min; MS m/z $[M+H]^+$ 269.

5-cyclopropyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Int 204.1: 1-cyclopropyl-3-iodo-5-methoxy-benzene

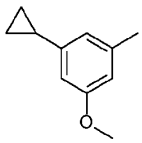


To a cooled (0°C) solution of 3-cyclopropyl-5-methoxy-aniline (12.3 mmol, 2 g) in 80 ml of an aqueous 4N HCl solution and 65 ml of acetonitrile, was slowly added a solution of sodium nitrite (13.5 mmol, 930 mg) in 2 ml of water while keeping temperature below 5°C. The mixture was stirred for 30 min at 0-5°C. Then was slowly added a solution of sodium iodide (24.5 mmol, 3.67 g) and the mixture was stirred at rt for 1h30. Until end of gas evolution then quenched with 50 ml of an aqueous 10% sodium hydrogenosulfite solution, 20 ml of diethylether and 80 ml of pentane. The organic layer was washed with water, dried

over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of diethylether in pentane to give the title compound as a colorless oil (2.67 g, 75% yield).

LCMS (**Method V**): Rt = 1.30 min; MS m/z $[M+H]^+$ 275;

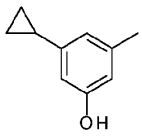
Int 204.2: **1-cyclopropyl-3-methoxy-5-methyl-benzene**



To an argon degassed solution of 1-cyclopropyl-3-iodo-5-methoxy-benzene (9.74 mmol, 2.67 g) in 50 ml of 1,4-dioxanne, was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (24.4 mmol, 3.4 ml) and potassium carbonate (24.4 mmol, 3.37 g). The suspension was stirred for 5 min at rt and then was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.49 mmol, 356 mg) and the mixture was stirred at 100°C for 1h. After cooling to rt, the mixture was diluted with 20 ml of diethylether and 80 ml of pentane and filtered over a Decalite® pad. The cake was rinsed with 20 ml of diethylether and the pooled organic layers are concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of diethylether in pentane to give the title compound as a yellow oil (1.2 g, 76% yield).

LCMS (**Method V**): Rt = 1.18 min; MS m/z $[M+H]^+$ 163

Int 204.3: **3-cyclopropyl-5-methyl-phenol**

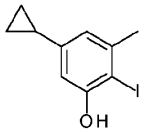


To a cooled (- 10°C) solution of 1-cyclopropyl-3-methoxy-5-methyl-benzene (8.51 mmol, 1.38 g) in 60 ml of dichloromethane under argon, was slowly added a 1N dichloromethane boron tribromide solution (8.51 mmol, 8.51 ml). The solution was stirred for 1h at - 10°C and 1h at 0°C then quenched under strong stirring with 50 ml of a saturated sodium hydrogenocarbonate aqueous solution, 50 ml of water and 100 ml of diethylether. The

organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 60% of diethylether in pentane to give the title compound as a pale yellow oil (770 mg, 61% yield).

LCMS (**Method V**): Rt = 0.88 min; MS m/z $[M+H]^+$ 149

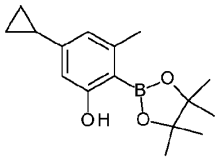
Int 204.4: **5-cyclopropyl-2-iodo-3-methyl-phenol**



Following procedure of **Int 134.1 and Int 153.1**, 3-cyclopropyl-5-methyl-phenol (5.2 mmol, 770 mg) gave the title compound (370 mg, 26% yield) as white solid.

LCMS (Method V): Rt = 0.88 min; MS m/z $[M-H]^+$ 273.

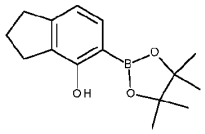
5-cyclopropyl-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



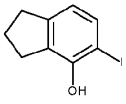
Following procedure of **Int 96.2**, 5-cyclopropyl-2-iodo-3-methyl-phenol (1.35 mmol, 370 mg) gave the title compound (not isolated and used crude at the next step).

LCMS (**Method V**): Rt = 1.41 min; MS m/z $[M+H]^+$ 275

Int 324.2: 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indan-4-ol

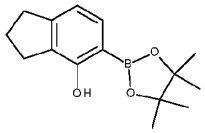


Int 324.1: 5-iodoindan-4-ol



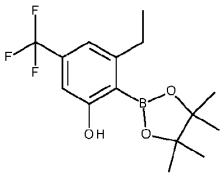
Following procedure of **Int 353.1** using indan-4-ol (14.9 mmol, 2 g), the title compound was obtained as a colourless oil (700 mg, 18% yield).
LCMS (**Method V**): Rt = 1.15; MS m/z $[M-H]^+$ = 259

Int 324.2: 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indan-4-ol

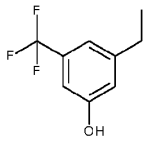


Following procedure of **Int 96.2** using 5-iodoindan-4-ol (2.69 mmol, 700 mg), the title compound was obtained as a brown oil (588 mg, 84% yield)
LCMS (**Method V**): Rt = 1.47; MS m/z $[M+H]^+$ = 261

Int 380.3 : 3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) phenol

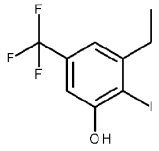


Int 380.1: 3-ethyl-5-(trifluoromethyl)phenol



Under Ar, to a solution of 3-bromo-5-(trifluoromethyl)phenol (8.3 mmol, 2g) in 20 ml of 1,4-dioxane were added potassium phosphate tribasic (16.6 mmol, 3.5 g), ethylboronic acid (9.96 mmol, 736 mg and [1,1'-bis(diphenylphospino)ferrocene]dichloropalladium(II) (0.41 mmol, 304 mg). The mixture was stirred at 110°C for 3h. After cooling down to rt, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50 % of EtOAc in cyclohexane to give the title compound as a yellow oil (1.05g, 67% yield).
LCMS (**Method V**): Rt = 0.94; MS m/z $[M-H]^+$ = 189

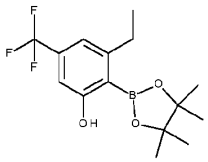
Int 380.2: **3-ethyl-2-iodo-5-(trifluoromethyl)phenol**



Under argon, to a cooled (0-5°C) suspension of NaH (60% in oil – 11.6 mmol, 464 mg) in 10 ml of anhydrous toluene was slowly added a solution of 3-ethyl-5-(trifluoromethyl)phenol (5.52 mmol, 1.05 g) in 15 ml of toluene while keeping temperature below 10 °C. The mixture was stirred for 45 min at 0-5 °C, then the mixture was cooled down to -5 °C and a solution of iodine (5.52 mmol, 1.4 g) in 15 ml of toluene was slowly added while keeping temperature at -5°C. The mixture was then stirred at 0°C for 10 min, then quenched with 100 ml of a 1N aqueous HCl solution and 100 ml of EtOAc. The organic layer was successively washed with 100 ml of an aqueous 10% sodium bisulfite solution and water then dried over Na_2SO_4, filtered and concentrated under reduced pressure. To the residue was added a mixture of 10 ml of N,N-dimethylformamide and 2 ml of formic acid and the resulting solution was stirred at 160°C for 3h, then cooled down to rt. The mixture was then diluted in 150 ml of diethylether and washed with 3X 100 ml of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 100% of diethylether in cyclohexane to give the title compound as a colorless liquid (415 mg, 37% yield).

LCMS (**Method V**): Rt = 1.25; MS m/z $[M-H]^+$ = 315

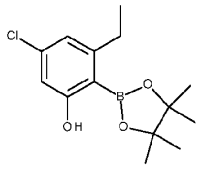
Int 380.3: **3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) phenol**



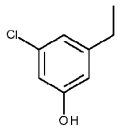
Following procedure of **Int 96.2**, 3-ethyl-2-iodo-5-(trifluoromethyl)phenol (1.31 mmol, 415mg) gave the title compound as an orange oil (not isolated and used crude for the next step).

LCMS (**Method V**): Rt = 1.43; MS m/z $[M-H]^+$ = 315

Int 381.3: 5-chloro-3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



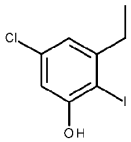
Int 381.1: 3-chloro-5-ethyl-phenol



Following procedure of **Int 380.1**, 3-bromo-5-chloro-phenol (4.8 mmol, 1g) gave the title compound as a yellow liquid (542 mg, 72% yield).

LCMS (**Method V**): Rt = 1.06; $[M-H]^+$ = 155

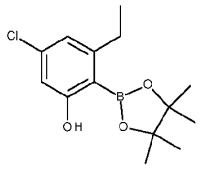
Int 381.2: 5-chloro-3-ethyl-2-iodo-phenol



Following procedure of **Int 380.2**, 3-chloro-5-ethyl-phenol (2.82 mmol, 442 mg) gave the title compound as a colourless oil (180 mg, 21 % yield)

LCMS (**Method V**): Rt = 1.21; MS m/z $[M-H]^+$ = 281

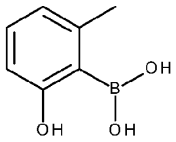
Int 381.3: 5-chloro-3-ethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Following procedure of **Int 96.2**, 5-chloro-3-ethyl-2-iodo-phenol (0.64 mmol, 180 mg) gave the title compound as a brown oil (not isolated and used crude for the next step).

LCMS (**Method V**): Rt = 153; MS m/z $[M+H]^+$ = 283

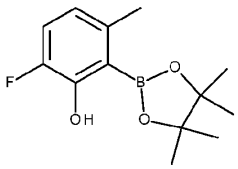
Int 354.1: (2-hydroxy-6-methyl-phenyl)boronic acid



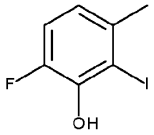
Under argon, at 0°C, to a solution of (2-methoxy-6-methyl-phenyl)boronic acid (4.28 mmol, 710 mg) in 15 ml of anhydrous DCM was added dropwise a 1N boron tribromide solution in DCM (10.7 mmol, 10.7 ml) and the mixture was stirred at 0°C for 30min, then quenched with 30 ml of EtOAc and 20 ml of ice-water under strong stirring. The organic layer was washed with 10 ml of water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 10% of MeOH in DCM to give the title compound as a yellow solid (330 mg, 51% yield).

LCMS (**Method V**): Rt = 0.48; MS m/z $[M-H]^+$ = 151

Int 353.2: 6-fluoro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



Int 353.1: 6-fluoro-2-iodo-3-methyl-phenol

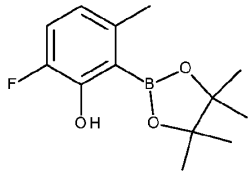


Under argon, to a cooled (0-5°C) suspension of NaH (60% in oil – 33.33 mmol, 1.33 g) in 50 ml of toluene was slowly added a solution of 2-fluoro-5-methyl-phenol (15.86 mmol, 2 g) in 25 ml of toluene while keeping temperature below 10°C. The mixture was stirred for 45 min at 0-5°C. The mixture was cooled down to -10°C, then a solution of iodine (15.86 mmol, 3 g) in 50 ml of toluene was slowly added while keeping temperature below -10°C. The resulting mixture was stirred at 0°C for 10 min, then quenched with 100 ml of

diethylether, 50 ml of an aqueous 2N HCl solution and 10 ml of an aqueous sodium bisulfite 10% solution. The organic layer was washed twice with water, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with 5% of diethylether in pentane to give the title compound as a white solid (2.37g, 55% yield).

LCMS (**Method V**): Rt = 1.01; MS m/z $[M-H]^+$ = 251

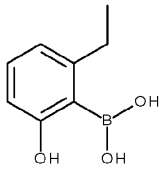
Int 353.2: 6-fluoro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



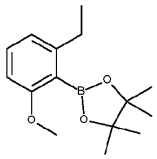
Following procedure of **Int 96.2**, 6-fluoro-2-iodo-3-methyl-phenol (9.4 mmol, 2.37 g) gave the title compound as a brown oil (not isolated and used crude for the next step).

LCMS (**Method V**): Rt = 153; MS m/z $[M+H]^+$ = 283

Int 358.2: (2-ethyl-6-hydroxy-phenyl)boronic acid



Int 358.1: **2-(2-ethyl-6-methoxy-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

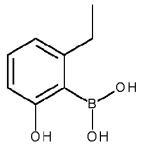


To a solution of 2-bromo-1-ethyl-3-methoxy-benzene (23.25 mmol, 5 g) in 50 ml of 1,4-dioxane was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (34.87 mmol, 8.85 g) and anhydrous potassium acetate (69.74 mmol, 6.84 g). The resulting mixture was degazed under stirring by argon bubbling for 10 min. Then was added [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.93 mmol,

680 mg) and the mixture was stirred at 100°C for 13h under argon. After cooling down to rt, the mixture was diluted with 100 ml of diethylether and 100 ml of water and filtered over a pad of decalite. The cake was rinsed with 50 ml of diethylether and the organic layers were pooled and washed with 2x50 ml of water, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50% of diethylether in pentane to give the title compound (1.77 g, 34 % yield) as a colourless oil.

LCMS (**Method V**): Rt = 1.29; MS m/z $[M+H]^+$ = 263

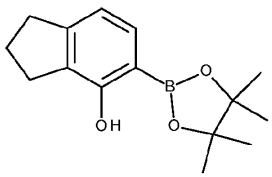
Int 358.2: (2-ethyl-6-hydroxy-phenyl)boronic acid



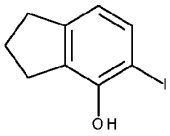
Under argon, at -10°C, to a solution of 2-(2-ethyl-6-methoxy-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.63 mmol, 427 mg) in 15 ml of anhydrous DCM was dropwise added a 1N boron tribromide solution in DCM (4.07 mmol, 4.07 ml) and the mixture was stirred at -10°C for 2h. Then 30 ml of diethylether and 20 ml of a 1% sodium bisulfite aqueous solution were added under strong stirring. The organic layer was washed with 2x10 ml of water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a yellow solid (270 mg, 100% yield).

LCMS (**Method V**): Rt = 0.58; MS m/z $[M-H]^+$ = 165

Int 324.2 : 6-fluoro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



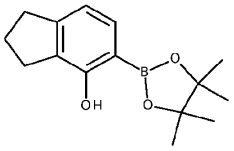
Int 324.1 : **5-iodoindan-4-ol**



Following procedure of **Int 353.1**, indan-4-ol (14.9 mmol, 2 g) gave the title compound as a colourless oil (700 mg, 18% yield).

LCMS (**Method V**): Rt = 1.15; MS m/z $[M-H]^+$ = 259

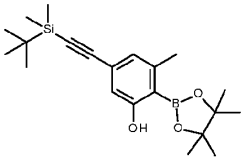
Int 324.2: **6-fluoro-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol**



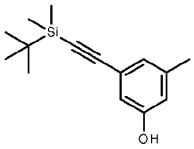
Following procedure of **Int 96.2**, 5-iodoindan-4-ol (2.69 mmol, 700 mg) gave the title compound as a brown oil (588 mg, 84% yield)

LCMS (**Method V**): Rt = 1.47; MS m/z $[M+H]^+$ = 261

Int 508.3: 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



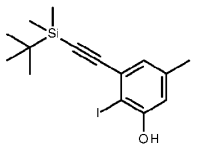
Int 508.1: 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-5-methyl-phenol



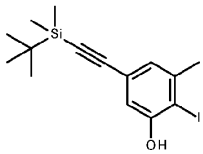
To a solution of 3-bromo-5-methyl-phenol (2.00 g, 10.7 mmol) in 20 ml of DMF were added tert-butyl-ethynyl-dimethyl-silane (5.99 mL, 0.0321 mol) and NEt_3 (4.46 mL, 32.1 mmol. The mixture was purged with N_2, then $PdCl_2dppf$ (873 mg, 1.07 mol) and CuI (204 mg, 1.07 mmol) were added. The mixture was purged again with N_2 then stirred at 80°C for 3h. After cooling down to rt, the mixture was concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel using a gradient of heptane/EtOAc (from 100/0 to 80/20, then isocratic), to give the title compound as a dark orange oil (1.73 g, 66%). ^{1}H NMR (400 MHz, DMSO) δ (ppm): 9.40 (s, 1H), 6.56 (td, J = 1.4, 0.7 Hz, 1H), 6.47 (ddd, J = 2.4, 1.6, 0.8 Hz, 1H), 6.46 – 6.44 (m, 1H), 2.05 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

Int 508.2 and Int 508.2bis: 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-5-methyl-phenol (Int 508.2) and 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-3-methyl-phenol (Int 508.2bis)



and



Int 508.2 Int 508.2bis

At 0°C, to a solution of 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-5-methyl-phenol (1.73 g, 0.00702 mol) in 70 ml of toluene was added NaH (60% in mineral oil) (60.0 %, 0.562 g, 0.0140 mol). The mixture was stirred for 10 min then I_2 (1.78 g, 0.00702 mol) was added. The reaction mixture was allowed to warm to rt and stirred for 18h. The reacting mixture was diluted with EtOAc then quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of heptane/DCM (from 100/0 to 80/20, then isocratic), then repurified by preparative chiral SFC (Stationary phase: Chiralpak® AD-3 4.6x100 mm, Mobile phase: CO_2/MeOH 90/10) to give 3-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-5-methyl-phenol (**Int 508.2**) as a white solid (1.02 g, 39 %) and 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-3-methyl-phenol (**Int 508.2bis**) as a yellow oil (173 mg, 7%).

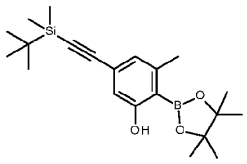
Int 508.2:

1H NMR (400 MHz, DMSO) δ (ppm): 10.37 (s, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.56 (d, J = 1.9 Hz, 1H), 2.18 (s, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

Int 508.2bis:

1H NMR (400 MHz, DMSO) δ (ppm): 10.26 (s, 1H), 6.64 (dd, J = 1.9, 0.8 Hz, 1H), 6.51 (dd, J = 2.0, 0.8 Hz, 1H), 2.00 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H).

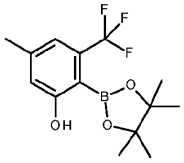
Int 508.3: 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol



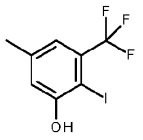
At 0°C, to a solution of 5-[2-[tert-butyl(dimethyl)silyl]ethynyl]-2-iodo-3-methyl-phenol (Int 508.2bis - 140 mg, 0.376 mmol) and NEt_3 (0.367 mL, 2.63 mmol) in 5 ml of dioxane was added dropwise HBPin (0.273 mL, 1.88 mmol). The vial was purged with N_2, then Pd(OAc)2 (8.44 mg, 3.76e-5 mol) and CyJohnPhos (26.4 mg, 7.52e-5 mol) were added. The solution was purged again with N2 then stirred at 80 °C for 1 h. After cooling down to rt, the mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane 100% to give the title compound as a white solid (65 mg, 46%).

^{1}H NMR (400 MHz, DMSO) δ (ppm): 9.32 (s, 1H), 6.69 (s, 1H), 6.60 (s, 1H), 2.21 (s, 3H), 1.29 (s, 12H), 0.95 (s, 9H), 0.15 (s, 6H).

Int 509.2: 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl) phenol



Int 509.1: 2-iodo-5-methyl-3-(trifluoromethyl)phenol

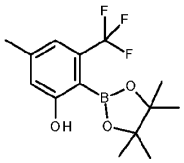


At 0°C, under N_2, to a mechanically stirred solution of 3-methyl-5-(trifluoromethyl)phenol (10.0 g, 0.0568 mol) in 200 ml of toluene, was slowly added NaH (60% in mineral oil) (2.27 g, 0.0568 mol) and the mixture was stirred for 30 min. Then I_2 (14.4 g, 0.0568 mol) was added and the mixture was stirred at 0 °C for 1.5h. The reaction mixture was warmed to rt

and acidified with aqueous HCl 1M until pH = 5. The resulting solution was extracted with EtOAc (3 times). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/DCM (from 100/0 to 80/20) to give 10 g of a colorless oil which 5 g was purified by preparative chiral SFC (Stationary phase: Chiralpak® 2EP 20x250 mm, Mobile phase: CO_2/MeOH 85/15) to afford the title compound (635 mg).

^{1}H NMR (400 MHz, DMSO-D_6) δ (ppm): 10.85 (s, 1H), 7.03 (d, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 2.27 (s, 3H).

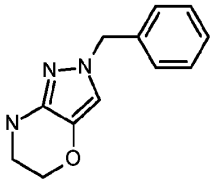
Int 509.2: 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenol



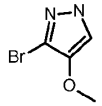
Under N_2, in a microwave vial, to a solution of 2-iodo-5-methyl-3-(trifluoromethyl)phenol (100 mg, 3.31 mmol) and Et_3N (0.235 g, 0.00232 mol) in 3 ml of 1,4-dioxane dry was slowly added HBPin (0.212 g, 0.00166 mol). the reaction mixture was then purged with N_2. Then palladium (II) diacetate (0.00372 g, 1.66e-5 mol) and CyJohnPhos (0.0116 g, 3.31e-5 mol) were added. The vial was purged again with N_2, then sealed and heated at 80 °C overnight. After cooling down to rt, the mixture was filtered and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (from 100/0 to 60/40), then DCM/MeOH (100/0 to 95/5) to give the title compound as a pale yellow solid (200 mg, quant., 78% purity).

LCMS (**Method T):** Rt = 7.03 min; MS m/z $[M-H]^-$ = 301

Int 360.6 : 2-benzyl-6,7-dihydro-5H-pyrazolo[4,3-b][1,4]oxazine



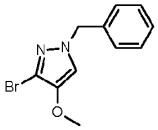
Int 360.1: 3-bromo-4-methoxy-1H-pyrazole



To a solution of 4-methoxy-1H-pyrazole (1.00 g, 0.0102 mol) in 80 ml of DMF was added NBS (1.81 g, 0.0102 mol) and the mixture was stirred at rt for 2h. The mixture was quenched with a saturated aqueous solution $Na_2S_2O_3$ then extracted twice with DCM. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (1.03 g, 57%) which was used without further purification in the next step.

1H NMR (500 MHz, DMSO) δ (ppm): 12.71 (s, 1H), 7.57 (s, 1H), 3.71 (s, 3H) (+ remaining DMF)

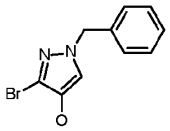
Int 360.2: 1-benzyl-3-bromo-4-methoxy-pyrazole



To a stirred solution of 3-bromo-4-methoxy-1H-pyrazole (830 mg, 0.00469 mol) and benzyl bromide (0.668 mL, 0.00563 mol) in 40 ml of DMF was added cesium carbonate (1.83 g, 0.00563 mol) and the solution was stirred at rt for 1h. Additional benzyl bromide (0.278 mL, 0.00234 mol) and cesium carbonate (0.764 g, 0.00234 mol) were added and the mixture was stirred at rt for 1h. The mixture was quenched with water and extracted twice with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was taken up in heptane and concentrated under reduced pressure (repeated 3 times) to give the title compound (1.20 g, 96 %), which was used without further purification in the next step.

1H NMR (400 MHz, DMSO) δ (ppm): 7.72 (s, 1H), 7.39 – 7.30 (m, 3H), 7.26 – 7.22 (m, 2H), 5.21 (s, 2H), 3.71 (s, 3H).

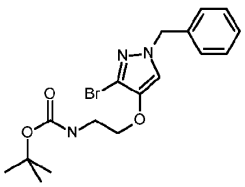
Int 360.3: 1-benzyl-3-bromo-pyrazol-4-ol



At rt, to a solution of 1-benzyl-3-bromo-4-methoxy-pyrazole (1.20 g, 0.00449 mol) in 12 ml of 1,2-dichloroethane was carefully added $AlCl_3$ (3.00 g, 0.0225 mol). The mixture was stirred for 1 h, then cooled with an ice bath and carefully neutralized with a 1N aqueous solution of NaOH. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (0.819 g, 72 %), which was used without further purification in the next step.

LCMS (**Method S**): Rt = 1.16; MS m/z [M+H]+ = 253.1/255.1

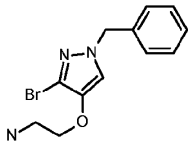
Int 360.4: tert-butyl N-[2-(1-benzyl-3-bromo-pyrazol-4-yl)oxyethyl]carbamate



In a sealed tube, a solution of 1-benzyl-3-bromo-pyrazol-4-ol (815 mg, 0.00322 mol), tert-butyl N-(2-hydroxyethyl)carbamate (0.747 mL, 0.00483 mol) and Cyanomethylenetributylphosphorane (1.69 mL, 0.00644 mol) in 6 ml of toluene was stirred at 100 °C for 1h. After cooling down to rt, the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using heptane/EtOAc (90/10 to 70/30) to give the title compound as a pale brown oil (0.870 g, 68 %).

LCMS (**Method S**): Rt = 1.36; MS m/z [M+H]+ = 340.1/342.1

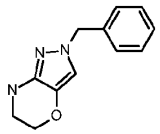
Int 360.5: 2-(1-benzyl-3-bromo-pyrazol-4-yl)oxyethanamine



TFA (1.00 mL, 0.0135 mol) was added to a solution of tert-butyl N-[2-(1-benzyl-3-bromo-pyrazol-4-yl)oxyethyl]carbamate (0.500 g, 0.00126 mol) in 10 ml of dichloromethane. The solution was stirred at rt for 18 h. The reaction was cooled with an ice bath and slowly basified with a 1N aqueous solution of NaOH until pH about 8-9. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (0.292 g, 78 %) as a pale orange oil.

1H NMR (400 MHz, DMSO) δ (ppm): 7.78 (s, 1H), 7.57 – 7.29 (m, 3H), 7.28 – 7.19 (m, 2H), 6.36 (bs, 2H), 5.22 (s, 2H), 3.98 (t, J = 5.4 Hz, 2H), 3.06 (t, J = 5.4 Hz, 2H).

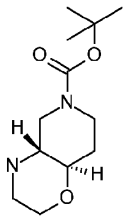
Int 360.6: 2-benzyl-6,7-dihydro-5H-pyrazolo[4,3-b][1,4]oxazine



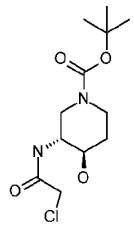
In a sealed tube, a solution of 2-(1-benzyl-3-bromo-pyrazol-4-yl)oxyethanamine (0.370 g, 0.00125 mol) in 15 ml of tetrahydrofuran was purged with N_2. GPhos Pd G3 (0.113 g, 0.000125 mol) was added, the mixture was purged again with N_2. NaOTMS 1M in THF (1.00 mol/L, 2.50 mL, 0.00250 mol) was added, the tube was sealed, and the mixture was heated at 80°C for 18h. After cooling down to rt, EtOAc and water were added to the reaction. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM / MeOH (100/0 to 95/5) to give the title compound (0.165 g, 61%).

LCMS (**Method S**): Rt = 1.15; MS m/z [M+H]+ = 216.2

Int 344.3: tert-butyl (4aR,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate



Int 344.1: tert-butyl (3R,4R)-3-[(2-chloroacetyl)amino]-4-hydroxy-piperidine-1-carboxylate

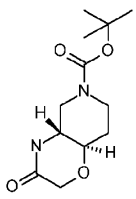


To a stirred solution of tert-butyl (3R,4R)-3-amino-4-hydroxy-piperidine-1-carboxylate (3.00 g, 13.9 mmol) in 8 ml of water and 48 ml of acetone were added sodium acetate (2.5 g, 30.5 mmol) and 2-chloroacetyl chloride (1.33 mL, 16.6 mmol). The reaction mixture was stirred at rt for 18h. The reaction mixture was concentrated under reduced pressure.

Water and DCM were added, the aqueous layer was extracted with DCM. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (3.72 g, 92 %) which was used without further purification in the next step.

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.06 (d, J = 7.5 Hz, 1H), 4.92 (d, J = 4.8 Hz, 1H), 4.08 (s, 2H), 3.80 – 3.76 (m, 1H), 3.69 – 3.66 (m, 1H), 3.44 (m, 2H), 2.92 (t, J = 11.7 Hz, 1H), 1.84 (m, 1H), 1.40 (s, 9H), 1.31 (m, 2H).

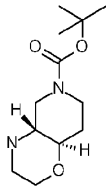
Int 344.2: tert-butyl (4aR,8aR)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate



At 0°C, to a stirred solution of tert-butyl (3R,4R)-3-[(2-chloroacetyl)amino]-4-hydroxy-piperidine-1-carboxylate (3.72 g, 0.0127 mol) in 57 ml of dichloromethane was added dropwise tBuOK (1.43 g mg, 0.0127 mol) in 145 ml of propan-2-ol. The reaction mixture was stirred at rt for 18h. The reaction mixture was concentrated under reduced pressure, and EtOAc and water were added. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using DCM/(MeOH/NH_4OH(10%)) (100/0 to 93/7) to give the title compound as a white solid (2.04 g, 63 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.22 (s, 1H), 4.17 – 4.11 (m, 1H), 4.08 (d, J = 3.8 Hz, 2H), 4.05 (s, 1H), 3.37 (m, 1H), 3.01 – 2.94 (m, 1H), 2.81 (s, 1H), 1.88 – 1.81 (m, 1H), 1.40 (d, J = 3.0 Hz, 9H), 1.38 – 1.29 (m, 2H).

Int 344.3: tert-butyl (4aR,8aR)-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine-6-carboxylate



At 0°C, under N_2, to a stirred solution of tert-butyl (4aR,8aR)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carboxylate (2.53 g, 0.00987 mol) in 55 ml of dichloromethane were added TMSCl (1.50 mL, 0.0118 mol) and $LiAlH_4$ (1M in THF) (13.8 mL, 0.0138 mol). The reaction mixture was stirred at rt for 18 h. Then, 2 ml of (3M) NaOH solution was slowly added, and the resulting mixture was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 2.03 g of the title compound which was used without further purification in the next step.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.96 – 3.92 (m, 1H), 3.89 – 3.85 (m, 1H), 3.73 – 3.64 (m, 1H), 3.45 (td, J = 11.2, 3.1 Hz, 1H), 3.08 – 2.95 (m, 1H), 2.81 – 2.61 (m, 3H), 2.48 – 2.43 (m, 1H), 2.21 – 2.11 (m, 1H), 1.65 (ddt, J = 12.6, 4.8, 2.6 Hz, 1H), 1.38 (s, 9H), 1.34 – 1.22 (m, 2H).

Pharmacological data

BIOLOGICAL ASSAYS AND DATA

The activity of a compound according to the present invention can be assessed by the following in vitro methods.

IL-1β secretion assay

Monocytic THP-1 cells were maintained in RPMI 1640 media (Gibco 21875) + 10% FBS, (Gibco 10500) + 1% penicillin/streptomycin (Gibco 15140-122). Cells were then plated at 40,000 cells per well in 384-well cell culture plates (Corning 3542) and maintained with RPMI1640 (Gibco 11835) + 5% FBS (Gibco 10500). Activation of the NLRP3 inflammasome requires both an NF-kB-dependent priming step and the addition of a NLRP3 activator. The priming step was induced by LPS (10ng/mL, InvivoGen ref tlrl-3pelps) for 3h at 37°C, then compound, in a 1:3 serial dilution series in DMSO (final concentration DMSO 0.1%), and the activator nigericin (Sigma Aldrich, ref: SML1779) 10μM (final concentration) were added to the cells and co-incubated for 2 hours. 16 μL supernatant was removed, and IL-1β levels were monitored using an HTRF assay (Human IL1b Kits HTRF Cisbio ref: 62HILBPEH) according to manufacturers' instructions.

TNF-α secretion assay

Monocytic THP-1 cells were maintained in RPMI 1640 media (Gibco 21875) + 10% FBS, (Gibco 10500) + 1% penicillin/streptomycin (Gibco 15140-122). Cells were then plated at 40,000 cells per well in 384-well cell culture plates (Corning 3542) and maintained with RPMI1640 (Gibco 11835) + 5% FBS, (Gibco 10500). Experimental compounds were prepared and added as described above. TNF-α secretion was triggered by the addition of 10ng/mL LPS (invivoGen, tlrl-3pelps) and cells were incubated for 3 hours. TNF-α levels were monitored directly in the cells plate using an Lumit assay (Lumit TNFa-Human Immunoassay – Promega W6051) according to manufacturers' instructions.

Data interpretation

Data were expressed as percentage of inhibition (I%) as compared to a maximum signal control containing no small molecule (I% = 0%) according to the formula: I%=(1-((Sample-Min))/((Max-Min)))×100, where:

Sample: Signal obtained in the presence of each compound tested,

Max: Maximum signal in the absence of compound added,

Min: Minimum or background signal obtained in the absence of activation signal.

Relative IC50 (IC50 rel) were obtained from a dose response curve with 10 concentrations. Final IC50 rels are expressed as the geometric mean.

Relative IC50 values were estimated with Biost@t-SPEED v2.4 internal software based on SAS system using the 4-parameter logistic model according to Ratkovsky and Reedy (*D.A. Ratkovsky, T.J. Reedy, Choosing near-linear parameters in the four parameters logistic model radioligands and related assays. Biometrics, 42 (1986), 575–582)*: Y=A+C/((1+exp(-B*(log(X)-M)))), where:

A: Lower asymptote (BOTTOM),

A+C: Upper asymptote (TOP),

M: the logarithm of the concentration estimated at the inflexion point (the logarithm of the relative IC50),

B: Slope at the inflexion point of the curve.

The results of NLRP3 IC50 (that is to say IL-1β IC50) and TNF-α IC50 are summarized in the table below:

Example	**IL-1β IC50 (µM)**	**TNF-α IC50 (µM)**
1	0.407	>10
2	1.960	
3	2.030	

Example	**IL-1β IC50 (µM)**	**TNF-α IC50 (µM)**
4	0.251	>10
5	0.290	>10
6	0.235	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
7	5.470	
8	0.020	>10
9	0.113	>10
10	0.178	>10
11	0.003	>10
12	0.171	>10
13	0.002	>10
14	0.605	>10
15	0.406	>10
16	0.025	>10
17	0.473	>10
18	0.173	>10
19	1.480	
20	0.044	>10
21	0.020	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
22	0.153	>10
23	0.192	>10
24	0.638	
25	0.109	>10
26	0.352	>10
27	1.260	
28	0.109	>10
29	0.332	>10
30	0.431	>10
31	0.520	>10
32	3.500	
33	0.239	>10
34	0.095	>10
35	0.501	>10
36	0.096	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
37	0.893	
38	0.090	>10
39	0.238	>10
40	0.420	>10
41	0.252	>10
42	0.134	>10
43	0.603	
44	0.862	
45	0.281	>10
46	0.389	>10
47	1.040	
48	0.386	>10
49	0.672	
50	0.549	
51	1.050	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
52	1.250	
53	0.275	>10
54	0.132	>10
55	0.176	>10
56	0.111	>10
57	0.248	>10
58	0.064	>10
59	0.203	>10
60	0.386	>10
61	0.090	>10
62	0.052	>10
63	0.006	>10
64	0.222	>10
65	0.151	>10
66	0.304	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
67	0.306	>10
68	1.220	
69	0.200	>10
70	0.467	>10
71	0.270	>10
72	0.107	>10
73	0.056	>10
74	0.411	>10
75	0.183	9,6
76	0.066	8.6
77	0.135	>10
78	0.436	>10
79	0.285	9.5
80	0.208	>10
81	0.164	9.8

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
82	0.481	
83	2.791	
84	1.765	
85	0.033	>10
86	0.506	>10
87	0.311	>10
88	1.150	
89	0.614	
90	0.659	
91	4.930	
92	2.200	
93	0.879	
94	1.920	
95	2.200	
96	0.124	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
97	0.038	
98	0.298	
99	0.752	
102	>10	
103	1.360	
105	0.335	
106	0.174	
107	0.385	
108	0.545	
109	0.089	
110	3.760	
111	0.496	
112	0.088	
113	0.857	
114	0.958	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
115	1.540	
116	0.454	>10
117	0.869	
118	0.758	
119	0.561	>10
120	2.520	
121	0.092	>10
122	0.149	>10
123	2.020	
124	1.050	
125	1.320	
126	0.484	>10
127	0.125	>10
128	0.779	
129	0.665	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
130	0.099	>10
131	0.387	>10
132	0.362	>10
133	0.068	>10
134	0.071	>10
135	0.997	
136	3.030	
137	0.411	>10
138	0.441	>10
139	0.235	>10
140	0.210	>10
141	0.131	>10
142	0.360	>10
143	0.221	>10
144	0.151	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
145	0.034	>10
146	0.242	>10
147	0.575	>10
148	0.922	
149	0.052	>10
150	1.789	
151	1.170	
152	5.980	
153	0.047	>10
154	0.344	>10
155	0.461	>10
156	1.060	
157	0.314	>10
158	0.085	>10
159	0.043	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
160	0.171	>10
161	0.028	>10
162	0.010	>10
163	0.007	>10
164	0.081	>10
165	0.042	5.62
166	3.310	
167	0.309	>10
168	3.380	
169	0.008	>10
170	0.012	>10
171	0.007	>10
172	0.036	>10
173	0.040	>10
174	0.170	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
175	0.522	>10
176	0.250	>10
177	0.091	7.38
178	0.007	>10
179	0.897	
180	0.473	>10
181	1.390	
182	1.650	
183	0.685	
184	0.660	
185	3.220	
186	1.050	
187	0.066	>10
188	0.414	>10
189	0.012	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
190	1.148	
191	1.117	
192	0.011	>10
193	0.534	9,83
194	0.004	>10
195	0.014	>10
196	0.452	>10
197	0.009	>10
198	0.016	>10
199	0.004	>10
200	0.023	>10
201	0.076	>10
203	0.332	9.99
204	0.054	>10
206	0.325	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
207	0.174	3.01
208	0.972	
209	0.002	>10
210	0.001	>10
211	0.034	>10
212	0.039	>10
213	0.115	>10
214	0.036	>10
215	1.460	
216	0.128	>10
217	0.127	>10
219	0.103	>10
220	0.108	>10
221	0.018	>10
222	0.042	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
223	0.001	>10
224	0.001	>10
225	0.003	>10
226	0.002	>10
227	1.190	
228	0.271	>10
229	0.042	>10
230	0.556	9,14
231	0.219	>10
232	0.502	7.63
233	0.164	>10
234	0.355	>10
235	0.070	7.13
236	0.551	9.65
237	0.024	4.12

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
238	0.047	4.29
239	0.200	>10
240	0.421	>10
241	0.250	>10
242	2.120	
243	0.021	>10
245	0.064	>10
246	0.012	>10
247	0.168	>10
248	0.081	>10
249	0.151	>10
250	0.249	>10
251	0.021	>10
252	0.461	>10
253	6.750	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
254	0.460	9,97
255	0.249	>10
256	0.001	>10
257	7.490	
258	0.030	>10
259	0.067	>10
260	0.180	>10
261	0.001	>10
262	0.017	>10
263	0.180	>10
264	0.069	>10
265	0.314	>10
266	0.073	>10
267	0.185	>10
268	0.263	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
269	0.404	>10
270	0.493	>10
271	0.690	
272	2.34	6,58
273	0.456	>10
274	0.171	>10
275	0.127	>10
276	0.515	>10
277	0.051	2,04
278	0.050	>10
279	0.277	>10
280	0.076	>10
283	0.135	
284	0.087	>10
285	0.065	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
286	0.151	
287	0.115	
288	0.143	
289	0.140	
290	0.145	
291	0.001	>10
292	0.265	
293	0.084	>10
295	0.002	>10
296	0.028	>10
297	0.011	>10
298	0.003	>10
299	0.015	>10
300	0.177	
301	0.868	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
302	0.013	>10
303	3.870	
304	0.142	
305	2.820	
306	1.510	
307	0.410	
308	0.009	>10
309	0.249	
310	0.496	
311	0.002	>10
312	0.056	>10
313	0.0003	>10
314	0.018	>10
315	0.511	
316	0.287	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
317	3.000	
318	0.883	
320	0.116	
321	0.001	>10
322	0.080	>10
323	0.003	>10
324	0.056	>10
325	0.275	
326	0.198	
327	0.292	
328	0.219	
329	0.711	
330	0.987	
331	1.080	
332	0.396	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
333	0.460	
334	0.073	
335	0.481	
336	1.160	
337	2.880	
338	0.046	>10
339	0.133	
340	0.0004	>10
341	0.001	>10
342	0.002	>10
343	0.047	>10
344	0.223	
345	0.125	
346	0.212	
348	0.199	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
349	0.953	
350	0.001	>10
351	0.167	
352	0.375	
353	0.029	>10
354	0.020	>10
355	1.170	
356	0.061	>10
357	0.048	>10
358	0.011	>10
359	0.098	>10
360	0.420	
361	0.008	>10
362	3.540	
363	0.016	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
364	0.858	
365	0.028	>10
366	0.025	>10
367	0.0005	>10
368	0.188	
369	0.476	
370	1.270	
371	0.001	>10
372	0.094	>10
373	0.0011	>10
374	0.042	>10
375	0.0004	>10
376	0.180	
377	0.296	
378	0.001	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
379	0.001	>10
380	0.004	>10
381	0.003	>10
382	0.012	>10
383	1.010	
384	0.0004	>10
385	0.002	>10
386	0.019	>10
387	0.031	>10
388	0.001	>10
389	0.002	>10
390	0.033	>10
391	0.031	>10
392	0.001	>10
393	0.461	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
394	0.310	
395	0.234	
397	0.023	>10
398	0.017	>10
399	0.564	
400	0.093	>10
402	0.022	
403	0.366	
404	0.00075	
405	0.089	>10
406	0.078	>10
407	0.003	>10
408	0.002	>10
409	0.638	
410	2.18	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
411	0.344	
412	0.018	>10
413	0.5	
414	0.699	
415	4.66	
416	0.001	>10
417	0.716	
418	0.013	>10
419	0.127	
420	0.601	
421	1.23	
422	1.14	
423	0.00048	>10
424	0.396	
425	0.055	>10

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
426	0.952	
427	0.002	>10
428	1.02	
429	<0.00036	>10
430	<0.0003	>10
431	0.062	>10
432	0.005	>10
433	0.002	>10
434	0.042	>10
435	0.003	>10
436	0.002	>10
437	0.001	>10
438	0.411	
439	0.569	
440	3.28	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
441	4.67	
442	0.195	
443	0.01	>10
444	4.06	
445	1.900	
446	0.815	
448	0.370	
449	4.190	
450	2.040	
451	1.650	
452	0.005	
455	7.150	
456	0.002	
457	0.432	
458	0.002	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
459	0.001	
460	<0.0003	
461	0.001	
462	0.251	
463	3.780	
466	0.1	
467	0.014	
468	0.544	
469	0.001	
470	0.00038	
471	0.001	
472	0.001	
473	0.005	
474	<0.0003	
475	0.093	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
476	0.209	
477	<0.0003	
479	0.005	
480	0.006	
481	0.002	
482	0.172	
483	0.001	
484	0.025	
485	0.045	
486	<0.0003	
487	0.001	
488	0.912	
489	0.232	
490	0.001	
491	0.185	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
492	0.003	
493	0.171	
494	0.001	
496	0.546	
497	0.0004	
498	0.951	
499	0.003	
500	0.062	
501	<0.0003	
502	0.347	
503	0.0005	
504	1.08	
505	0.0004	
506	0.135	
507	0.001	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
508	0.04	
509	0.016	
510	0.28	
511	0.571	
512	0.276	
513	1.77	
514	0.196	
515	0.044	
516	1.08	
517	1.34	
518	1.22	

Example	IL-1β IC50 (μM)	TNF-α IC50 (μM)
519	0.007	
520	0.055	
521	0.028	
522	0.021	
523	0.681	
524	0.008	
525	0.631	
526	0.001	
527	0.020	
528	0.0049	

The compounds of the present invention have significant inhibitory activity on secretion of IL-1 beta by THP-1 cells with minimal to no interference with the NF-kB pathway as measured by the TNFalpha secretion after LPS priming.

It is therefore apparent that the compounds of formula (I) have an inhibitory activity on NOD-like receptor protein 3 (NLRP3) inflammasome.

The compounds of formula (I) may thus be used as inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

The compounds of formula (I) may thus be used as medicaments, especially medicaments which are inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

Thus, according to another of its aspects, a subject of the present disclosure is medicaments that comprise a compound of formula (I), or an addition salt thereof with a pharmaceutically acceptable acid.

These medicaments are employed therapeutically in the treatment of neurodegenerative diseases, in particular Parkinson's disease, frontotemporal Dementia, Multiple System Atrophy, Alzheimer's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or Brain injury.

According to another embodiment, the present disclosure relates to pharmaceutical compositions comprising as active principle, a compound of formula (I). These pharmaceutical compositions contain an effective dose of at least one compound of formula (I), or a pharmaceutically acceptable salt of the said compound.

These pharmaceutical compositions may also contain at least one pharmaceutically acceptable excipient.

The said excipients are chosen, according to the pharmaceutical form and the desired mode of administration, from the usual excipients known to those skilled in the art.

The compounds of formula (I) may be used in the prevention and/or in the treatment of pathologies involving NOD-like receptor protein 3 (NLRP3) inflammasome pathway.

The present disclosure, according to another of its aspects, also provides a method of treating and/or preventing the pathologies indicated above.

Thus, is also described a method of treating and/or preventing Parkinson's disease, frontotemporal Dementia, Multiple System Atrophy, Alzheimer's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or Brain injury, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to one embodiment, is also described a method of treating and/or preventing Parkinson's disease, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a

pharmaceutically acceptable salt thereof.

According to another embodiment, is also described a method of treating and/or preventing frontotemporal Dementia, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another embodiment, is also described a method of treating and/or preventing Multiple System Atrophy, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

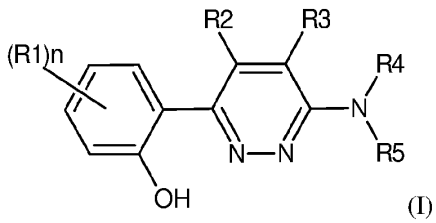
According to another embodiment, is also described a method of treating and/or preventing Alzheimer's Disease, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another embodiment, is also described a method of treating and/or preventing Multiple Sclerosis, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another embodiment, is also described a method of treating and/or preventing Amyotrophic Lateral Sclerosis, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to another embodiment, is also described a method of treating and/or preventing Brain injury, including administering to a subject in need thereof a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

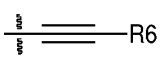
Numbered Embodiment 1 : A compound of formula (I) or a pharmaceutically acceptable salt thereof:



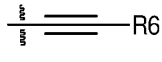
(I)

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R4 and **R5** form together with the nitrogen atom to which they are attached:

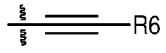
- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

said monocyclic heterocycloalkyl ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-

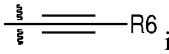
C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Numbered Embodiment 2: A compound of formula (I) or a pharmaceutically acceptable salt thereof of Embodiment 1, wherein

n is 1or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring; and

R4 and **R5** form together with the nitrogen atom to which they are attached:

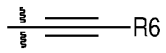
- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

said monocyclic heterocycloalkyl ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group,

a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Numbered Embodiment 3: A compound of formula (I) or a pharmaceutically acceptable salt thereof of Embodiment 1, wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

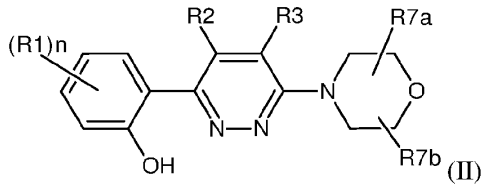
R4 and **R5** form together with the nitrogen atom to which they are attached:

- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

said monocyclic heterocycloalkyl ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-

C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

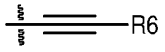
Numbered Embodiment 4: A compound of formula (II) or a pharmaceutically acceptable salt thereof:



(II)

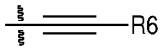
wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

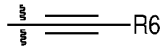
or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R7a and **R7b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-

C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Numbered Embodiment 5 : A compound of formula (II) or a pharmaceutically acceptable salt thereof of Embodiment 4, wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a halo(C_1-C_4)alkyl group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

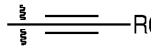
R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a halo(C_1-C_4)alkyl group ;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R7a and **R7b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a halo-(C_1-C_4)alkyl- group, a NH_2-C(=O)- group, NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_2-C_5)acyl group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-(C_3-C_6)cycloalkyl- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, an oxo group, or a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group.

Numbered Embodiment 6 : A compound of formula (II) or a pharmaceutically acceptable salt thereof of any of Embodiments 4 or 5, wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a halo(C_1-C_4)alkyl group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group or a halo(C_1-C_4)alkyl group ;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R7a represents a hydrogen atom, a (C_1-C_4)alkyl- group, a halo-(C_1-C_4)alkyl- group, a NH_2-C(=O)- group, NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_2-C_5)acyl group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-(C_3-C_6)cycloalkyl- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, an oxo group or a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group; and

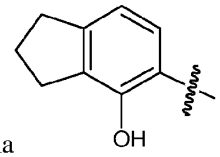
R7b represents a hydrogen atom, or a hydroxy-(C_1-C_4)alkyl- group.

Numbered Embodiment 7 : A compound of formula (II) or a pharmaceutically acceptable salt thereof of any of Embodiments 4 to 6, wherein

n is 1 or 2

R1 represent independently of each other a methyl group, an ethyl group, an isopropyl group, an ethynyl group, F, Cl, a methoxy group, a cyclopropyl group, a trifluoromethoxy group or a trifluoromethyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group so as to form the

following formula  in which the symbol ≈ represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a -CHF_2 group, a trifluoromethyl group, a OH-CH_2- group, a methyl group, an ethyl group, or an isopropyl group;

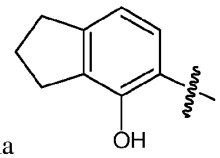
or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentyl ring which is fused to the pyridazine ring; and

R7a and **R7b** represent independently of each other a hydrogen atom, a methyl group, a CH_2F- group, NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a SH-CH_2- group, a CN-CH_2- group, a CH_3-NH-$(CH_2)_2$- group, a OH-CH_2- group, a OH-CD_2- group, a OH-$(CH_2)_2$- group, a OH-$C(CH_3)_2$- group, a CH_3-CH(OH)- group, a CH_3-C(=O)-NH-CH_2- group, a CH_3-C(=O)-NH-CH_2-CH_2- group a $CH(CH_3)_2$-C(=O)-NH-CH_2- group, a NH_2-C(=O)- group, a $NH(CH_3)$-C(=O)- group, a $N(CH_3)_2$-C(=O)- group, a NH_2-cyclopropyl- group, a NH_2-C(=O)-CH_2- group, a $NH(CH_3)$-C(=O)-CH_2- group, a $N(CH_3)_2$-C(=O)-CH_2- group, a CH_3-CH_2-C(=O)- group, an oxo group, or a CH_3-O-CH_2- group.

Numbered Embodiment 8 : A compound of formula (II) or a pharmaceutically acceptable salt thereof of any of Embodiments 4 to 7, wherein

n is 1 or 2;

R1 represent independently of each other a methyl group, an ethyl group, an isopropyl group, an ethynyl group, F, Cl, a methoxy group, a cyclopropyl group, a trifluoromethoxy group or a trifluoromethyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group so as to form the following formula  in which the symbol ≈ represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring;

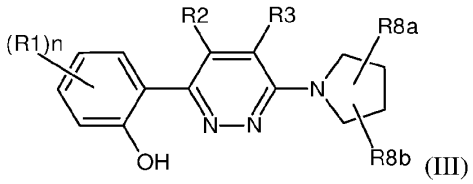
R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a -CHF_2 group, a trifluoromethyl group, a OH-CH_2- group, a methyl group, an ethyl group, or an isopropyl group;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentyl ring which is fused to the pyridazine ring;

R7a represents a hydrogen atom, a methyl group, a CH_2F- group, NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a SH-CH_2- group, a CN-CH_2- group, a CH_3-NH-$(CH_2)_2$- group, a OH-CH_2- group, a OH-CD_2- group, a OH-$(CH_2)_2$- group, a OH-$C(CH_3)_2$- group, a CH_3-CH(OH)- group, a CH_3-C(=O)-NH-CH_2- group, a CH_3-C(=O)-NH-CH_2-CH_2- group a $CH(CH_3)_2$-C(=O)-NH-CH_2- group, a NH_2-C(=O)- group, a NH(CH_3)-C(=O)- group, a $N(CH_3)_2$-C(=O)- group, a NH_2-cyclopropyl- group, a NH_2-C(=O)-CH_2- group, a NH(CH_3)-C(=O)-CH_2- group, a $N(CH_3)_2$-C(=O)-CH_2- group, a CH_3-CH_2-C(=O)- group, an oxo group, or a CH_3-O-CH_2- group; and

R7b represents a hydrogen atom or a OH-CH_2- group.

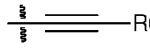
Numbered Embodiment 9 : A compound of formula (III) or a pharmaceutically acceptable salt thereof:



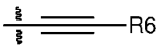
(III)

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring; and

R8a and **R8b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Numbered Embodiment 10 : A compound of formula (III) or a pharmaceutically acceptable salt thereof of Embodiment 9, wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 and **R3** represent a hydrogen atom, or a halo(C_1-C_4)alkyl group; and

R8a and **R8b** represent independently of each other a hydrogen atom, a NH_2- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, or an oxo group.

Numbered Embodiment 11 : A compound of formula (III) or a pharmaceutically acceptable salt thereof of any of Embodiments 9 or 10, wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 represents a halo(C_1-C_4)alkyl group or a hydrogen atom;

R3 represents a hydrogen atom;

R8a represents a hydrogen atom, a NH_2- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, or an oxo group.; and

R8b represents a hydrogen atom, or an oxo group.

Numbered Embodiment 12: A compound of formula (III) or a pharmaceutically acceptable salt thereof of any of Embodiments 9 to 11, wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

R2 represents a hydrogen atom or a -CHF_2 group;

R3 represents a hydrogen atom; and

R8a and **R8b** represent independently of each other a hydrogen atom, a NH_2-group, a NH_2-(CH_2)- group, a $N(CH_3)_2$-(CH_2)- group, a OH-CH_2- group, a CH_3-O-CH_2-group, a hydroxyl group, or an oxo group.

Numbered Embodiment 13: A compound of formula (III) or a pharmaceutically acceptable salt thereof of any of Embodiments 9 to 12, wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

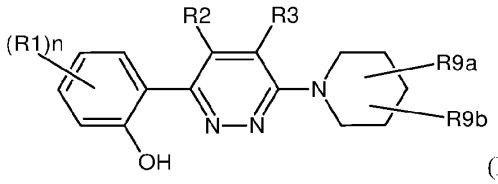
R2 represents a hydrogen atom or a -CHF_2 group;

R3 represents a hydrogen atom;

R8a represents a hydrogen atom, a NH_2- group, a NH_2-(CH_2)- group, a $N(CH_3)_2$-(CH_2)- group, a OH-CH_2- group, a CH_3-O-CH_2- group, a hydroxyl group, or an oxo group; and

R8b represents a hydrogen atom, or an oxo group.

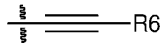
Numbered Embodiment 14: A compound of formula (IV) or a pharmaceutically acceptable salt thereof:



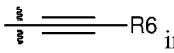
(IV)

wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R9a and **R9b** represent independently of each other a hydrogen atom, a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-

C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

Numbered Embodiment 15 : A compound of formula (IV) or a pharmaceutically acceptable salt thereof of Embodiment 14, wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 and **R3** represent a hydrogen atom; and

R9a and **R9b** represent independently of each other a hydrogen atom, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a hydroxyl group, a cyano group, an oxo group or a halogen atom.

Numbered Embodiment 16 : A compound of formula (IV) or a pharmaceutically acceptable salt thereof of any of Embodiments 14 or 15, wherein

n is 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, or a halo(C_1-C_4)alkyl group;

R2 and **R3** represent a hydrogen atom;

R9a represents a hydrogen atom, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a hydroxy-(C_1-C_4)alkyl- group, a hydroxyl group, a cyano group, or a halogen atom; and

R9b represents a hydrogen atom, an oxo group, or a halogen atom.

Numbered Embodiment 17 : A compound of formula (IV) or a pharmaceutically acceptable salt thereof of any of Embodiments 14 to 16, wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

R2 and **R3** represent a hydrogen atom; and

R9a and **R9b** represent independently of each other a hydrogen atom, a NH_2 group, a $N(CH_3)_2$- group, a CH_3-CH_2-NH- group, a NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a NH_2-cyclopropyl- group, a CH_3-(C=O)-NH-CH_2- group, a OH-CH_2- group, a hydroxyl group, a cyano group, an oxo group or a fluorine atom (F).

Numbered Embodiment 18 : A compound of formula (IV) or a pharmaceutically acceptable salt thereof of any of Embodiments 14 to 17, wherein

n is 2;

R1 represent independently of each other a chlorine atom, a methyl group, or a trifluoromethyl group;

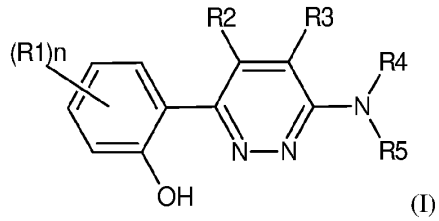
R2 and **R3** represent a hydrogen atom;

R9a represents a hydrogen atom, a NH_2 group, a $N(CH_3)_2$- group, a CH_3-CH_2-NH- group, a NH_2-CH_2- group, a $N(CH_3)_2$-CH_2- group, a NH_2-cyclopropyl- group, a CH_3-(C=O)-NH-CH_2- group, a OH-CH_2- group, a hydroxyl group, a cyano group, or a fluorine atom (F); and

R9b represents a hydrogen atom, an oxo group, or a fluorine atom (F).

CLAIMS

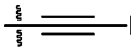
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

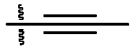
wherein

n is 1 or 2;

R1 represent independently of each other a halogen atom, a (C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a (C_3-C_6)cycloalkyl group;

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group;

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a (C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, a halo(C_1-C_4)alkyl group, or a group of formula 

in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the pyridazine ring;

or **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring;

R4 and **R5** form together with the nitrogen atom to which they are attached:

- a 3 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 2 to 6 carbon atoms,

- a 8 to 11 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one to three additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 4 to 10 carbon atoms, or

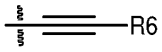
- a 7 to 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 11 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a OH-(C_3-C_6)cycloalkyl- group, a mono(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a di(C_1-C_4)alkylamino-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group, a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group or a -CO_2H group.

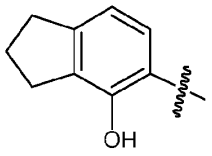
2. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, wherein **n** is 1.

3. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, wherein **n** is 2.

4. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein **R1** represent independently of

each other a halogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a halo(C_1-C_4)alkoxy group, a (C_3-C_6)cycloalkyl group, a group of formula  in which **R6** is a hydrogen atom or a methyl group and the symbol  represents the attachment site between the carbon atom and the phenyl ring, or a halo(C_1-C_4)alkyl group, in particular **R1** represent independently of each other a fluorine atom, a chlorine atom, a methyl group, an ethyl group, an isopropyl group, a methoxy group, a trifluoromethoxy group, a cyclopropyl group, a -CHF_2 group, an ethynyl group or a trifluoromethyl group,

or two **R1** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentane ring which is fused to the phenol group, in particular these two R1 represent a group of formula

 in which the symbol  represents the attachment site between the carbon atom of the phenol ring and the carbon atom of the pyridazine ring.

5. A compound of formula (I) or a pharmaceutically acceptable salt thereof according any one of claims 1 to 4, wherein

- when **n** is 1, **R1** is in ortho, meta or para position on the phenyl with respect to pyridazine ring, or
- when **n** is 2, the two **R1** are in ortho and in para position on the phenyl with respect to pyridazine ring, or
- when **n** is 2, the two **R1** are in ortho and in meta position on the phenyl with respect to pyridazine ring.

6. A compound of formula (I) or a pharmaceutically acceptable salt thereof according any one of claims 1 to 5, wherein

R2 and **R3** represent independently of each other a hydrogen atom, a cyano group, a halo(C_1-C_4)alkyl group, a hydroxy(C_1-C_4)alkyl group, or a (C_1-C_4)alkyl group;

in particular **R2** and **R3** represent independently of each other a hydrogen atom, a cyano group, a -CHF_2 group, a trifluoromethyl group, a -CH_2OH group, a methyl group, an ethyl group or an isopropyl group.

7. A compound of formula (I) or a pharmaceutically acceptable salt thereof according any one of claims 1 to 5, wherein

R2 and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a (C_5-C_6)carbocyclic ring which is fused to the pyridazine ring, in particular **R2** and **R3** which are on adjacent carbon atoms form together with the atoms connecting them a cyclopentyl ring which is fused to the pyridazine ring.

8. A compound of formula (I) or a pharmaceutically acceptable salt thereof according any one of claims 1 to 6, wherein

R4 and **R5** form together with the nitrogen atom to which they are attached:

- a 4 to 7 membered monocyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one additional heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 3 to 6 carbon atoms,

- a 8 to 10 membered bicyclic heterocycloalkyl ring comprising one nitrogen atom and optionally one or two additional heteroatoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 6, 7, 8 or 9 carbon atoms, or

- a 7 to 10 or 12 membered bicyclic heterocyclic spiro ring comprising one nitrogen atom and optionally one to three additional heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom and comprising 5 to 8 carbon atoms,

said monocyclic heterocycloalkyl ring, bicyclic heterocycloalkyl ring and bicyclic heterocyclic spiro ring being unsubstituted or substituted by one to two substituents independently selected from a (C_1-C_4)alkyl- group, a NH_2 group, a mono(C_1-C_4)alkylamino- group, a di(C_1-C_4)alkylamino- group, a NH_2-(C_1-

C_4)alkyl- group, a mono(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, a di(C_1-C_4)alkylamino-(C_1-C_4)alkyl- group, NH_2-(C_3-C_6)cycloalkyl- group, a (C_2-C_5)acylamino-(C_1-C_4)alkyl- group, a (C_2-C_5)acylamino- group, a (C_2-C_5)acyl- group, a hydroxy-(C_1-C_4)alkyl- group, a SH-(C_1-C_4)alkyl- group; a CN-(C_1-C_4)alkyl- group, a (C_1-C_4)alkoxy-(C_1-C_4)alkyl- group, a hydroxyl group, an oxo group, a (C_3-C_6)cycloalkyl group, a halogen atom, a halo(C_1-C_4)alkyl- group, a cyano group, a NH_2-C(=O)- group, a mono(C_1-C_4)alkylamino-C(=O)- group, a di(C_1-C_4)alkylamino-C(=O)- group, a NH_2-C(=O)-(C_1-C_4)alkyl- group, a mono(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group, or a di(C_1-C_4)alkylamino-C(=O)-(C_1-C_4)alkyl- group,

in particular **R4** and **R5** form together with the nitrogen atom to which they are attached:

- an azepanyl ring unsubstituted or substituted by one OH-CH_2- group;

- a morpholino ring unsubstituted or substituted by one or two substituents independently selected from a methyl group, a CH_2F- group, NH_2-CH_2- group, a N(CH_3)$_2$-CH_2- group, a CH_3-NH-(CH_2)$_2$- group, a SH-CH_2- group, a CN-CH_2- group, a OH-CH_2- group, a OH-CD_2- group, a OH-(CH_2)$_2$- group, a OH-C(CH_3)$_2$- group, a CH_3-CH(OH)- group, a CH_3-C(=O)-NH-CH_2- group, a CH_3-C(=O)-NH-CH_2- CH_2- group a CH(CH_3)$_2$-C(=O)-NH-CH_2- group, a NH_2-C(=O)- group, a NH(CH_3)-C(=O)- group, a N(CH_3)$_2$-C(=O)- group, a NH_2-cyclopropyl- group, a NH_2-C(=O)-CH_2- group, a NH(CH_3)-C(=O)-CH_2- group, a N(CH_3)$_2$-C(=O)-CH_2- group, a CH_3-CH_2-C(=O)- group, an oxo group, and a CH_3-O-CH_2- group,

- a thiomorpholino ring unsubstituted or substituted by one to two oxo groups;

- a piperidinyl ring unsubstituted or substituted by one to two substituents independently selected from a NH_2 group, a NH_2-CH_2- group, a NH(CH_2CH_3)- group, a N(CH_3)$_2$- group, a NH_2-cyclopropyl- group, a N(CH_3)$_2$-CH_2- group, a OH-CH_2- group, a CH_3-C(=O)-NH-CH_2- group, a cyano group, a hydroxyl group, an oxo group and a fluorine atom,

- a pyrrolidinyl ring unsubstituted or substituted by one to two substituents independently selected from a NH_2- group, a NH_2-CH_2- group, a N(CH_3)$_2$-CH_2- group, a OH-CH_2- group, a CH_3-O-CH_2- group, a hydroxyl group, and an oxo group,

- an isoxazolidinyl ring unsubstituted or substituted by one hydroxyl group,

- a piperazinyl ring unsubstituted or substituted by one to two substituents independently selected from a methyl group, an oxo group and a OH-CH_2- group;

- a hexahydropyrimidinyl ring substituted by one oxo group;

- an azetidinyl ring unsubstituted or substituted by one OH-CH_2- group,

- a tetrahydroquinolinyl ring or a dihydroquinolinyl ring such as 3,4-dihydro-2H-quinolinyl ring, unsubstituted or substituted by one hydroxyl group

- a hexahydropyridooxazinyl ring such as a hexahydro-2H-pyrido[3,4-b][1,4]oxazinyl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazinyl group, or a hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazinyl ring, unsubstituted or substituted by one cyclobutyl group, one methyl group, one ethyl group, one 2,2,2-trifluoroethyl group, one 2-fluoroethyl group, one 3-fluoropropyl group, one isopropropyl group or one acetyl group;

- a hexahydropyranooxazinyl ring such as hexahydro-2H-pyrano[3,4-b][1,4]oxazinyl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazinyl group, or such as a hexahydro-2H-pyrano[4,3-b][1,4]oxazinyl ring, for instance a 3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazinyl ring, unsubstituted;

- a dihydropyridooxazinyl ring such as dihydropyrido[3,4-b][1,4]oxazinyl ring or dihydropyrido[4,3-b][1,4]oxazinyl ring, for instance 2,3-dihydropyrido[3,4-b][1,4]oxazinyl ring or 2,3-dihydropyrido[4,3-b][1,4]oxazinyl ring, unsubstituted;

- a dihydropyrazolooxazinyl ring such as dihydro-2H-pyrazolo[4,3-b][1,4]oxazinyl ring, for instance 5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazinyl ring, unsubstituted;

- a dihydrobenzoxazinyl ring such as dihydro-1,4-benzoxazinyl ring, for instance 2,3-dihydro-1,4-benzoxazinyl ring substituted by one hydroxyl group;

- a tetrahydronaphthyridinyl ring or a dihydronaphthyridinyl ring such as 3,4-dihydro-2H-1,6-naphthyridinyl ring substituted by one hydroxyl group;

- a hexahydronaphthyridinyl ring such as hexahydro-2H-1,7-naphthyridinyl ring for instance a 3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridinyl ring substituted by one methyl group and one oxo group;

- a octahydronaphthyridinyl ring such as octahydro-1,7-naphthyridinyl ring or octahydro-1,5-naphthyridinyl ring for instance a 2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridinyl ring, a 2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridinyl ring, or a

2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridinyl ring, substituted by one oxo group, one methyl group, or one acetyl group;

- an octahydropyrrolopyridinyl ring or a hexahydropyrrolopyridinyl ring such as hexahydro-1H-pyrrolo[3,4-c]pyridinyl ring, octahydropyrrolo[2,3-c]pyridinyl ring, or hexahydro-2H-pyrrolo[2,3-c]pyridinyl ring, for instance 2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridinyl ring, 2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridinyl ring or 3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridinyl ring, unsubstituted or substituted by one methyl group, one ethyl group, one acetyl group, one isopropyl group or one oxo group ;

- an octahydropyrrolooxazinyl ring or a hexahydropyrrolooxazinyl ring such as hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring, for instance 2,3,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring, 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring or 3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl ring, unsubstituted or substituted by one methyl group, one ethyl group or one acetyl group;

- a hexahydrocyclopentaoxazinyl ring such as 3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazinyl ring substituted by one hydroxyl group;

- an octahydropyridooxazinyl ring such as octahydropyrido[4,3-b][1,4]oxazinyl ring, for instance 2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazinyl ring, unsubstituted;

- an indolinyl ring substituted by one hydroxyl group or one -CH_2OH group;

- a hexahydropyrrolopyrrolyl ring such as hexahydropyrrolo[3,4-b]pyrrolyl ring, hexahydro-1H-pyrrolo[3,2-b]pyrrolyl ring, or hexahydro-2H-pyrrolo[3,4-b]pyrrolyl ring, for instance 2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrolyl ring, 2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrolyl ring, or a 3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrolyl ring unsubstituted or substituted by one methyl group, one ethyl group or one acetyl group;

- a hexahydrofuropyrrolyl ring such as hexahydrofuro[3,4-c]pyrrolyl ring for instance 1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrolyl ring, unsubstituted;

- a azabicyclooctanyl ring such as 6-azabicyclo[3.2.1]octanyl ring substituted by one hydroxyl group ;

- a diazabicyclononanyl ring such as 3,6-diazabicyclo[3.2.2]nonanyl ring substituted by one methyl group

- a oxaazabicyclooctanyl ring such as 3-oxa-8-azabicyclo[3.2.1]octanyl ring unsubstituted ;

- an azaspirononanyl ring such as an azaspiro[3.5]nonanyl ring, unsubstituted or substituted by one substituent selected from a NH_2 group, a CH_3-C(=O)-NH- group, and a hydroxyl group;

- an azaspirooctanyl ring such as an azaspiro[3.4]octanyl ring, unsubstituted or substituted by one hydroxyl group;

- an azaspiroheptanyl ring such as an azaspiro[3.3]heptanyl ring, unsubstituted or substituted by one hydroxyl group;

- a diazaspirodecanyl ring such as 1,9-diazaspiro[4.5]decanyl ring substituted by one methyl group;

- a diazaspirononanyl ring such as a diazaspiro[3.5]nonanyl ring, unsubstituted or substituted by one methyl group;

- a diazaspiroheptanyl ring such as a diazaspiro[3.3]heptanyl ring, unsubstituted or substituted by one a methyl group;

- an oxadiazaspirononanyl ring such as 8-oxa-2,5-diazaspiro[3.5]nonanyl ring substituted by one methyl group;

- an oxadiazaspirodecanyl ring such as 2-oxa-6,9-diazaspiro[4.5]decanyl ring, 9-oxa-2,6-diazaspiro[4.5]decanyl ring, or 6-oxa-2,9-diazaspiro[4.5]decanyl ring unsubstituted or substituted by one ethyl group or one methyl group;

- an oxadiazaspiroundecanyl ring such as 4-oxa-1,8-diazaspiro[5.5]undecanyl ring substituted by one methyl group;

- an dioxadiazaspirododecanyl ring such as 1,11-dioxa-4,8-diazaspiro[5.6]dodecanyl ring substituted by one ethyl group;

- an oxaazaspirononanyl ring such as a oxaazaspiro[3.5]nonanyl ring; and

- an oxaazaspiroheptanyl ring such as an oxaazaspiro[3.3]heptanyl ring.

9. A compound of formula (I) or a pharmaceutically acceptable salt thereof according any one of claims 1 to 8, said compound being chosen from:

(1) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-4-ol;

(2) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidine-4-carbonitrile;

(3) 7-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-7-azaspiro[3.5]nonan-2-ol;

(4) 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol;

(5) 2-[6-[(3R)-3-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(6) 2-[6-[(3S)-3-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(7) 2-[6-(2,7-diazaspiro[3.5]nonan-7-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid;
(8) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(9) 2-[6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(10) 2-[6-[(4aR,8aS)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol Enantiomer 1;
(11) 2-[6-[(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; formic acid Enantiomer 2;
(12) 2-[6-[(4aR,8aS)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 1;
(13) 2-[6-[(4aS,8aR)-6-cyclobutyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 2;
(14) 2-[6-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(15) 2-[6-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(16) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(17) 2-[6-[3-(1-aminocyclopropyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;
(18) 2-[6-[(3S)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;
(19) 2-[6-[4-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;
(20) 2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(21) 3,5-dichloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(22) 2-[6-[(3R)-3-(aminomethyl)-1-piperidyl]pyridazin-3-yl]-3,5-dichloro-phenol;
(23) 2-[6-[(3S)-3-(aminomethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dichloro-phenol;
(24) 2-[6-[2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
(25) 2-[6-[(3R)-3-(aminomethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dichloro-phenol;

(26) 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(27) 2-[6-[(2R)-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(28) 2-[6-[(3S)-3-(hydroxymethyl)-1-piperidyl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(29) 3-methyl-2-[6-(4-methylpiperazin-1-yl)pyridazin-3-yl]-5-(trifluoromethyl) phenol;

(30) 2-[6-[3-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(31) 2-[6-[(3R)-3-amino-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;formic acid;

(32) 2-[6-(2-amino-7-azaspiro[3.5]nonan-7-yl)pyridazin-3-yl]-3,5-dichloro-phenol;

(33) 3,5-dichloro-2-[6-[(2R)-2-(methoxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(34) 3,5-dichloro-2-[6-[(3S)-3-(hydroxymethyl)-1-piperidyl]pyridazin-3-yl]phenol;

(35) 3,5-dichloro-2-[6-[(2S)-2-(methoxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(36) 3,5-dichloro-2-[6-[(3R)-3-(hydroxymethyl)-1-piperidyl]pyridazin-3-yl]phenol;

(37) 7-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-7-azaspiro[3.5]nonan-2-ol;

(38) 3,5-dichloro-2-(6-morpholinopyridazin-3-yl)phenol;

(39) 3,5-dichloro-2-[6-[(2S)-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]phenol;

(40) 3,5-dichloro-2-[6-[(3S)-3-[(dimethylamino)methyl]pyrrolidin-1-yl]pyridazine-3-yl]phenol;

(41) 3,5-dichloro-2-[6-[(3R)-3-[(dimethylamino)methyl]pyrrolidin-1-yl]pyridazin-3-yl]phenol;

(42) 6-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-6-azaspiro[3.4]octan-2-ol;

(43) 3,5-dichloro-2-[6-[(2R)-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]phenol;

(44) 3-fluoro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(45) 3-fluoro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(46) 2-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-2-azaspiro[3.3]heptan-6-ol;

(47) N-[7-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-7-azaspiro[3.5]nonan-2-yl]acetamide;

(48) 3-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(49) 3,5-dichloro-2-[6-(4,4-difluoro-1-piperidyl)pyridazin-3-yl]phenol;
(50) 3,5-dichloro-2-[6-[(3R)-3-[(dimethylamino)methyl]-1-piperidyl]pyridazin-3-yl]phenol;
(51) 3,5-dichloro-2-[6-[(3S)-3-[(dimethylamino)methyl]-1-piperidyl]pyridazin-3-yl]phenol;
(52) 2-[6-[2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 1;
(53) 2-[6-[-2-(1-hydroxy-1-methyl-ethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 2;
(54) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;
(55) 3,5-dichloro-2-[6-(2-methyl-2,7-diazaspiro[3.5]nonan-7-yl)pyridazin-3-yl]phenol;
(56) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;
(57) N-[[(3R)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide;
(58) N-[[(3S)-1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide;
(59) 2-[6-[-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 1;
(60) 2-[6-[-2-[(dimethylamino)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol Enantiomer 2;
(61) 1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;
(62) (4S)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;
(63) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;
(64) 3,5-dichloro-2-[6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridazin-3-yl]phenol;
(65) 2-[6-[(3R)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(66) 3,5-dichloro-2-[6-(2-oxa-7-azaspiro[3.5]nonan-7-yl)pyridazin-3-yl]phenol;

(67) (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]piperidin-3-ol;
(68) 2-[6-[(3S)-3-(ethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(69) 2-[6-[(3S)-3-amino-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(70) (3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-3-ol;
(71) (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-3-ol;
(72) 2-[4-ethyl-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;
(73) 5-chloro-2-[4-ethyl-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]phenol;
(74) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-isopropyl-pyridazin-3-yl]-5-methyl-phenol;
(75) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-isopropyl-pyridazin-3-yl]phenol;
(76) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;
(77) 2-[4-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl]-5-methyl-phenol;
(78) 5-chloro-2-[4-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl]phenol;
(79) 2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(80) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4,5-dimethyl-pyridazin-3-yl]-5-methyl-phenol;
(81) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4,5-dimethyl-pyridazin-3-yl]phenol;
(82) 2-[6-[(3S)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;
(83) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.5]nonan-7-ol;
(84) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.4]octan-6-ol;
(85) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]phenol;

(86) (4S)-4-hydroxy-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-2-one;

(87) 2-[6-[(2R)-2-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid;

(88) 2-[6-[(3R)-3-(methoxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(89) 2-[6-[(2R)-2-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;2,2,2-trifluoroacetic acid;

(90) 6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-3-(2-hydroxy-4-methyl-phenyl)pyridazine-4-carbonitrile;

(91) 3,5-dimethyl-2-[6-(1-methyl-1,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl]phenol;

(92) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(93) 5-fluoro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]phenol;

(94) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.4]octan-6-ol Enantiomer 1;

(95) 2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2-azaspiro[3.4]octan-6-ol Enantiomer 2;

(96) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methoxy-3-methyl-phenol;

(97) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(98) 2-[6-[2-[(1S)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol Diastereoisomer 2;

(99) 2-[6-[2-[(1S)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol Diastereoisomer 1;

(102) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-4-methyl-phenol;

(103) 3-(4-chloro-2-hydroxy-phenyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile;

(105) N-[[(2S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(106) N-[[(2R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(107) 2-[6-[3-(hydroxymethyl)azepan-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(108) 2-[6-[2-[(1R)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol Diastereoisomer 1;

(109) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol;

(110) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-5-methyl-phenol;

(111) 2-[6-[rac-(4aS,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(112) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol;

(113) (4R)-2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]isoxazolidin-4-ol

(114) 2-[6-[1-(hydroxymethyl)-6-azabicyclo[3.2.1]octan-6-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(115) 2-[6-[(2S)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(116) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methoxy-phenol;

(117) 3,5-dichloro-2-[6-[(2S)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]phenol;

(118) 2-[6-[(2R)-2-(hydroxymethyl)azetidin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(119) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methoxy-3-methyl-phenol;

(120) 3,5-dimethyl-2-[6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyridazin-3-yl]phenol;

(121) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethoxy)phenol;

(122) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl) pyrrolidin-2-one;

(123) 2-[6-[(3R)-3-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol, 2,2,2-trifluoroacetic acid;

(124) 2-[6-[(3S)-3-(aminomethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(125) 2-[6-[(4aR,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(126) 1-[4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]propan-1-one;

(127) 5-chloro-2-[6-[(3S)-3-(hydroxymethyl)pyrrolidin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(128) 2-[6-[(3S)-3-(dimethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(129) N-[[(3R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]morpholin-3-yl]methyl]acetamide;

(130) (4S)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one;

(131) (4S)-4-amino-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]pyrrolidin-2-one;

(132) (4R)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(133) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-5-methyl-pyridazin-3-yl]-3-methyl-phenol;

(134) 5-(difluoromethyl)-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(135) 2-[6-[(2S)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(136) 2-[6-[(2R)-2-(1-aminocyclopropyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(137) (4R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl) pyrrolidine-2-one;

(138) (4S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-4-(hydroxymethyl) pyrrolidin-2-one;

(139) (3R)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl)pyrrolidin-2-one;

(140) (3S)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3-(hydroxymethyl)pyrrolidin-2-one;

(141) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,6-dimethylphenol;

(142) 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide;

(143) 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N-methylacetamide;

(144) 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(145) 5-chloro-2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl] pyridazin-3-yl]phenol;

(146) 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl] acetamide;

(147) 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl] acetamide;

(148) 2-[6-[(3R)-3-(dimethylamino)-1-piperidyl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(149) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-3-methyl-phenol;

(150) 2-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N,N-dimethylacetamide;

(151) 2-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl]-N,N-dimethylacetamide;

(152) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-4,6-dimethylphenol;

(153) 3-(difluoromethyl)-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(154) 3,5-dimethyl-2-[6-[rac-(4aR,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[3,4-b][1,4]oxazin-1-yl]pyridazin-3-yl]phenol;

(155) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-(trifluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(156) 1-[(2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl] propan-1-one;

(157) 1-[(2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholin-2-yl] propan-1-one;

(158) 6-(2-hydroxy-4,6-dimethyl-phenyl)-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl] pyridazine-4-carbonitrile;

(159) 3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazine-4-carbonitrile;

(160) 5-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-(trifluoromethyl) pyridazine-3-yl]phenol;

(161) 3,5-dichloro-2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(162) 4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3-dihydro-1,4-benzoxazin-6-ol;

(163) 6-(4-chloro-2-hydroxy-6-methyl-phenyl)-3-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazine-4-carbonitrile;

(164) N-[[(3S)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(165) 2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(166) (2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N-methylmorpholine-2-carboxamide;

(167) N-[[(3R)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(168) 2-[6-[(4aR,7aR)-4-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl] pyridazin-3-yl]-3,5-dimethylphenol;

(169) 5-chloro-2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl] -3-methylphenol;

(170) 2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(171) 5-chloro-2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(172) 3-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-phenol;

(173) 2-[6-[(2R,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(174) 2-[6-[2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(175) 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 1;

(176) 6-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-azaspiro[3.5]nonan-2-ol Isomer 2;

(177) 3-chloro-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(178) 2-[6-[(2R,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(179) (4S)-2-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]isoxazolidin-4-ol;

(180) 2-[6-[2-[(1R)-1-hydroxyethyl]morpholin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol Diastereoisomer 2;

(181) (2S)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholine-2-carboxamide;

(182) (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N-methylmorpholine-2-carboxamide;

(183) (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]morpholine-2-carboxamide;

(184) (2R)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-N,N-dimethylmorpholine-2-carboxamide;

(185) 2-[6-[(4aS,7aS)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(186) 2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(187) 2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(188) 5-chloro-2-[4-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(189) 5-chloro-2-[5-(hydroxymethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(190) 2-[6-[rac-(4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethylphenol;

(191) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,4-dimethylphenol;

(192) 2-[6-[(2S)-2-[dideuterio(hydroxy)methyl]morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(193) 4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-2,3-dihydro-1,4-benzoxazin-7-ol;

(194) 2-[5-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(195) 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(196) 3,5-dimethyl-2-[6-(2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]phenol;

(197) 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(198) 2-[6-[(2S,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(199) 2-[6-[(2S,6S)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(200) 2-[6-[(2R,6R)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(201) 2-[6-[(2R,6R)-2,6-bis(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(203) 3,5-dichloro-2-(6-thiomorpholinopyridazin-3-yl)phenol;

(204) 5-cyclopropyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(206) 2-[6-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(207) 2-[6-[(3aR,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(208) 2-[6-(8-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecan-4-yl)pyridazin-3-yl]-3,5-dimethylphenol;

(209) 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(210) 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(211) N-[[(3S)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(212) N-[[(3R)-1-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3-piperidyl]methyl]acetamide;

(213) 1-[rac-(4aR,8aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(214) 1-[rac-(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(215) 2-[6-(2,3-dihydropyrido[3,4-b][1,4]oxazin-1-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(216) N-[[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(217) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-7-ol;

(219) 2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(220) 2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(221) 2-[6-[rac-(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(222) 1-[rac-(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(223) 2-[6-[rac-(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(224) 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(225) 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(226) 2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(227) 2-[6-(6-ethyl-2-oxa-6,9-diazaspiro[4.5]decan-9-yl)pyridazin-3-yl]-3,5-dimethylphenol;

(228) 1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-5-yl]ethanone;

(229) 2-[6-[rac-(3aS,6aS)-3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(230) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-6-ol;

(231) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-8-ol;

(232) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-quinolin-5-ol;

(233) 2-[6-[(2R)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(234) 2-[6-[(2S)-2-(2-hydroxyethyl)morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(235) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-5-(hydroxymethyl) piperidin-2-one;

(236) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-5-ol;

(237) 3,5-dichloro-2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(238) 3,5-dichloro-2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(239) 1-[6-(2,4-dichloro-6-hydroxy-phenyl)pyridazin-3-yl]hexahydropyrimidin-2-one;

(240) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-4-ol;

(241) 2-[6-[4-(hydroxymethyl)indolin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(242) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4-dihydro-2H-1,6-naphthyridin-5-ol;

(243) 2-[6-[rac-(3aS,6aS)-5-ethyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(245) 5-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methylphenol;

(246) 3-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methylphenol;

(247) 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(248) 2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(249) 5-chloro-2-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(250) (4S)-4-amino-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(251) 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(252) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(253) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-7-ol;

(254) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]indolin-6-ol;

(255) 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(256) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(257) 1-[rac-(4aS,7aS)-4-[6-(2-hydroxy-4,6-dimethylphenyl)pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(258) 3-methyl-2-[6-[(2R)-2-methylmorpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(259) 3-methyl-2-[6-[(2S)-2-methylmorpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(260) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(261) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(262) 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(263) 1-[(4aS,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(264) rac-(3aS,7aR)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one, hydrochloride;

(265) 2-[6-[rac-(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(266) 2-[6-[(2R)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(267) N-[[(2R)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(268) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(269) rac-(3aS,7aS)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one, hydrochloride;

(270) 2-[6-[(3aR,6aR)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(271) 2-[6-[(3aS,6aS)-5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(272) 2-[6-(3,4-dihydro-2H-quinolin-1-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(273) 3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(274) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-isopropyl-3-methyl-phenol;

(275) N-[[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]methyl]acetamide;

(276) N-[[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]methyl]-2-methylpropanamide;

(277) N-[2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide;

(278) N-[2-[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]ethyl]acetamide;

(279) N-[[(2R)-4-[6-(4-chloro-2-hydroxy-6-methylphenyl)pyridazin-3-yl]morpholin-2-yl]methyl]-2-methylpropanamide; and

(280) N-[[(2S)-4-[6-(4-chloro-2-hydroxy-6-methylphenyl)pyridazin-3-yl]morpholin-2-yl]methyl]acetamide.

(283) 2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(284) 2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(285) N-[[(2S)-4-[6-(4-chloro-2-hydroxy-6-methylphenyl)pyridazin-3-yl]morpholin-2-yl]methyl]-2-methylpropanamide;

(286) (4S)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(287) (3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(288) (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(289) 3-methyl-2-[6-[rac-(4aR,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(290) (4aR,8aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1,7-naphthyridin-8-one;

(291) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(292) (4R)-4-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(293) (4S)-4-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(295) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(296) 2-[6-[(2S,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(297) 2-[6-[(2S,6S)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(298) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(299) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(300) 1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-2,3,4,4a,5,6,7,8a-octahydro-1,7-naphthyridin-8-one;

(301) 2-[6-[(4aR,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(302) 2-[6-[(2R,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(303) 3,5-dimethyl-2-[6-[(2S)-2-(sulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(304) 1-[rac-(4aR,8aS)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(305) 3,5-dimethyl-2-[6-[(2R)-2-(sulfanylmethyl)morpholin-4-yl]pyridazin-3-yl]phenol;

(306) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(307) 5-chloro-3-methyl-2-[6-[rac-(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol;

(308) 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(309) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(310) 2-[6-[(4aR,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(311) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(312) 2-[6-[(4aR,8aS)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(313) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(314) 2-[6-[(4aR,8aS)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(315) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(316) (4R)-4-hydroxy-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]piperidin-2-one;

(317) 2-[6-(4-ethyl-1,11-dioxa-4,8-diazaspiro[5.6]dodecan-8-yl)pyridazin-3-yl]-3,5-dimethylphenol;

(318) 3-methyl-2-[6-[rac-(4aR,7aR)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride;

(320) 3-methyl-2-[6-[rac-(4aR,7aS)-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride;

(321) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(322) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(323) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(324) 5-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]-4-methyl-pyridazin-3-yl]indan-4-ol;

(325) (3R)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(326) (3S)-3-(hydroxymethyl)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]pyrrolidin-2-one;

(327) 2-[(2R)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile;

(328) 2-[(2S)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-2-yl]acetonitrile;

(329) (6R)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one;

(330) (6S)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-6-(hydroxymethyl)piperazin-2-one;

(331) 3-methyl-2-[6-[(2R)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(332) 3-methyl-2-[6-[(2S)-2-[2-(methylamino)ethyl]morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(333) 2-[6-[(4aR,7aS)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(334) 2-[6-[(4aS,7aR)-6-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(335) 1-[rac-(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(336) 1-[(4aR,8aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(337) 1-[rac-(4aR,7aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(338) 5-chloro-2-[6-[(2R)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(339) 5-chloro-2-[6-[(2S)-2-(fluoromethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(340) 2-[6-[(rac-3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(341) 2-[6-[(rac-3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(342) 3,5-dimethyl-2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol;

(343) 2-[6-[(4aS,8aS)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(344) 2-[6-[(4aR,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(345) 5-[4-(difluoromethyl)-6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]indan-4-ol;

(346) 3-methyl-2-[6-[rac-(3aS,6aS)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;hydrochloride;

(348) 1-[(4aR,7aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(349) 1-[(4aS,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(350) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(351) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-6-fluoro-phenol;

(352) 1-[(4aS,7aR)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]ethanone;

(353) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-6-fluoro-3-methyl-phenol;

(354) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(355) 2-[6-[(4aS,8aR)-6-(2,2,2-trifluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(356) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-6-fluoro-phenol;

(357) 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-phenyl)-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(358) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol;

(359) 2-[6-[(2S,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(360) 2-[6-(5,6-dihydro-2H-pyrazolo[4,3-b][1,4]oxazin-7-yl)pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(361) 3-methyl-2-[6-[rac-(4aR,7aS)-6-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(362) 2-[6-(2,3-dihydropyrido[4,3-b][1,4]oxazin-4-yl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(363) 1-[(4aS,8aR)-4-[6-[2-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(364) 2-[6-[rac-(3aS,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(365) 2-[6-[(2R,6R)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(366) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(367) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(368) 2-(hydroxymethyl)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-3-one;

(369) 1-[(3aR,7aR)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(370) 1-[(3aS,7aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(371) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(372) (4S)-1-[5-(difluoromethyl)-6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-4-hydroxy-pyrrolidin-2-one;

(373) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(374) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(375) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(376) 3-methyl-2-[6-[rac-(4aR,7aR)-6-ethyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(377) 1-[rac-(3aS,6aS)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]ethanone;

(378) 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(379) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(380) 1-[(4aS,8aR)-4-[6-[2-ethyl-6-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(381) 1-[(4aS,8aR)-4-[6-(4-chloro-2-ethyl-6-hydroxy-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(382) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(383) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(384) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(385) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(386) 1-[(4aS,8aR)-4-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(387) 1-[(4aS,8aR)-4-[5-(difluoromethyl)-6-(2-hydroxy-4-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(388) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol;

(389) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(390) 2-[6-[(2S,6S)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(391) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(392) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(393) 2-[6-[(3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(394) 1-[(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(395) 1-[(3aR,7aR)-1-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(397) 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(398) 1-[(4aR,8aS)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(399) 3,5-dichloro-2-[6-(1,1-dioxo-1,4-thiazinan-4-yl)pyridazin-3-yl]phenol;

(400) 3,5-dichloro-2-[6-(1-oxo-1,4-thiazinan-4-yl)pyridazin-3-yl]phenol;

(402) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(403) 3,5-dimethyl-2-[6-[rac-(4aS,8aR)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol;

(404) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(405) 1-[(4aS,8aR)-4-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(406) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(407) 2-[6-[(3aS,7aR)-2,3,3a,4,5,6,7,7a-octahydropyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(408) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol;

(409) 1-[(4aS,8aR)-4-[6-(2-hydroxy-6-methyl-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(410) 3,5-dimethyl-2-[6-(3-methyl-3,6-diazabicyclo[3.2.2]nonan-6-yl)pyridazin-3-yl]phenol;

(411) 2-[6-[(4aS,8aR)-2,3,4a,5,6,7,8,8a-octahydropyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(412) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(413) 1-[(3aR,7aR)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(414) 1-[(3aS,7aS)-1-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(415) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(416) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(417) 3-methyl-2-[6-(3-methyl-3,6-diazabicyclo[3.2.2]nonan-6-yl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(418) 3-ethyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(419) (2S)-2-(hydroxymethyl)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-3-one;

(420) (2R)-2-(hydroxymethyl)-4-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]morpholin-3-one;

(421) 3,5-dimethyl-2-[6-[rac-(4aS,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]phenol;

(422) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol;

(423) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-phenol;

(424) 1-[(4aS,8aR)-4-[6-(2-ethyl-6-hydroxy-phenyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(425) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-(difluoromethyl)pyridazin-3-yl]-3-ethyl-phenol;

(426) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(427) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(428) 3,5-dimethyl-2-[6-(9-methyl-1,9-diazaspiro[4.5]decan-1-yl)pyridazin-3-yl]phenol;

(429) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(430) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(431) 1-[(4aS,8aR)-4-[6-(2-hydroxy-4-methyl-phenyl)-5-methyl-pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(432) 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-phenol;

(433) 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(434) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-methyl-pyridazin-3-yl]-3,5-dimethyl-phenol;

(435) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(436) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(437) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(438) 3-methyl-2-[6-[rac-(4aS,8aR)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(439) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-5-methyl-pyridazin-3-yl]-3-ethyl-phenol;

(440) 3,5-dimethyl-2-[6-(9-methyl-6-oxa-2,9-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl]phenol;

(441) 3,5-dimethyl-2-[6-(1-methyl-4-oxa-1,8-diazaspiro[5.5]undecan-8-yl)pyridazin-3-yl]phenol;

(442) 1-[(4aS,8aR)-4-[6-(4-chloro-2-hydroxy-phenyl)-5-(difluoromethyl)pyridazin-3-yl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-6-yl]ethanone;

(443) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-ethyl-pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(444) 3,5-dimethyl-2-[6-(6-methyl-9-oxa-2,6-diazaspiro[4.5]decan-2-yl)pyridazin-3-yl]phenol;

(445) 3,5-dimethyl-2-[6-[(5S)-9-methyl-6-oxa-2,9-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(446) 3,5-dimethyl-2-[6-[(5R)-9-methyl-6-oxa-2,9-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(448) 3-methyl-2-[6-[rac-(4aS,8aS)-3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(449) 3,5-dimethyl-2-[6-(8-methyl-4-oxa-1,8-diazaspiro[5.5]undecan-1-yl)pyridazin-3-yl]phenol;

(450) 3,5-dimethyl-2-[6-[(5R)-6-methyl-9-oxa-2,6-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(451) 3,5-dimethyl-2-[6-[(5S)-6-methyl-9-oxa-2,6-diazaspiro[4.5]decan-2-yl]pyridazin-3-yl]phenol;

(452) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(455) 3,5-dimethyl-2-[6-(2-methyl-8-oxa-2,5-diazaspiro[3.5]nonan-5-yl)pyridazin-3-yl]phenol;

(456) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(457) 1-[(3aR,7aR)-1-[6-(2-hydroxy-4-methyl-phenyl)-5-methyl-pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(458) 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(459) 2-[6-[rac-(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol;

(460) 2-[6-[rac-(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(461) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol;

(462) 1-[(4aR,8aR)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]ethanone;

(463) 1-[(4aS,8aS)-5-[6-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]ethanone;

(466) (4aS,6S,7aR)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol;

(467) (4aR,6R,7aS)-4-[6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b][1,4]oxazin-6-ol;

(468) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(469) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-chloro-phenol;

(470) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-ethyl-pyridazin-3-yl]-5-methyl-phenol;

(471) 5-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]indan-4-ol;

(472) 2-[6-[(4aS,8aR)-6-isopropyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(473) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-(trifluoromethyl)phenol;

(474) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(475) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-methyl-pyridazin-3-yl]-5-methyl-phenol;

(476) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol;

(477) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-methyl-phenol;

(479) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-fluoro-phenol;

(480) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]-4-methyl-pyridazin-3-yl]-5-fluoro-phenol;

(481) 2-[6-[(4aS,8aR)-6-methyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(482) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(483) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(484) 3-methyl-2-[6-[rac-(3aS,6aS)-1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(485) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(486) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-(trifluoromethyl)phenol;

(487) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(488) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-5-(difluoromethyl)pyridazin-3-yl]-3,5-dimethyl-phenol;

(489) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(490) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(491) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(492) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-ethyl-5-(trifluoromethyl)phenol;

(493) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol

(494) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol;

(496) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(497) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(498) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(499) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3-methyl-phenol;

(500) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(501) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-chloro-phenol;

(502) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(503) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(504) 2-[6-[(3aS,7aR)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(505) 2-[6-[(3aR,7aS)-6-ethyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(506) 2-[6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(507) 2-[6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-4-(difluoromethyl)pyridazin-3-yl]-5-methyl-phenol;

(508) 5-ethynyl-2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-3-methyl-phenol;

(509) 2-[6-[(2S)-2-(hydroxymethyl)morpholin-4-yl]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;

(510) 1-[(3aS,7aS)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(511) 1-[(3aR,7aR)-1-[5-(difluoromethyl)-6-[2-hydroxy-4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(512) 1-[(3aS,7aS)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(513) 1-[(3aR,7aR)-1-[4-(difluoromethyl)-6-(2-hydroxy-4,6-dimethyl-phenyl)pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(514) 1-[(3aR,7aR)-1-[6-[2-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-pyridazin-3-yl]-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-6-yl]ethanone;

(515) 2-[6-[(4aS,8aS)-5-methyl-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(516) 2-[6-[(4aR,8aR)-5-methyl-2,3,4,4a,6,7,8,8a-octahydro-1,5-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(517) 2-[6-[(4aR,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(518) 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(519) 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(520) 2-[6-[(4aS,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(521) 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol;

(522) 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-methyl-phenol;

(523) 2-[6-[(4aR,8aR)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(524) 2-[6-[(4aS,8aS)-7-methyl-2,3,4,4a,5,6,8,8a-octahydro-1,7-naphthyridin-1-yl]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

(525) 2-[6-[(4aS,8aR)-6-(2-fluoroethyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-phenol;

(526) 2-[6-[(4aS,8aR)-6-ethyl-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-5-chloro-3-ethyl-phenol;

(527) 2-[6-[(4aS,8aR)-6-(3-fluoropropyl)-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-4-yl]pyridazin-3-yl]-3,5-dimethyl-phenol; and

(528) 5-methyl-2-[4-methyl-6-[rac-(3aS,7aR)-6-isopropyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]pyridazin-3-yl]phenol.

10. Medicament, characterized in that it comprises a compound of formula (I) according to any one of claims 1 to 9, or pharmaceutically acceptable salt thereof.

11. Pharmaceutical composition, characterized in that it comprises a compound of formula (I) according to any one of claims 1 to 9, or pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

12. A compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof for use as a medicine.

13. A compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof for use as inhibitor of NOD-like receptor protein 3 (NLRP3) inflammasome.

14. A compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof for use in the prevention and/or in the treatment of Parkinson's disease, frontotemporal Dementia, Multiple System Atrophy, Alzheimer's disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis or brain injury.