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Canadian Intellectual Property Office

CA 3145338 A1 2021/01/14

(21) 3 145 338

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2020/07/07
(87) Date publication PCT/PCT Publication Date: 2021/01/14
(85) Entrée phase nationale/National Entry: 2021/12/24
(86) N° demande PCT/PCT Application No.: EP 2020/069074
(87) N° publication PCT/PCT Publication No.: 2021/005034
(30) Priorité/Priority: 2019/07/09 (EP19185088.2)

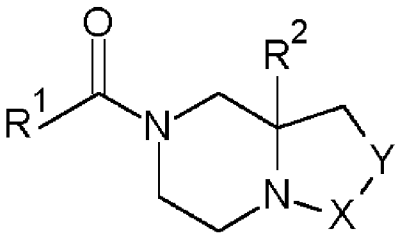
(51) Cl.Int./Int.Cl. *C07D 498/04* (2006.01), *A61K 31/5383* (2006.01), *A61K 31/542* (2006.01), *C07D 513/04* (2006.01), *C07D 519/00* (2006.01)

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(54) Titre : NOUVEAUX COMPOSES HETEROCYCLIQUES
(54) Title: NEW HETEROCYCLIC COMPOUNDS



(I)

(57) Abrégé/Abstract:
The invention provides new heterocyclic compounds having the general formula (I) wherein R^1, R^2, X, and Y are as defined herein, compositions including the compounds, processes of manufacturing the compounds and methods of using the compounds.

(21) 3 145 338

(13) A1

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 January 2021 (14.01.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/005034 A1

(51) International Patent Classification:
C07D 498/04 (2006.01) *A61K 31/5383* (2006.01)
C07D 513/04 (2006.01) *A61P 25/00* (2006.01)
C07D 519/00 (2006.01) *A61K 31/542* (2006.01)

(21) International Application Number:
PCT/EP2020/069074

(22) International Filing Date:
07 July 2020 (07.07.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
19185088.2 09 July 2019 (09.07.2019) EP

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

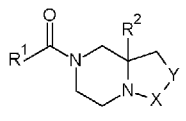
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,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

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

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

WO 2021/005034 A1

(54) Title: NEW HETEROCYCLIC COMPOUNDS



(I)

(57) Abstract: The invention provides new heterocyclic compounds having the general formula (I) wherein R^1, R^2, X, and Y are as defined herein, compositions including the compounds, processes of manufacturing the compounds and methods of using the compounds.

NEW HETEROCYCLIC COMPOUNDS

Field of the Invention

The present invention relates to organic compounds useful for therapy or prophylaxis in a mammal, and in particular to monoacylglycerol lipase (MAGL) inhibitors for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer, mental disorders, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine and/or depression in a mammal.

Background of the Invention

Endocannabinoids (ECs) are signaling lipids that exert their biological actions by interacting with cannabinoid receptors (CBRs), CB1 and CB2. They modulate multiple physiological processes including neuroinflammation, neurodegeneration and tissue regeneration (Iannotti, F.A., *et al.*, *Progress in lipid research* **2016**, *62*, 107-28.). In the brain, the main endocannabinoid, 2-arachidonoylglycerol (2-AG), is produced by diacyglycerol lipases (DAGL) and hydrolyzed by the monoacylglycerol lipase, MAGL. MAGL hydrolyses 85% of 2-AG; the remaining 15% being hydrolysed by ABHD6 and ABDH12 (Nomura, D.K., *et al.*, *Science* **2011**, *334*, 809.). MAGL is expressed throughout the brain and in most brain cell types, including neurons, astrocytes, oligodendrocytes and microglia cells (Chanda, P.K., *et al.*, *Molecular pharmacology* **2010**, *78*, 996; Viader, A., *et al.*, *Cell reports* **2015**, *12*, 798.). 2-AG hydrolysis results in the formation of arachidonic acid (AA), the precursor of prostaglandins (PGs) and leukotrienes (LTs). Oxidative metabolism of AA is increased in inflamed tissues. There are two principal enzyme pathways of arachidonic acid oxygenation involved in inflammatory processes, the cyclo-oxygenase which produces PGs and the 5-lipoxygenase which produces LTs. Of the various cyclooxygenase products formed during inflammation, PGE2 is one of the most important. These products have been detected at sites of inflammation, e.g. in the

cerebrospinal fluid of patients suffering from neurodegenerative disorders and are believed to contribute to inflammatory response and disease progression. Mice lacking MAGL (Mgll-/-) exhibit dramatically reduced 2-AG hydrolase activity and elevated 2-AG levels in the nervous system while other arachidonoyl-containing phospho- and neutral lipid species including anandamide (AEA), as well as other free fatty acids, are unaltered. Conversely, levels of AA and AA-derived prostaglandins and other eicosanoids, including prostaglandin E2 (PGE2), D2 (PGD2), F2 (PGF2), and thromboxane B2 (TXB2), are strongly decreased. Phospholipase A_2 (PLA_2) enzymes have been viewed as the principal source of AA, but $cPLA_2$-deficient mice have unaltered AA levels in their brain, reinforcing the key role of MAGL in the brain for AA production and regulation of the brain inflammatory process.

Neuroinflammation is a common pathological change characteristic of diseases of the brain including, but not restricted to, neurodegenerative diseases (e.g. multiple sclerosis, Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy and mental disorders such as anxiety and migraine). In the brain, production of eicosanoids and prostaglandins controls the neuroinflammation process. The pro-inflammatory agent lipopolysaccharide (LPS) produces a robust, time-dependent increase in brain eicosanoids that is markedly blunted in Mgll–/– mice. LPS treatment also induces a widespread elevation in pro-inflammatory cytokines including interleukin-1-a (IL-1-a), IL-1b, IL-6, and tumor necrosis factor-a (TNF-a) that is prevented in Mgll–/– mice.

Neuroinflammation is characterized by the activation of the innate immune cells of the central nervous system, the microglia and the astrocytes. It has been reported that anti-inflammatory drugs can suppress in preclinical models the activation of glia cells and the progression of disease including Alzheimer's disease and mutiple sclerosis (Lleo A., *Cell Mol Life Sci.* **2007**, *64*, 1403.). Importantly, genetic and/or pharmacological disruption of MAGL activity also blocks LPS-induced activation of microglial cells in the brain (Nomura, D.K., *et al.*, *Science* **2011**, *334*, 809.).

In addition, genetic and/or pharmacological disruption of MAGL activity was shown to be protective in several animal models of neurodegeneration including, but not restricted to, Alzheimer's disease, Parkinson's disease and multiple sclerosis. For example, an irreversible MAGL inhibitor has been widely used in preclinical models of

neuroinflammation and neurodegeneration (Long, J.Z., *et al.*, *Nature chemical biology* **2009**, *5*, 37.). Systemic injection of such inhibitor recapitulates the Mgll-/- mice phenotype in the brain, including an increase in 2-AG levels, a reduction in AA levels and related eicosanoids production, as well as the prevention of cytokines production and microglia activation following LPS-induced neuroinflammation (Nomura, D.K., *et al.*, *Science* **2011**, *334*, 809.), altogether confirming that MAGL is a druggable target.

Consecutive to the genetic and/or pharmacological disruption of MAGL activity, the endogenous levels of the MAGL natural substrate in the brain, 2-AG, are increased. 2-AG has been reported to show beneficial effects on pain with, for example, anti-nociceptive effects in mice (Ignatowska-Jankowska B. *et al.*, *J. Pharmacol. Exp. Ther.* **2015**, *353*, 424.) and on mental disorders, such as depression in chronic stress models (Zhong P. *et al.*, *Neuropsychopharmacology* **2014**, *39*, 1763.).

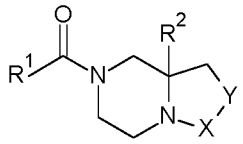
Furthermore, oligodendrocytes (OLs), the myelinating cells of the central nervous system, and their precursors (OPCs) express the cannabinoid receptor 2 (CB2) on their membrane. 2-AG is the endogenous ligand of CB1 and CB2 receptors. It has been reported that both cannabinoids and pharmacological inhibition of MAGL attenuate OLs's and OPCs's vulnerability to excitotoxic insults and therefore may be neuroprotective (Bernal-Chico, A., *et al.*, *Glia* **2015**, *63*, 163.). Additionally, pharmacological inhibition of MAGL increases the number of myelinating OLs in the brain of mice, suggesting that MAGL inhibition may promote differentiation of OPCs in myelinating OLs in vivo (Alpar, A., *et al.*, *Nature communications* **2014**, *5*, 4421.). Inhibition of MAGL was also shown to promote remyelination and functional recovery in a mouse model of progressive multiple sclerosis (Feliu A. *et al.*, *Journal of Neuroscience* **2017**, *37* (35), 8385.).

Finally, in recent years, metabolism is talked highly important in cancer research, especially the lipid metabolism. Researchers believe that the de novo fatty acid synthesis plays an important role in tumor development. Many studies illustrated that endocannabinoids have anti-tumorigenic actions, including anti-proliferation, apoptosis induction and anti-metastatic effects. MAGL as an important decomposing enzyme for both lipid metabolism and the endocannabinoids system, additionally as a part of a gene expression signature, contributes to different aspects of tumourigenesis (Qin, H., *et al.*, *Cell Biochem. Biophys.* **2014**, *70*, 33; Nomura DK *et al.*, *Cell* **2009**, *140*(1), 49-61; Nomura DK *et al.*, *Chem. Biol.* **2011**, *18*(7), 846-856).

In conclusion, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for the treatment or prevention of neuroinflammation, neurodegenerative diseases, pain, cancer and mental disorders. Furthermore, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for providing neuroprotection and myelin regeneration. Accordingly, there is a high unmet medical need for new MAGL inhibitors.

Summary of the Invention

In a first aspect, the present invention provides compounds of Formula (I), or pharmaceutically acceptable salts thereof,



(I)

wherein R^1, R^2, X, and Y are as defined herein.

In a further aspect, the present invention provides a process of manufacturing the compounds of formula (I) as described in any one of the synthetic schemes disclosed herein.

In a further aspect, the present invention provides a compound of formula (I) as described herein, when manufactured according to the processes described herein.

In a further aspect, the present invention provides a compound of formula (I) as described herein, for use as therapeutically active substance.

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

In a further aspect, the present invention provides a compound of formula (I) as described herein for use in a method of inhibiting monoacylglycerol lipase in a mammal.

In a further aspect, the present invention provides a compound of formula (I) as described herein for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

In a further aspect, the present invention provides a compound of formula (I) as described herein, for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

Detailed Description of the Invention

Definitions

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

The term "alkyl" refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms ("C_1-C_6-alkyl"), e.g., 1, 2, 3, 4, 5, or 6 carbon atoms. In some embodiments, the alkyl group contains 1 to 3 carbon atoms, e.g., 1, 2 or 3 carbon atoms. Some non-limiting examples of alkyl include methyl, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, tert-butyl, and 2,2-dimethylpropyl. A particularly preferred, yet non-limiting example of alkyl is methyl.

The term "alkoxy" refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. In some preferred embodiments, the alkoxy group contains 1 to 6 carbon atoms ("C_1-C_6-alkoxy"), e.g. 1, 2, 3, 4, 5, or 6 carbon atoms. In other embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other embodiments, the alkoxy group contains 1 to 3 carbon atoms. Some non-limiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy,

1,1-dimethylpropoxy, 2,2-dimethylpropoxy, and tert-butoxy. A particularly preferred, yet non-limiting example of alkoxy is methoxy.

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

The term "cycloalkyl" as used herein refers to a saturated or partly unsaturated monocyclic or bicyclic hydrocarbon group of 3 to 14 ring carbon atoms ("C_{3-14}-cycloalkyl"). In some preferred embodiments, the cycloalkyl group is a saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. "Bicyclic cycloalkyl" refers to cycloalkyl moieties consisting of two saturated carbocycles having two carbon atoms in common, i.e., the bridge separating the two rings is either a single bond or a chain of one or two ring atoms, and to spirocyclic moieties, i.e., the two rings are connected via one common ring atom. In one embodiment, the cycloalkyl group is a saturated monocyclic hydrocarbon group of 3 to 6 ring carbon atoms, e.g., of 3, 4, 5 or 6 carbon atoms. Some non-limiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and 1-bicyclo[1.1.1]pentanyl.

The term "aryl" refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of 6 to 14 ring members ("C_{6-14}-aryl"), preferably, 6 to 12 ring members, and more preferably 6 to 10 ring members, and wherein at least one ring in the system is aromatic. Preferred, yet non-limiting examples of aryl includes phenyl and 3-bicyclo[4.2.0]octa-1(6),2,4-trienyl.

The term "heteroaryl" refers to a mono- or multivalent, monocyclic, bicyclic or tricyclic, preferably bicyclic ring system having a total of 5 to 14 ring members ("C_{1-13}-heteroaryl"), preferably, 5 to 12 ring members, and more preferably 5 to 10 ring members, wherein at least one ring in the system is aromatic, and at least one ring in the system contains one or more heteroatoms. Preferably, "heteroaryl" refers to a 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. Most preferably, "heteroaryl" refers to a 5-10 membered heteroaryl comprising 1 to 2 heteroatoms independently selected from O and N. Some non-limiting examples of

heteroaryl include 1H-pyrazol-4-yl, pyridazine, pyridyl, pyrimidinyl, oxazol-5-yl, isoxazol-4-yl, 1H-triazol-5-yl, 1H-imidazol-5-yl, 1H-benzimidazol-2-yl, and thiazolyl.

The term "hydroxy" refers to an –OH group.

The term "cyano" refers to a –CN (nitrile) group.

The term "oxo" refers to a double bonded oxygen (=O).

The term "haloalkyl" refers to an alkyl group, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a halogen atom, preferably fluoro. Preferably, "haloalkyl" refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms of the alkyl group have been replaced by a halogen atom, most preferably fluoro. Particularly preferred, yet non-limiting examples of haloalkyl are fluoromethyl, difluoromethyl, trifluoromethyl, 3,3,3-trifluoropropyl, 2,2-difluoropropyl, 1-fluoro-1-methyl-ethyl, 2-fluoro-1,1-dimethyl-ethyl, 2-fluoro-2-methyl-propyl, trifluoromethyl and 2,2,2-trifluoroethyl.

The term "haloalkoxy" refers to an alkoxy group, wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by a halogen atom, preferably fluoro. Preferably, "haloalkoxy" refers to an alkoxy group wherein 1, 2 or 3 hydrogen atoms of the alkoxy group have been replaced by a halogen atom, most preferably fluoro. Prticularly preferred, yet non-limiting examples of haloalkoxy are trifluoromethoxy, 3,3,3-trifluoropropoxy, 2,2,2-trifluoro-1-methyl-ethoxy, and 3-fluoro-2-fluoro-propoxy.

The term "alkenyl" denotes a mono- or bivalent linear or branched hydrocarbon group of 2 to 6 carbon atoms with at least one double bond ("C_2-C_6-alkenyl"), e.g. 1 or 2 double bonds. In particular embodiments, alkenyl has 2 to 4 carbon atoms with at least one double bond, e.g. 1 or 2 double bonds. Examples of alkenyl include ethenyl, propenyl, prop-2-enyl, isopropenyl, n-butenyl (e.g. (Z)-but-1-enyl), iso-butenyl, allyl, 2-methylallyl, 2-methylprop-1-enyl, and propa-1,2-dienyl.

The term "alkynyl" denotes a mono- or bivalent linear or branched hydrocarbon group of 2 to 6 carbon atoms with at least one triple bond ("C_2-C_6-alkynyl"), e.g. 1 or 2 triple bonds. In particular embodiments, alkynyl has 2 to 4 carbon atoms with at least one triple bond. Examples of alkynyl include ethynyl, ethyndiyl, propynyl, n-butynyl or isobutynyl.

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

The term “protective group” (PG) denotes the group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Protective groups can be removed at the appropriate point. Exemplary protective groups are amino-protective groups, carboxy-protective groups or hydroxy-protective groups. Particular protective groups are the tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc) and benzyl (Bn). Further particular protective groups are the tert-butoxycarbonyl (Boc) and the fluorenylmethoxycarbonyl (Fmoc). More particular protective group is the tert-butoxycarbonyl (Boc). Exemplary protective groups and their application in organic synthesis are described, for example, in “Protective Groups in Organic Chemistry” by T. W. Greene and P. G. M. Wutts, 5th Ed., 2014, John Wiley & Sons, N.Y.

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

According to the Cahn-Ingold-Prelog Convention, the asymmetric carbon atom can be of the "R" or "S" configuration.

The abbreviation “MAGL” refers to the enzyme monoacylglycerol lipase. The terms “MAGL” and “monoacylglycerol lipase” are used herein interchangeably.

The term “treatment” as used herein includes: (1) inhibiting the state, disorder or condition (e.g. arresting, reducing or delaying the development of the disease, or a relapse thereof in case of maintenance treatment, of at least one clinical or subclinical symptom thereof); and/or (2) relieving the condition (i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms). The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient or to the physician. However, it will be appreciated that when a medicament is administered to a patient to treat a disease, the outcome may not always be effective treatment.

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

The term “neuroinflammation” as used herein relates to acute and chronic inflammation of the nervous tissue, which is the main tissue component of the two parts of the nervous system; the brain and spinal cord of the central nervous system (CNS), and the branching peripheral nerves of the peripheral nervous system (PNS). Chronic neuroinflammation is associated with neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and multiple sclerosis. Acute neuroinflammation usually follows injury to the central nervous system immediately, e.g., as a result of traumatic brain injury (TBI).

The term “traumatic brain injury” (“TBI”, also known as “intracranial injury”), relates to damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile.

The term “neurodegenerative diseases” relates to diseases that are related to the progressive loss of structure or function of neurons, including death of neurons. Examples

of neurodegenerative diseases include, but are not limited to, multiple sclerosis, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

The term "mental disorders" (also called mental illnesses or psychiatric disorders) relates to behavioral or mental patterns that may cause suffering or a poor ability to function in life. Such features may be persistent, relapsing and remitting, or occur as a single episode. Examples of mental disorders include, but are not limited to, anxiety and depression.

The term "pain" relates to an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Examples of pain include, but are not limited to, nociceptive pain, chronic pain (including idiopathic pain), neuropathic pain including chemotherapy induced neuropathy, phantom pain and phsychogenic pain. A particular example of pain is neuropathic pain, which is caused by damage or disease affecting any part of the nervous system involved in bodily feelings (i.e., the somatosensory system). In one embodiment, "pain" is neuropathic pain resulting from amputation or thoracotomy. In one embodiment, "pain" is chemotherapy induced neuropathy.

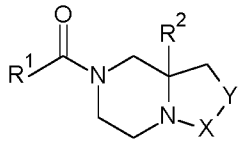
The term "neurotoxicity" relates to toxicity in the nervous system. It occurs when exposure to natural or artificial toxic substances (neurotoxins) alter the normal activity of the nervous system in such a way as to cause damage to nervous tissue. Examples of neurotoxicity include, but are not limited to, neurotoxicity resulting from exposure to substances used in chemotherapy, radiation treatment, drug therapies, drug abuse, and organ transplants, as well as exposure to heavy metals, certain foods and food additives, pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances.

The term "cancer" refers to a disease characterized by the presence of a neoplasm or tumor resulting from abnormal uncontrolled growth of cells (such cells being "cancer cells"). As used herein, the term cancer explicitly includes, but is not limited to, hepatocellular carcinoma, colon carcinogenesis and ovarian cancer.

The term "mammal" as used herein includes both humans and non-humans and includes but is not limited to humans, non-human primates, canines, felines, murines, bovines, equines, and porcines. In a particularly preferred embodiment, the term "mammal" refers to humans.

Compounds of the Invention

In a first aspect (A1), the present invention provides compounds of Formula (I)

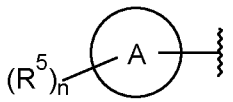


(I)

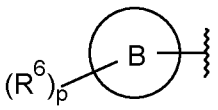
or a pharmaceutically acceptable salts thereof, wherein:

X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

Y is –O–, –S–, –SO–, or $-SO_2-$;

R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are optionally substituted with 1-5 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, cyano, hydroxy, and a group  ;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3 is a group  ;

R^4 is hydrogen, halogen or hydroxy;

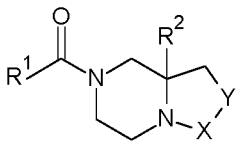
R^5 is hydrogen, halogen, hydroxy, amino, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano; wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with 1-2 substituents selected from halogen, cyano, amino, hydroxy, C_1-C_6-alkyl and C_1-C_6-alkoxy;

A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl, 3- to 14-membered heterocyclyl or C_3-C_{14}-cycloalkyl; and

n and p are each independently 1, 2, 3, 4 or 5.

In a second aspect (A2), the present invention provides compounds of Formula (I)

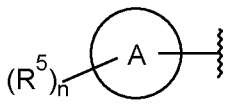


(I)

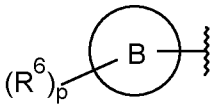
or a pharmaceutically acceptable salts thereof, wherein:

X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

Y is –O–, –S–, –SO–, or $-SO_2-$;

R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are optionally substituted with 1-5 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, cyano, hydroxy, and a group  ;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3 is a group  ;

R^4 is hydrogen, halogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano;

A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl, 3- to 14-membered heterocyclyl or C_3-C_{14}-cycloalkyl; and

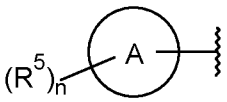
n and p are each independently 1, 2, 3, 4 or 5.

The invention further provides the following enumerated embodiments (E) of the first and second Aspect A1 and A2:

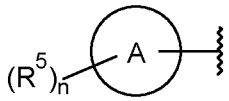
E1 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2CR^3R^4-$.

E2 The compound of formula (I) according to any one of A1, A2 and E1, or a pharmaceutically acceptable salt thereof, wherein Y is –O– or –S–.

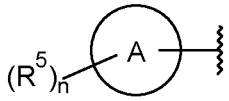
E3 The compound of formula (I) according to any one of A1, A2 and E1, or a pharmaceutically acceptable salt thereof, wherein Y is –O–.

E4 The compound of formula (I) according to any one of A1, A2, and E1 to E3, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group .

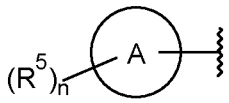
E5 The compound of formula (I) according to any one of A1, A2, and E1 to E3, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl substituted with 1-2 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group

.

E6 The compound of formula (I) according to any one of A1, A2, and E1 to E3, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl substituted with 2-3 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group

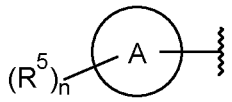
.

E7 The compound of formula (I) according to any one of A1, A2, and E1 to E3, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with 2 substituents independently selected from chloro, methoxy and a group

.

E8 The compound of formula (I) according to any one of A1, A2, and E1 to E3, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with 2-3

substituents independently selected from chloro, fluoro, methoxy and a group



.

E9 The compound of formula (I) according to any one of A1, A2, and E1 to E8, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

E10 The compound of formula (I) according to any one of A1, A2, and E1 to E9, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen or hydroxy.

E11 The compound of formula (I) according to any one of A1, A2, and E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo.

E12 The compound of formula (I) according to any one of A1, A2, and E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, hydroxy or oxo.

E13 The compound of formula (I) according to any one of A1, A2, and E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, cyano, hydroxy or oxo.

E14 The compound of formula (I) according to any one of A1, A2, and E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, fluoro, hydroxy or oxo.

E15 The compound of formula (I) according to any one of A1, A2, and E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, fluoro, cyano, hydroxy or oxo.

E16 The compound of formula (I) according to any one of A1, A2, and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, halogen, C_6-C_{14}-aryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano.

E17 The compound of formula (I) according to any one of A1, A2, and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, halogen, C_6-C_{14}-

aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy.

E18 The compound of formula (I) according to any one of A1, A2, and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^6 is halogen, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy.

E19 The compound of formula (I) according to any one of A1, A2, and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy.

E20 The compound of formula (I) according to any one of A1, A2, and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^6 is chloro, fluoro, trifluoromethyl or difluoromethoxy.

E21 The compound of formula (I) according to any one of A1, A2, and E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy.

E22 The compound of formula (I) according to any one of A1, A2, and E1 to E21, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

E23 The compound of formula (I) according to any one of A1, A2, and E1 to E21, or a pharmaceutically acceptable salt thereof, wherein n is 2.

E24 The compound of formula (I) according to any one of A1, A2, and E1 to E23, or a pharmaceutically acceptable salt thereof, wherein p is 1 or 2.

E25 The compound of formula (I) according to any one of A1, A2, and E1 to E23, or a pharmaceutically acceptable salt thereof, wherein p is 1, 2 or 3.

E26 The compound of formula (I) according to any one of A1, A2, and E1 to E25, or a pharmaceutically acceptable salt thereof, wherein A is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl.

E27 The compound of formula (I) according to any one of A1, A2, and E1 to E25, or a pharmaceutically acceptable salt thereof, wherein A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl.

E28 The compound of formula (I) according to any one of A1, A2, and E1 to E25, or a pharmaceutically acceptable salt thereof, wherein A is imidazolyl, pyrazolyl, oxo-pyridinyl or 1,2-dihydropyridinyl.

E29 The compound of formula (I) according to any one of A1, A2, and E1 to E25, or a pharmaceutically acceptable salt thereof, wherein A is imidazolyl, pyrazolyl, pyrrolyl, or 1,2-dihydropyridinyl.

E30 The compound of formula (I) according to any one of A1, A2, and E1 to E29, or a pharmaceutically acceptable salt thereof, wherein B is C_6-C_{14}-aryl, 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl.

E31 The compound of formula (I) according to any one of A1, A2, and E1 to E29, or a pharmaceutically acceptable salt thereof, wherein B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl.

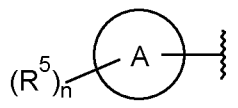
E32 The compound of formula (I) according to any one of A1, A2, and E1 to E29, or a pharmaceutically acceptable salt thereof, wherein B is phenyl or pyridinyl.

E33 The compound of formula (I) according to any one of A1, A2, and E1 to E29, or a pharmaceutically acceptable salt thereof, wherein B is phenyl, 1,2-dihydropyridinyl or pyridyl.

E34 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein:

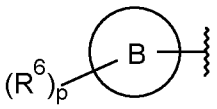
X is $–CH_2CR^3R^4–$ or $–CH=CR^3–$;

Y is –O–;

R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group 

;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3 is a group  ;

R^4 is hydrogen, halogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano;

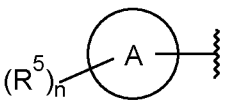
A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl; and

n and p are each independently 1 or 2.

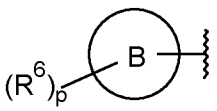
E35 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$;

Y is $-O-$;

R^1 is C_6-C_{14}-aryl substituted with 1-2 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group  ;

R^2 is hydrogen;

R^3 is a group  ;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy or oxo;

R^6 is halogen, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy;

A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl;

B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl;

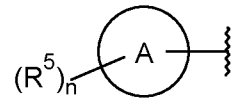
n is 2; and

p is 1 or 2.

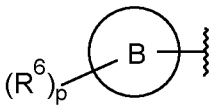
E36 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$;

Y is –O–;

R^1 is phenyl substituted with 2 substituents independently selected from chloro, methoxy and a group ;

R^2 is hydrogen;

R^3 is a group ;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, fluoro, hydroxy or oxo;

R^6 is chloro, fluoro, trifluoromethyl or difluoromethoxy;

A is imidazolyl, pyrazolyl, oxo-pyridinyl or 1,2-dihydropyridinyl;

B is phenyl or pyridinyl;

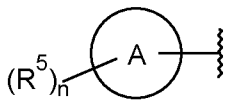
n is 2; and

p is 1 or 2.

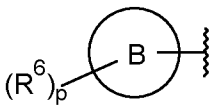
E37 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

Y is –O– or –S–;

R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group ;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3 is a group ;

R^4 is hydrogen, halogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy;

A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl;

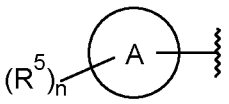
n is 1 or 2; and

p is 1, 2 or 3.

E38 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein:

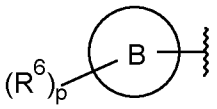
X is $-CH_2CR^3R^4-$;

Y is –O–;

R^1 is C_6-C_{14}-aryl substituted with 1-2 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group 

;

R^2 is hydrogen;

R^3 is a group 

;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, halogen, cyano, hydroxy or oxo;

R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy;

A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl;

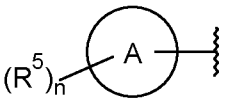
B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl; and

n and p are each independently 1 or 2.

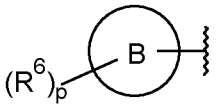
E39 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$;

Y is –O–;

R^1 is phenyl substituted with 2-3 substituents independently selected from chloro, fluro, methoxy and a group ;

R^2 is hydrogen;

R^3 is a group ;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, fluoro, cyano, hydroxy or oxo;

R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy;

A is imidazolyl, pyrazolyl, pyrrolyl, or 1,2-dihydropyridinyl;

B is phenyl, 1,2-dihydropyridinyl or pyridyl; and

n and p are each independently 1 or 2.

E40 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is selected from:

[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(5-chloro-4-methyl-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aR)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(9aS)-3-(4-fluoro-3-phenyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3S,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aR)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-imidazol-5-yl)phenyl]methanone;

[(3R,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one;

[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-hydroxyazetidin-1-yl)phenyl]methanone;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(9aS)-3-[6-(trifluoromethyl)-3-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(9aS)-3-[4-(difluoromethoxy)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(5-methyl-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-fluoro-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(4-bromo-5-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one;

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-bromo-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-5-yl-phenyl)methanone;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-phenyl-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone;

4-[3-[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrazole-3-carbonitrile;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-methoxyphenyl)phenyl]methanone;

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chlorothieno[2,3-b]pyridin-5-yl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone;

[(3S,9aS)-3-[5-chloro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methyl-4-pyridyl)phenyl]methanone;

[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(9aS)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-pyridyl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1,5-dimethylpyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-triazol-5-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,5-dimethoxy-phenyl)methanone;

[(3R,9aS)-3-[4-(difluoromethoxy)phenyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one;

5-[(9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-2-fluoro-benzonitrile;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-3-methyl-1H-indazol-5-yl)methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3R,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-fluoro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-[5-chloro-4-(difluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-(5-chloro-4-methyl-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(9aS)-3-(3-cyclopropyl-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-morpholino-phenyl)methanone;

2-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-6-methyl-benzonitrile;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(difluoromethoxy)phenyl]methanone;

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-3-quinolyl)methanone;

[(3S,9aS)-3-[5-fluoro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[3-(3-bicyclo[4.2.0]octa-1,3,5-trienyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

(2-chloro-3-methoxy-phenyl)-[3-[4-(difluoromethyl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

5-[(9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-2-fluoro-benzonitrile;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methylisoxazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-pyridazin-3-yl-phenyl)methanone;

(2-chloro-3-methoxy-phenyl)-[rac-(9aS)-3-[4-fluoro-3-[rac-(E)-prop-1-enyl]phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-pyridazin-4-yl-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(4-methyl-3-pyridyl)phenyl]methanone;

[(9aS)-3-[5-(trifluoromethyl)-2-pyridyl]-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-5-yl-phenyl)methanone;

[(9aS)-3-(4-fluoro-3-prop-1-ynyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(9aS)-3-(4-fluoro-3-phenyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methyl-2-pyridyl)phenyl]methanone;

[(3S,9aS)-3-[4-(trifluoromethoxy)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aR)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,4-dimethoxy-phenyl)methanone;

4-(2-chloro-3-((3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-hydroxy-3-(2,4,5-trifluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2,4,5-trifluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

(2-chloro-3-(isothiazol-4-yl)phenyl)((3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

4-(2-chloro-3-((3R,9aS)-3-(5-chloro-2-oxo-1,2-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

5-(2-chloro-3-((3R,9aS)-3-(3,4-dichlorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)oxazol-2(3H)-one;

5-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)oxazol-2(3H)-one;

4-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

4-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)-5-fluorophenyl)pyridin-2(1H)-one;

(2-chloro-3-methoxyphenyl)((9aS)-3-(4-fluoro-3-(oxazol-5-yl)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

5-(2-chloro-3-((3R,9aS)-3-(3,4-dichlorophenyl)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)oxazol-2(3H)-one;

(2-chloro-3-methoxyphenyl)((9aS)-3-(4-fluoro-3-(1-methyl-1H-pyrrol-3-yl)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

((3R,9aS)-3-(4-bromo-3-chlorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone;

4-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-6-methylpyridin-2(1H)-one;

5-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-6-methylpyridin-2(1H)-one;

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2-chlorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2,4-dichlorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-hydroxy-3-(4-(trifluoromethyl)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-hydroxy-3-(2,3,4-trifluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(3-chloro-4-(oxazol-5-yl)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
4-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)piperazin-2-one;
5-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1,3,4-oxadiazol-2(3H)-one;
((3R,9aS)-3-(3-bromo-5-chlorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-hydroxy-3-(3-(trifluoromethyl)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(3-chloro-5-(oxazol-5-yl)phenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
((3R,9aS)-3-(4-chloro-3-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2,3-difluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2,3-difluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
3-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrazole-5-carbonitrile;
((3S,9aS)-3-(benzo[d]thiazol-2-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone;
(2-chloro-3-methoxyphenyl)((3S,9aS)-3-hydroxy-3-(3-phenylisoxazol-5-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;
(2-chloro-3-methoxyphenyl)((3S,9aS)-3-(2-(4-fluorophenyl)thiazol-4-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

(2-chloro-3-methoxyphenyl)((3S,9aS)-3-hydroxy-3-(2-(6-methoxypyridin-3-yl)thiazol-4-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

(2-chloro-3-methoxyphenyl)((3S,9aS)-3-(5-chloro-6-(trifluoromethyl)pyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

((3S,9aS)-3-(4-bromo-5-methoxythiophen-2-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone;

((3S,9aS)-3-(3-bromoisoxazol-5-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone;

3-((3R,9aS)-8-(2-chloro-3-methoxybenzoyl)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazin-3-yl)-6-(trifluoromethyl)pyridin-2(1H)-one;

5-[(3#R!,9#a!#S!)-8-(2-chloro-3-methoxybenzoyl)-3,4,6,7,9,9#a!-hexahydro-1#H!-pyrazino[2,1-c][1,4]oxazin-3-yl]-3-chloro-2-fluorobenzonitrile;

5-(2-chloro-3-((3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-imidazole-2-carbonitrile;

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-hydroxy-3-(2-methyl-6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone;

5-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)pyridazin-4(1H)-one;

5-chloro-3-((3R,9aS)-8-(2-chloro-5-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl)octahydropyrazino[2,1-c][1,4]oxazin-3-yl)pyridin-2(1H)-one;

4-(2-chloro-3-((3R,9aS)-3-(5-chloro-2-oxo-1,2-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)-5-fluorophenyl)-1H-pyrrole-2-carbonitrile;

5-chloro-3-((3R,9aS)-8-(2-chloro-3-(4-fluoro-1H-pyrazol-3-yl)benzoyl)octahydropyrazino[2,1-c][1,4]oxazin-3-yl)pyridin-2(1H)-one;

4-(2-chloro-5-fluoro-3-((3R,9aS)-3-(4-oxo-6-(trifluoromethyl)-1,4-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

4-(2-chloro-5-fluoro-3-((3R,9aS)-3-(2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

4-(2-chloro-5-fluoro-3-((3S,9aS)-3-(4-oxo-6-(trifluoromethyl)-1,4-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

3-((3R,9aS)-8-(2-chloro-3-methoxybenzoyl)octahydropyrazino[2,1-c][1,4]oxazin-3-yl)-6-(trifluoromethyl)pyridin-2(1H)-one;

((3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-6-fluoro-3-methoxyphenyl)methanone;

((3R,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-6-fluoro-3-methoxyphenyl)methanone;

((3S,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-6-fluoro-3-methoxyphenyl)methanone;

5-chloro-3-((3R,9aS)-8-(2-chloro-6-fluoro-3-methoxybenzoyl)octahydropyrazino[2,1-c][1,4]oxazin-3-yl)pyridin-2(1H)-one; and

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone.

E41 The compound of formula (I) according to A1 or A2, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is selected from:

4-(2-chloro-3-((3R,9aS)-3-(5-chloro-2-oxo-1,2-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

4-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

4-(2-chloro-3-((3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)-5-fluorophenyl)pyridin-2(1H)-one;

4-(2-chloro-3-((3R,9aS)-3-(5-chloro-2-oxo-1,2-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)-5-fluorophenyl)-1H-pyrrole-2-carbonitrile;

4-(2-chloro-5-fluoro-3-((3R,9aS)-3-(2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl)phenyl)-1H-pyrrole-2-carbonitrile;

((3R,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-6-fluoro-3-methoxyphenyl)methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-imidazol-5-yl)phenyl]methanone;

[(3R,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3S,9aS)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one;

[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-hydroxyazetidin-1-yl)phenyl]methanone;

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone;

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(9aS)-3-[6-(trifluoromethyl)-3-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone;

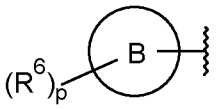
[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone;

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone; and

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[rac-(9aS)-3-[4-(difluoromethoxy)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone.

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

X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

R^3 is a group  ;

R^4 is hydrogen, halogen or hydroxy;

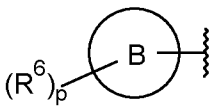
R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy;

B is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl; and

p is 1, 2 or 3.

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

X is $-CH_2CR^3R^4-$;

R^3 is a group  ;

R^4 is hydrogen or hydroxy;

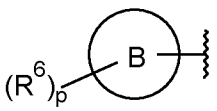
R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy;

B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl; and

p is 1 or 2.

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

X is $-CH_2CR^3R^4-$;

R^3 is a group  ;

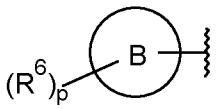
R^4 is hydrogen or hydroxy;

R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy;

B is phenyl, 1,2-dihydropyridinyl or pyridyl; and

p is 1 or 2.

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

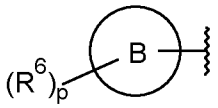
R^3 is a group  ; wherein

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy;

B is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl; and

p is 1, 2 or 3.

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

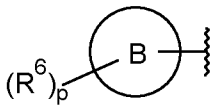
R^3 is a group  ; wherein

R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy;

B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl; and

p is 1 or 2.

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

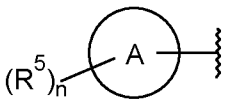
R^3 is a group  ; wherein

R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy;

B is phenyl, 1,2-dihydropyridinyl or pyridyl; and

p is 1 or 2.

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

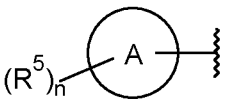
R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group ;

R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;

A is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl; and

n is 1 or 2.

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

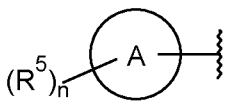
R^1 is C_6-C_{14}-aryl substituted with 1-2 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group ;

R^5 is hydrogen, halogen, cyano, hydroxy or oxo;

A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl; and

n is 1 or 2.

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

R^1 is phenyl substituted with 2 substituents independently selected from chloro, methoxy and a group ;

R^5 is hydrogen, fluoro, cyano, hydroxy or oxo;

A is imidazolyl, pyrazolyl, pyrrolyl or 1,2-dihydropyridinyl; and

n is 1 or 2.

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

R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;

A is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl; and

n is 1 or 2.

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

R^5 is hydrogen, halogen, cyano, hydroxy or oxo;

A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl; and

n is 1 or 2.

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

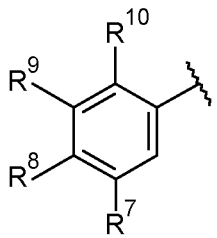
R^5 is hydrogen, fluoro, cyano, hydroxy or oxo;

A is imidazolyl, pyrazolyl, pyrrolyl or 1,2-dihydropyridinyl; and

n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^1 is

(a) 5- to 14-membered heteroaryl substituted with 1 substituent selected from halogen; or

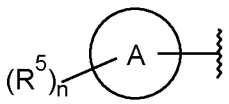
(b) a group 

; wherein

R^7 is hydrogen or C_1-C_6-alkoxy;

R^8 is hydrogen or C_1-C_6-alkoxy;

R^9 is hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy or a group



; wherein

R^5, A and n are as defined herein; and

R^{10} is hydrogen, halogen, or cyano.

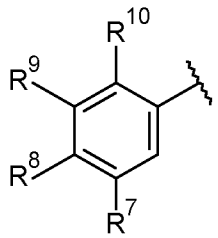
In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein

X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

Y is –O–;

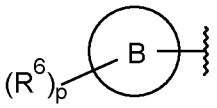
R^1 is

(a) 5- to 14-membered heteroaryl substituted with 1 substituent selected from halogen; or



(b) a group ;

R^2 is hydrogen or C_1-C_6-alkyl;



R^3 is a group

R^4 is hydrogen, halogen or hydroxy;

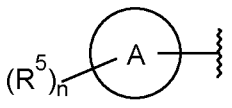
R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, cycloalkyl or cyano;

R^7 is hydrogen or C_1-C_6-alkoxy;

R^8 is hydrogen or C_1-C_6-alkoxy;

R^9 is hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy or a group



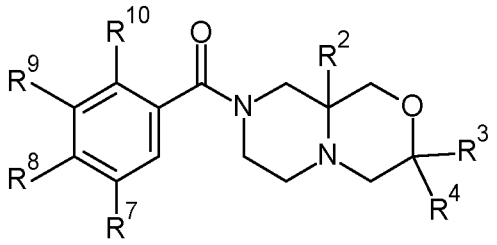
;

R^{10} is hydrogen, halogen, or cyano;

A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl; and

n and p are each independently 1 or 2.

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



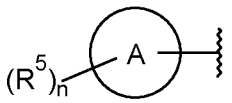
(II)

wherein R^2, R^3 and R^4 are as defined herein and wherein:

R^7 is hydrogen or C_1-C_6-alkoxy;

R^8 is hydrogen or C_1-C_6-alkoxy;

R^9 is hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy or a group



; wherein R^5, A and n are as defined herein; and

R^{10} is hydrogen, halogen, or cyano.

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

(i) heteroaryl selected from the group consisting of 1H-pyrazol-4-yl, pyridazine, pyridyl, pyrimidinyl, oxazol-5-yl, isoxazol-4-yl, 1H-triazol-5-yl, and 1H-imidazol-5-yl; or

(ii) phenyl; or

(iii) heterocyclyl selected from the group consisting of 1,2-dihydropyridine, 2-oxa-6-azaspiro[3.3]heptan-6-yl, morpholinyl, and azetidinyl.

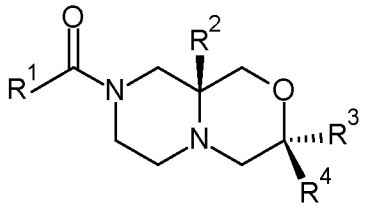
In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein B is

(i) heteroaryl selected from the group consisting of pyridyl, 1H-benzimidazol-2-yl, pyridazine, and thiazolyl; or

(ii) aryl selected from the group consisting of phenyl and 3-bicyclo[4.2.0]octa-1(6),2,4-trienyl; or

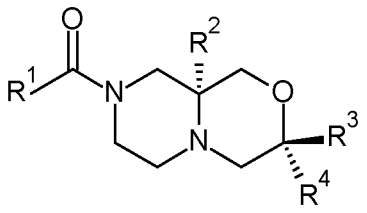
(iii) 1,2-dihydropyridine.

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



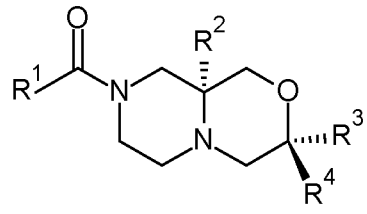
(III)

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



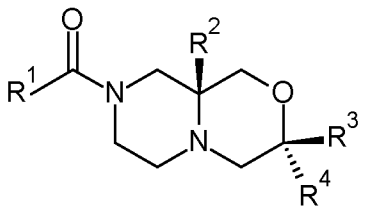
(IV)

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



(V)

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



(VI)

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

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

Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements.

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

Processes of Manufacturing

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

substituents and indices used in the following description of the processes have the significance given herein, unless indicated to the contrary.

If one of the starting materials, intermediates or compounds of formula (I) contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protective groups (as described e.g., in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wutts, 5th Ed., 2014, John Wiley & Sons, N.Y.) can be introduced before the critical step applying methods well known in the art. Such protective groups can be removed at a later stage of the synthesis using standard methods described in the literature.

If starting materials or intermediates contain stereogenic centers, compounds of formula (I) can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art e.g., chiral HPLC, chiral SFC or chiral crystallization. Racemic compounds can e.g., be separated into their antipodes via diastereomeric salts by crystallization with optically pure acids or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent. It is equally possible to separate starting materials and intermediates containing stereogenic centers to afford diastereomerically/enantiomerically enriched starting materials and intermediates. Using such diastereomerically/enantiomerically enriched starting materials and intermediates in the synthesis of compounds of formula (I) will typically lead to the respective diastereomerically/enantiomerically enriched compounds of formula (I).

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

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

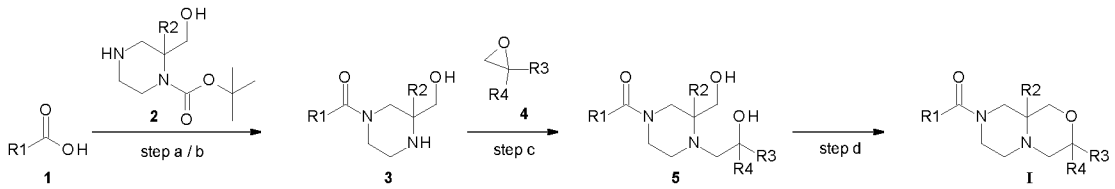
In more detail, the compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate

reaction conditions for the individual reaction steps are known to a person skilled in the art. Also, for reaction conditions described in literature affecting the described reactions see for example: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999).*

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

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

Compounds of formula (**I**) wherein R^1 and R^3 are as defined herein and wherein R^2 and R^4 are hydrogen may be synthesized according to the general procedure outlined in *Scheme 1.*



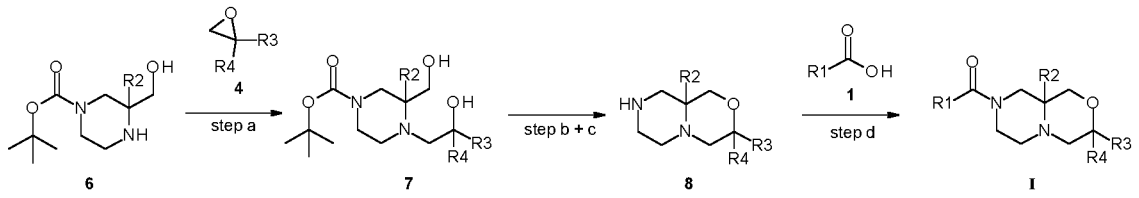
Scheme 1

Accordingly, the secondary amine **2** can be acylated with a carboxylic acid **1**, which are either commercially available or may be prepared by methods known to the man skilled in the art, using suitable conditions, for example coupling reagents such as HATU, T3P, EDC, in combination with a base such as TEA or DIPEA. Deprotection of the Boc group using an acid such as TFA or HCl leads to the corresponding intermediate **3** (Scheme 1, step a and b). Treatment of piperazine **3** with an epoxide **4,** which is either commercially

available or may be prepared by methods known to the man skilled in the art, in a solvent like methanol or ethanol, and in a temperature range between 100°C and 140°C affords the corresponding diol **5** (Scheme 1, step c). The two hydroxy groups of **5** are being cyclized, using a etherification reagent such as (cyanomethylene)tributylphosphorane (CMBP, Tsunoda reagent) to yield compound of formula (**I**) (Scheme 1, step d).

If R^3 is carrying a protecting group, for example a benzyl-group as a protecting group for a pyridone, a final deprotection step is required, using suitable conditions such as TFA in DCM, to eventually afford a compound of formula (**I**).

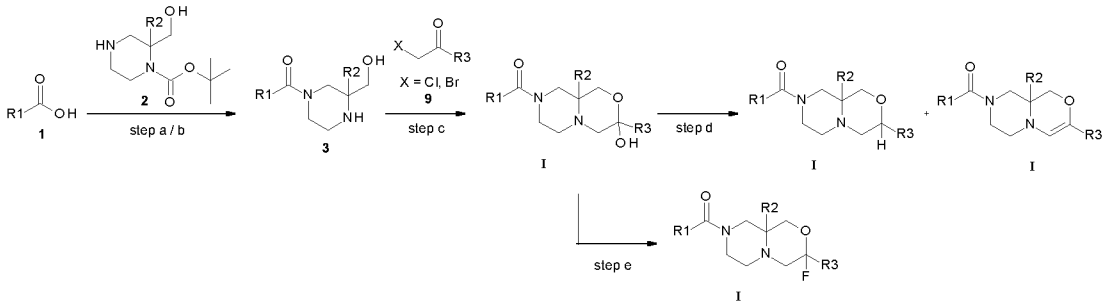
Compounds of formula (**I**) wherein R^1, R^2 and R^3 are as defined herein and wherein and R^4 is hydrogen may also be synthesized according to the general procedure outlined in *Scheme 2.*



Scheme 2

Treatment of secondary amine **6** with an epoxide **4** in a solvent like methanol or ethanol, and in a temperature range between 100°C and 140°C affords the corresponding intermediate **7** (Scheme 2, step a). The two hydroxy groups of **7** are being cyclized, using a etherification reagent such as (cyanomethylene)tributylphosphorane (CMBP, Tsunoda reagent, scheme 2, step b). Subsequent deprotection of the Boc group using an acid such as TFA or HCl leads to the corresponding morpholine analogue **8** (Scheme 2, step c). If R^3 is carrying a protecting group, for example a benzyl as a protecting group for a pyridone, this is deprotected as well during acid treatment (scheme 2, step c). The secondary amine **8** can then be acylated with a suitable carboxylic acid **1**, using conditions known in the art, for example coupling reagents such as HATU, T3P or EDC, in combination with a base such as TEA or DIPEA (scheme 2, step d), to afford a compound of formula (**I**).

Compounds of formula (**I**) wherein R^1, R^2, R^3 and R^4 are as defined herein, may also be synthesized according to the general procedure outlined in *Scheme 3a.*

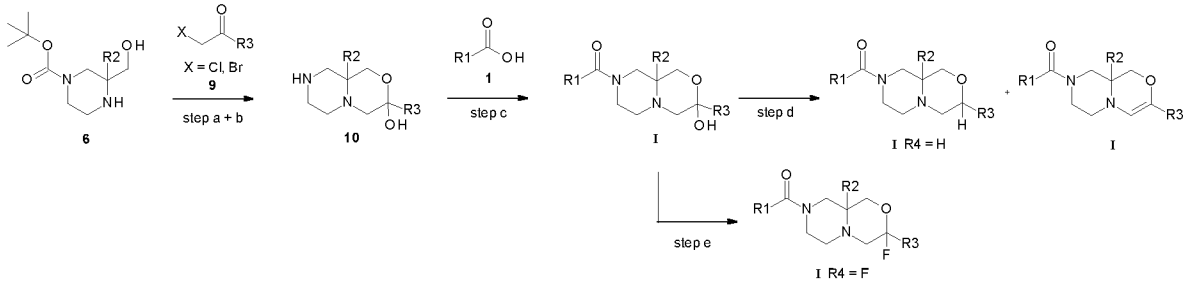


Scheme 3a

The secondary amine **2** can be acylated with a suitable carboxylic acid **1**, using conditions known in the art, for example coupling reagents such as HATU, T3P, EDC, in combination with a base such as TEA or DIPEA. Deprotection of the Boc group using an acid such as TFA or HCl leads to the corresponding intermediate **3** (Scheme 3a, step a and b). Treatment of piperazine **3** with a haloketone **9** (obtainable e.g. by the general procedure outlined in *Scheme 4*) in a solvent like THF and a base such as DIPEA, and in a temperature range between 0°C and 25°C affords the corresponding acetale **I**, corresponding to compounds of formula (**I**) wherein R^4 is hydroxy (Scheme 3a, step c). Further reaction of compounds of formula (**I**) wherein R^4 is hydroxy under dehydrating conditions, for example using TES and TFA in DCM at elevated temperatures between 50°C and 80°C leads to compounds of formula (**I**) wherein R^4 is hydrogen (Scheme 3a, step d). The alkene (X = –CH=CR^3–) can be isolated in some cases, if elimination is an additional reaction path, depending on the chosen conditions.

Treatment of compounds of formula (**I**) wherein R^4 is hydroxy with a nucleophilic fluorinating agent such as DAST, using a solvent such a DCM, at temperatures between -78°C and 25°C, yields compounds of formula (**I**) wherein R^4 is fluoride (scheme 3a, step e).

Compounds of formula (**I**) wherein R^1, R^2, R^3 and R^4 are as defined herein, may also be synthesized according to the general procedure outlined in *Scheme 3b*.

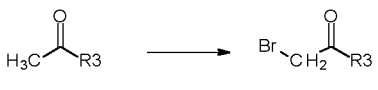


Scheme 3b

Treatment of the secondary amine **6** with an haloketone **9** in a solvent like THF and a base such as DIPEA, and in a temperature range between 0°C and 25°C affords the corresponding acetale. Deprotection of the Boc group using an acid such as TFA or HCl leads to compounds of formula **10** wherein R^4 is hydroxy (Scheme 3b, step a and b). The secondary amine of **10** can be acylated with a suitable carboxylic acid **1**, using conditions known in the art, for example coupling reagents such as HATU, T3P, EDC, in combination with a base such as TEA or DIPEA, leading to compounds of formula I with R^4 = OH (scheme 3b, step c). Further reaction of compounds of formula (**I**) wherein R^4 is hydroxy under dehydrating conditions, for example using TES and TFA in DCM at elevated temperatures between 50°C and 80°C leads to compounds of formula (**I**) wherein R^4 is hydrogen (Scheme 3, step d). The alkene (X = –CH=CR^3–) can be isolated in some cases, if elimination is an additional reaction path, depending on the chosen conditions.

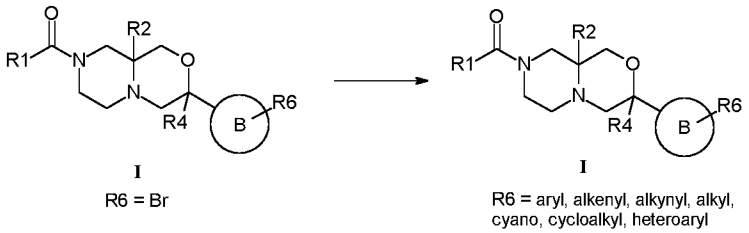
Treatment of compounds of formula (**I**) wherein R^4 is hydroxy with a nucleophilic fluorinating agent such as DAST, using a solvent such a DCM, at temperatures between -78°C and 25°C, yields compounds of formula (**I**) wherein R^4 is fluoride (scheme 3b, step e).

Bromoketone intermediates **9** can be obtained by reacting a ketone **11**, which is either commercially available or may be prepared by methods known to the man skilled in the art, with bromine in acetic acid, at elevated temperatures between 60 and 90°C (Scheme 4).



Scheme 4

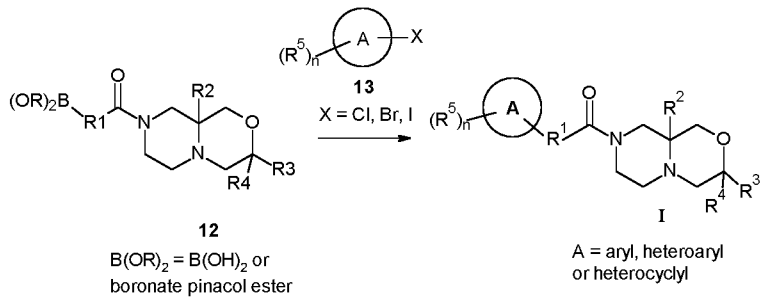
Compounds of formula (**I**) wherein R^1, R^2 and R^4 are as defined herein and wherein R^3 is B substituted with bromo, can be further modified according to the general procedure outlined in Scheme 5.



Scheme 5

Treatment of compounds of formula I, containing a bromoaryl as R^3 under typical conditions of a Suzuki–Miyaura reaction, a Sonogashira reaction, or other organometallic cross couplings known in the art lead to substituted compounds of formula I where the bromine has been replaced with an aryl, alkenyl, alkynyl, alkyl, cycloalkyl, heteroaryl or cyano moiety. This typically requires a suitable reaction partner such as a boronic acid, a potassium trifluoroborate, a pinacol boronate, a terminal alkyne or an organozinc compound, a suitable catalyst for example tetrakis(triphenylphosphine)palladium (0), $PdCl_2(dppf)$-CH_2Cl_2, $Pd_2(dba)_3$ + Xantphos, cataCXium A Pd G2, an organic or inorganic base such as sodium carbonate, TEA, TMEDA or cesium carbonate in a solvent system such as Dioxane / Water, DMF or toluene / water. Reactions are typically carried out at elevated temperatures between 100 and 120°C under inert atmosphere (argon). In the case of the Sonogashira coupling, the addition of copper(I)iodide is required to get to **I** where R^6 = alkynyl.

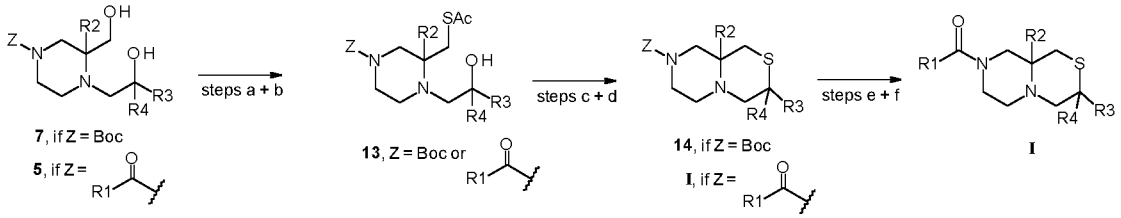
Compounds of formula (**I**) wherein R^2, R^3, R^4, R^5, and n are as defined herein and wherein R^1 is aryl or heteroaryl substituted with aryl, heteroaryl or heterocyclyl, can be obtained according to the procedure outlined in Scheme 6.



Scheme 6

Treatment of compounds of formula **12**, containing a boronic acid or boronate ester under typical conditions of a Suzuki–Miyaura reaction lead to substituted compounds of formula I where the boronate has been replaced with an aryl, heteroaryl or heterocyclyl moiety. This typically requires a suitable reaction partner **13** that can be for example a haloaryl, haloheteroaryl or haloheterocyclyl, and a suitable catalyst for example PdCl2(DPPF)-CH2Cl2, Pd2(dba)3 + Xantphos, (A-^{ta}Phos)$_2$PdCl$_2$, cataCXium A Pd G2, an organic or inorganic base such as sodium carbonate, TEA, TMEDA or cesium carbonate in a solvent system such as dioxane / water, DMF, toluene / water. Reactions are typically carried out at elevated temperatures between 100 and 120°C under inert atmosphere (argon).

Compounds of formula (**I**) wherein R^1, R^2, and R^3 are as defined herein, R^4 is hydrogen and wherein Y is –S– can also be obtained according to the general procedure outlined in *Scheme 7.*

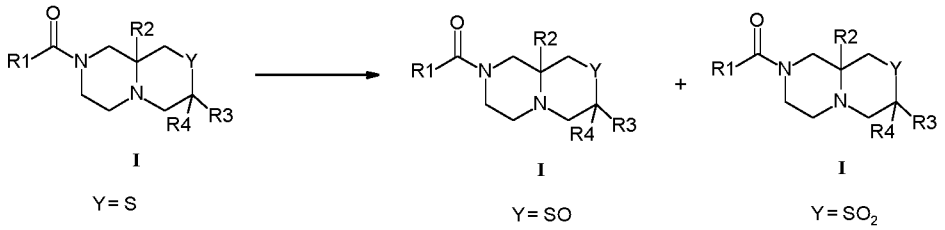


Scheme 7

Diols **5** or **7** are converted to their correnspondingmono-mesylates by treatment with methanesulfonyl chloride, a base such as triethylamine, and a catalyst such as 4-dimethylaminopyridine. Subsequent reaction with potassium thioacetate in a solvent such as DMSO provides intermediate 13 (Scheme 7, steps a and b). The remaining hydroxy group of **13** is then converted to the corresponding chloro intermediate by treatment with, for example, thionyl chloride, followed by addition of a base such as pyridine. The resulting chloro intermediate is then treated with sodium methoxide to afford the cyclized sulfides **I** (if Z = -CO-R1) or **14** (if Z = Boc) (scheme 7, steps c + d). In case of compounds of type **14**, deprotection of the Boc group using an acid such as TFA or HCl, and subsequent acylation with a suitable carboxylic acid **1**, using for example coupling reagents such as HATU, T3P, EDC, in combination with a base such as TEA or DIPEA, leads to compounds of formula I (scheme 7, steps e + f). According to *Bioorg. Med. Chem. Lett.* **2016**, *26* (23), p.5695-5702. and US 9,573,961 B2

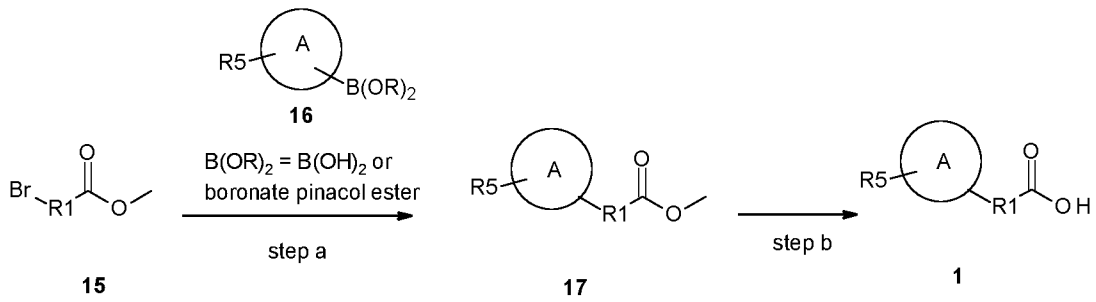
Compounds of formula (**I**) wherein R^1, R^2, and R^3 are as defined herein, R^4 is hydrogen and wherein Y is sulfur, can be further modified according to the general procedure outlined in

Scheme 8. Oxidizing the thioether **I** by employing a method known to man skilled in the art, for example by treating with mCPBA, hydrogen peroxide or sodium periodate, will lead to compounds of formula I, depending on the chosen conditions, as mixtures or pure compounds of type **I** with Y being a sulfoxide and or a sulfone. Mixtures of sulfones and sulfoxides of type **I** can then be separated be preparative HPLC or SFC to obtain pure products.



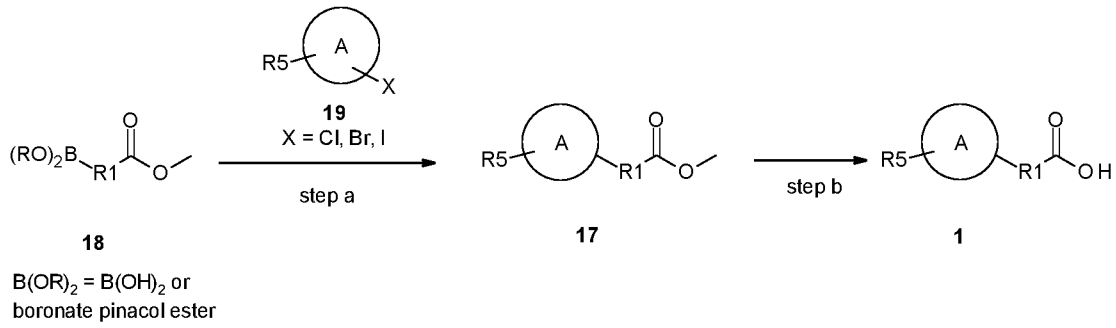
Scheme 8

Carboxylic acids **1**, wherein R^5 is as defined herein which are not commercially available can be prepared by methods known to the man skilled in the art, for example by the methods described below in schemes 9a – 9e.



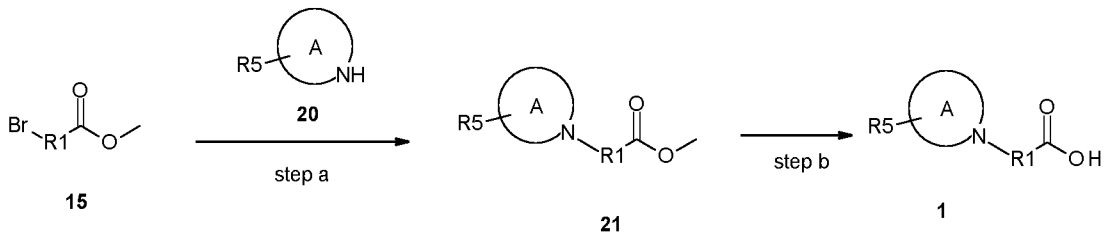
Scheme 9a

Starting from a bromo benzoate **15**, intermediate **17** can be obtained by using typical conditions for a Suzuki–Miyaura reaction. That requires a suitable boronic acid or boronate ester **16**, a palladium catalyst such as XPhos-Pd-G2, (A-^{ta}Phos)$_2$PdCl$_2$, (APhos)$_2$PdCl$_2$, a base such as K_3PO_4, K_2CO_3 or Cs_2CO_3 in a solvent system such as THF/H_2O or dioxane/H_2O. Reactions are typically carried out at elevated temperatures between 100 and 120°C under inert atmosphere (argon). Reactions of 2-heterocyclic boronates are ideally facilitated by additionally adding copper(I) chloride (Scheme 9a, step a). Saponification using a base such as lithium hydroxide in an aqueous solution leads to carboxylic acids of type **1** (Scheme 9a, step b).



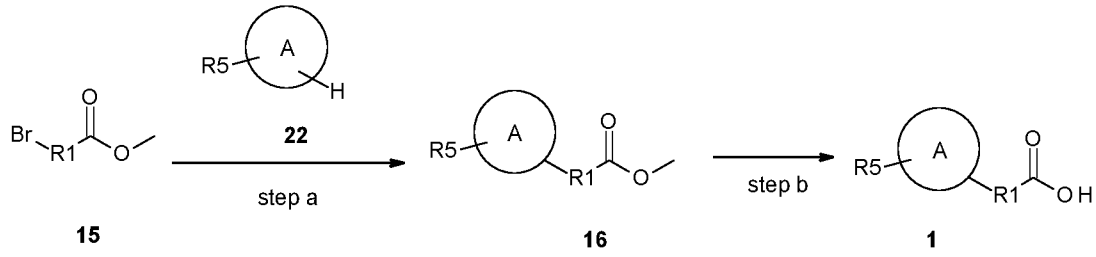
Scheme 9b

Starting from a boronic acid or boronate ester benzoate **18**, intermediate **17** can be also obtained by using typical conditions for a Suzuki–Miyaura reaction. That requires a suitable haloaryl, haloheteroaryl or haloheterocyclyl **19**, a palladium catalyst such as XPhos-Pd-G2, $(A\text{-}^{ta}Phos)_2PdCl_2$, $(APhos)_2PdCl_2$, a base such as K_3PO_4, K_2CO_3 or Cs_2CO_3 in a solvent system such as THF/H_2O or $Dioxane/H_2O$. Reactions are typically carried out at elevated temperatures between 100 and 120°C under inert atmosphere (argon). Reactions of 2-heteroaryl boronates are ideally facilitated by additionally adding copper(I) chloride (Scheme 9b, step a). Saponification using a base such as lithium hydroxide in an aqueous solution leads to carboxylic acids of type **1** (Scheme 9b, step b).



Scheme 9c

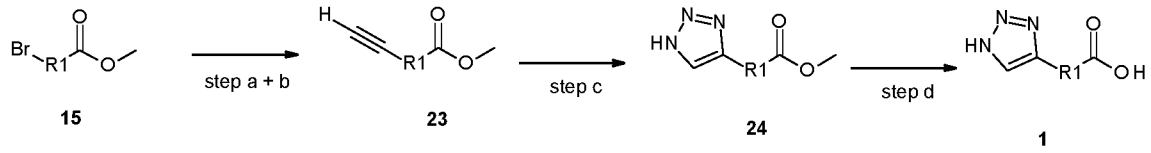
Starting from a bromo benzoate **15**, intermediate **21** can be obtained by using typical conditions for a Buchwald-Hartwig reaction. That requires a suitable amine **20**, a palladium catalyst such as $Pd_2(dba)_3$ with phosphin ligand such as DavePhos or Xantphos, a base such as K_3PO_4, K_2CO_3 or Cs_2CO_3 in a solvent such as toluene or dioxane. Reactions are typically carried out at elevated temperatures between 100 and 120°C under inert atmosphere using argon (Scheme 9c, step a). Saponification of **21** using a base such as lithium hydroxide in an aqueous solution leads to carboxylic acids of type **1** (Scheme 9c, step b).



Scheme 9d

In some cases, especially with A being an oxazole, the coupling to the bromo benzoate can be achieved directly by using the unsubstituted oxazole **22** (scheme 9d), as described in *Org. Lett.* **2010**, *12* (16), p. 3578-3581.

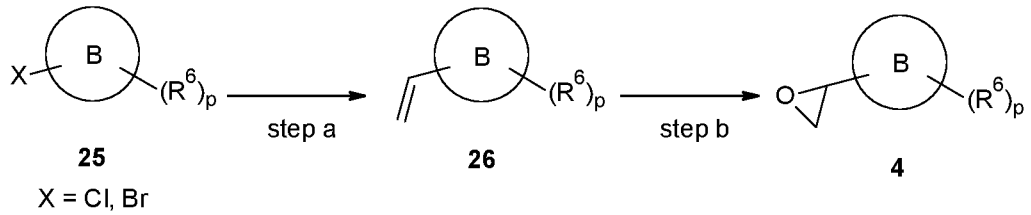
Saponification of **16** using a base such as lithium hydroxide in an aqueous solution leads to carboxylic acids of type **1** (Scheme 9d, step b).



Scheme 9e

Aryl/heteroaryl halide **15** can be cross coupled with ethynyltrimethylsilane using typical conditions for a Sonogashira reaction ($Pd(dppf)Cl_2$, copper (I) iodide, diethylamine, DMF, 120°C). Deprotection with potassium carbonate in THF/MeOH at room temperature leads to alkyne intermediate **23** (Scheme 9e, steps a+b). Treatment of **23** with azidotrimethylsilane using a suitable copper catalyst such as copper (I) iodide in a solvent system such as DMF / MeOH at elevated temparatures between 100 and 130°C leads to triazole **24** (Scheme 9e, step c). Saponification of **24** using a base such as lithium hydroxide in an aqueous solution leads to carboxylic acids of type **1** (Scheme 9e, step d).

Oxiranes **4**, wherein B, R^6 and p are as defined herein, which are not commercially available can be prepared by methods known to the man skilled in the art, for example by the methods described below.



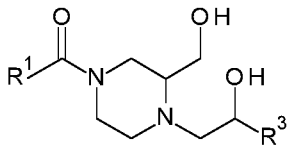
Scheme 10

Treating arylhalides or heteroarylhalides **25** with potassium trifluoro(vinyl)borate under typical Suzuki-Miyaura conditions (1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, triethylamine, in ethanol under argon at 100° - 130°C) leads to vinylarenes or vinylheteroarens **26** (scheme 10, step a). These can be oxidized toward oxiranes **4** by using for example methyltrioxorhenium plus 1H-pyrazole and hydrogen peroxide, in DCM, at 0°C; NBS in water and dioxane, at room temperature, then treatment with aq. NaOH at 0°C; mCPBA in DCM at room temperature (Scheme 10, step b).

In one aspect, the present invention provides a process of manufacturing the compounds of formula (I) as described in any one of the schemes disclosed herein.

In a further aspect, the present invention provides processes of manufacturing the compounds of formula (I) as described herein, comprising:

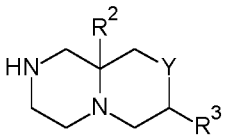
(a) reacting a diol **5**, wherein R^1 and R^3 are as defined herein,



5

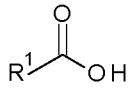
with an etherification reagent, such as (cyanomethylene)tributylphosphorane (CMBP, Tsunoda reagent) to yield said compound of formula (**I**), wherein X is –CH_2CHR^3–, Y is –O–, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(b) reacting an amine **8a**, wherein Y, R^2 and R^3 are as defined herein,



8a

with a carboxylic acid **1**, wherein R^1 is as defined herein,



1

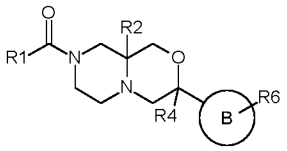
in the presence of a base, such as trimethylamine or diisopropylamine, and a coupling reagent, such as HATU, T3P or EDC*HCl, to yield said compound of

formula (I), wherein X is $–CH_2CHR^3–$, Y, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(c) submitting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy to dehydrating conditions, for example using TES and TFA at elevated temperatures, to yield a compound of formula (I) wherein Y is as defined herein, X is $–CH_2CHR^3–$ and R^1 to R^3 are as defined herein and/or a compound of formula (I) wherein Y is as defined herein, X is $–CH=CR^3–$ and R^1 to R^3 are as defined herein; or

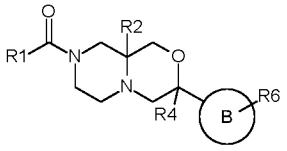
(d) reacting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy, with a nucleophilic fluorinating agent, such as DAST, to yield a compound of formula (I) wherein X is $–CH_2CFR^3–$ and R^1 to R^3 are as defined herein; or

(e) submitting a compound of formula (I),



I

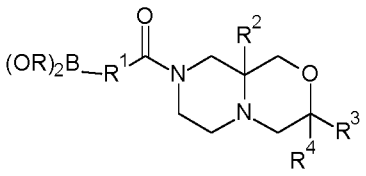
wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is bromo, to a transition metal catalyzed cross-coupling reaction, such as a Suzuki–Miyaura reaction or a Sonogashira reaction, to afford compound of formula (I)



I

wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is selected from aryl, alkenyl, alkynyl, alkyl, cyano, cycloalkyl, and heteroaryl; or

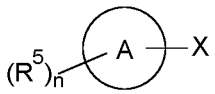
(f) submitting a compound **12**, wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^4 are as defined herein,



12

$B(OR)_2 = B(OH)_2$ or boronate pinacol ester

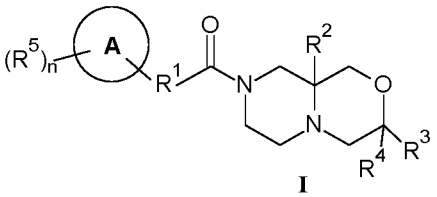
to a Suzuki-Miyaura cross coupling reaction with a compound **13**, wherein A, R^5, and n are as defined herein



13

X = Cl, Br, I, OTf

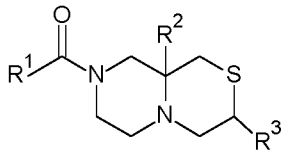
in the presence of a transition metal catalyst, e.g. $PdCl_2(dppf)\text{-}CH_2Cl_2$, $Pd_2(dba)_3$ + Xantphos, $(A\text{-}^{ta}Phos)_2PdCl_2$, or cataCXium A Pd G2, and an organic or inorganic base such as sodium carbonate, triethylamine, TMEDA or cesium carbonate; to afford said compound of formula (I), wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^5 and n are as defined herein



I

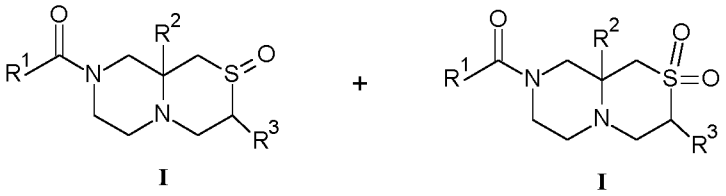
; or

(g) reacting a compound of formula (I), wherein Y is sulfur and R^1, R^2, and R^3 are as defined herein,



I

with an oxidizing agent, such as mCPBA, hydrogen peroxide or sodium periodate, to afford a compound of formula (I), wherein Y is a sulfoxide or a sulfone and R^1, R^2, and R^3 are as defined herein.



I I

In one aspect, the present invention provides a compound of formula (I) as described herein, when manufactured according to any one of the processes described herein.

MAGL Inhibitory Activity

Compounds of the present invention are MAGL inhibitors. Thus, in one aspect, the present invention provides the use of compounds of formula (I) as described herein for inhibiting MAGL in a mammal.

In a further aspect, the present invention provides compounds of formula (I) as described herein for use in a method of inhibiting MAGL in a mammal.

In a further aspect, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for inhibiting MAGL in a mammal.

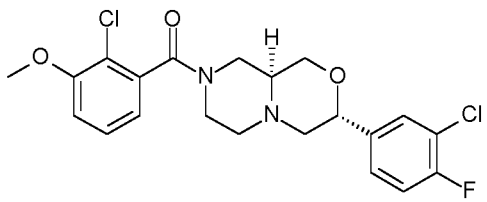
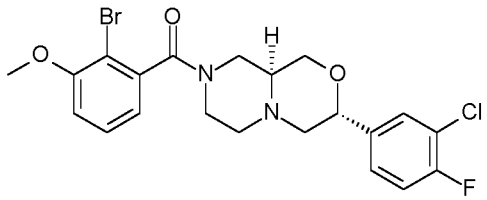
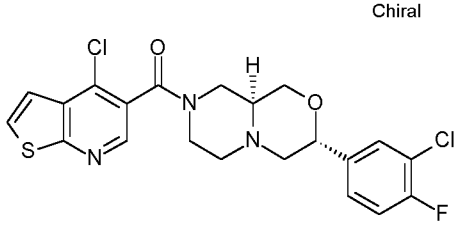
In a further aspect, the present invention provides a method for inhibiting MAGL in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

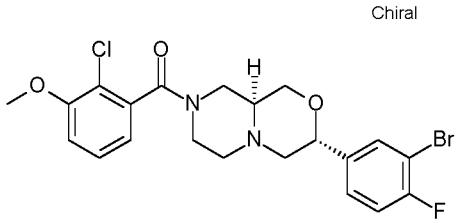
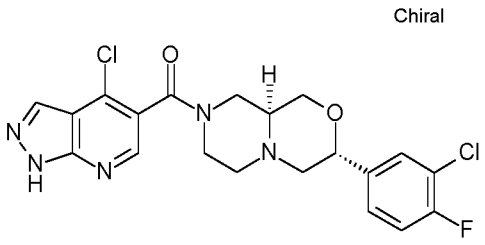
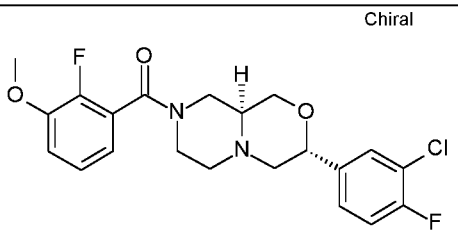
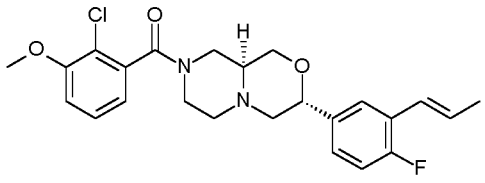
Compounds were profiled for MAGL inhibitory activity by determining the enzymatic activity by following the hydrolysis of the natural substrate 2-arachidonoylglycerol (2-AG) resulting in arachidonic acid, which can be followed by mass spectrometry. This assay is hereinafter abbreviated “2-AG assay”.

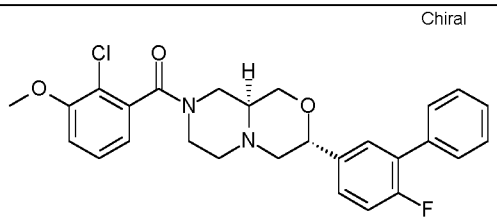
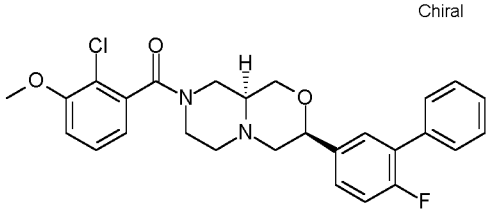
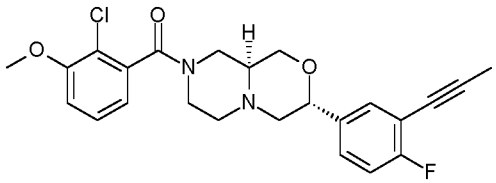
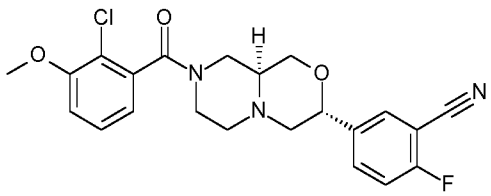
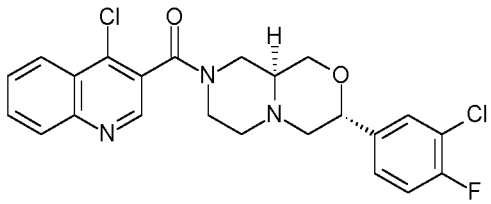
The 2-AG assay was carried out in 384 well assay plates (PP, Greiner Cat# 784201) in a total volume of 20 µL. Compound dilutions were made in 100% DMSO (VWR Chemicals 23500.297) in a polypropylene plate in 3-fold dilution steps to give a final concentration range in the assay from 12.5 µM to 0.8 pM. 0.25µL compound dilutions (100% DMSO) were added to 9 µL MAGL in assay buffer (50 mM TRIS (GIBCO, 15567-027), 1 mM EDTA (Fluka, 03690-100 mL), 0.01% (v/v) Tween. After shaking, the plate was incubated for 15 min at RT. To start the reaction, 10 µL 2-arachidonoylglycerol in assay buffer was added. The final concentrations in the assay was 50 pM MAGL and 8 µM 2-arachidonoylglyerol. After shaking and 30 min incubation at RT, the reaction was

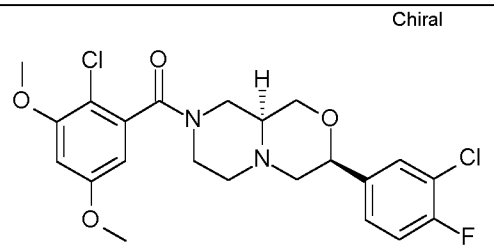
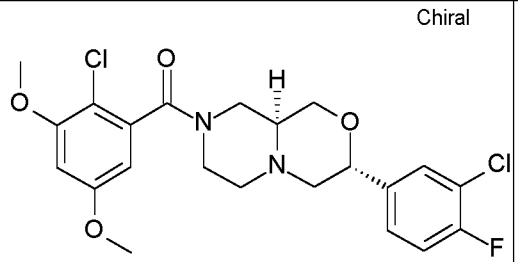
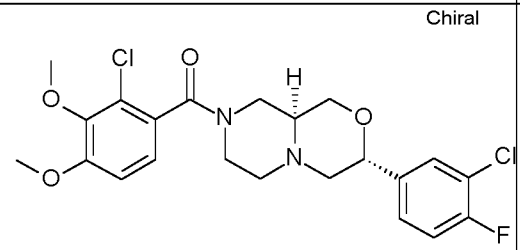
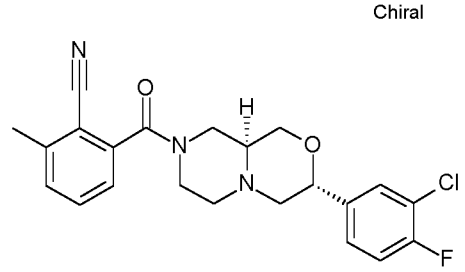
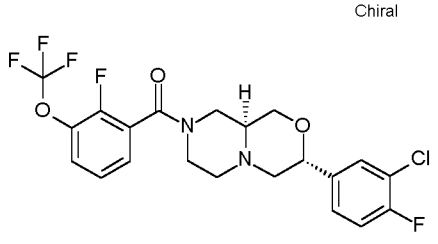
quenched by the addition of 40µL of ACN containing 4µM of d8-arachidonic acid. The amount of arachidonic acid was traced by an online SPE system (Agilent Rapidfire) coupled to a triple quadrupole mass spectrometer (Agilent 6460). A C18 SPE cartridge (G9205A) was used in an ACN/water liquid setup. The mass spectrometer was operated in negative electrospray mode following the mass transitions 303.1 → 259.1 for arachidonic acid and 311.1 → 267.0 for d8-arachidonic acid. The activity of the compounds was calculated based on the ratio of intensities [arachidonic acid / d8-arachidonic acid].

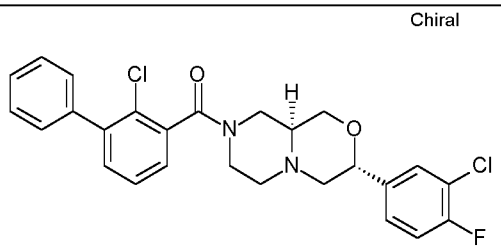
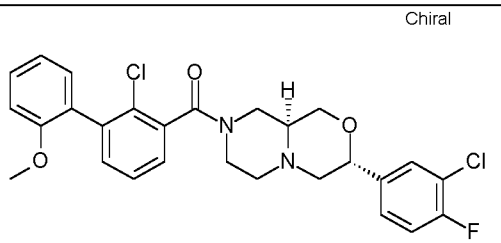
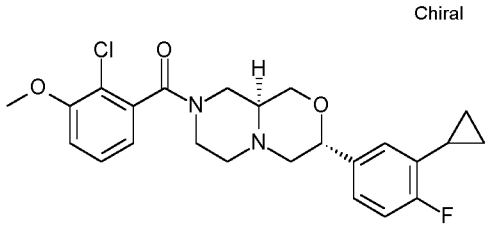
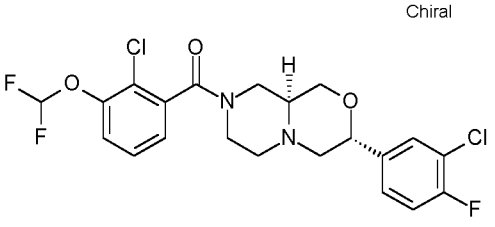
Table 1

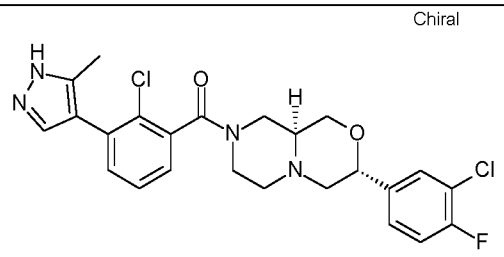
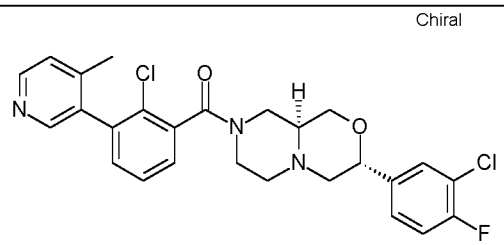
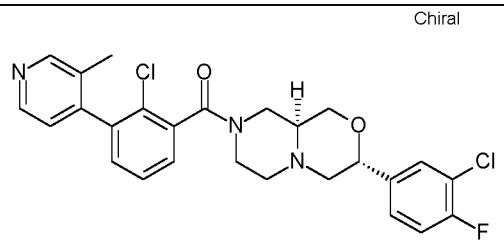
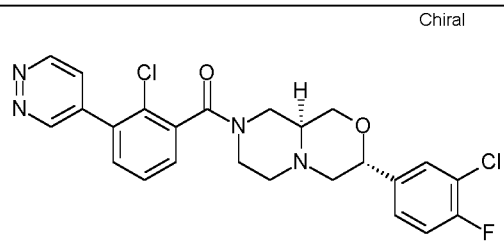
Ex.	Structure	**IUPAC Name**	**MAGL IC50 (nM)**
1		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**18.3**
2		(2-bromo-3-methoxy-phenyl)-[rac-(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**14.6**
5		(4-chlorothieno[2,3-b]pyridin-5-yl)-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-	**28.2**

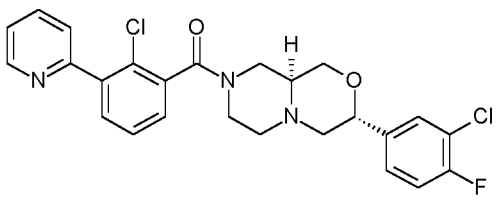
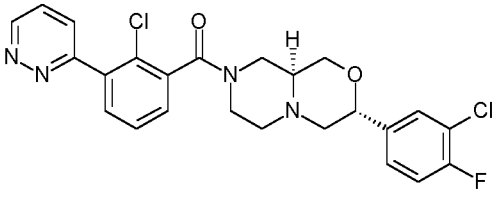
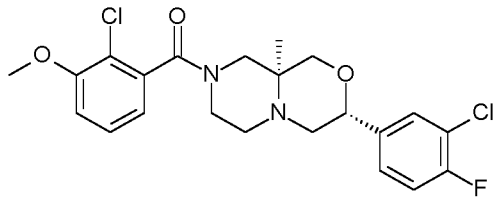
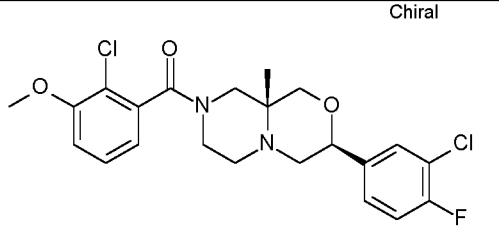
		c][1,4]oxazin-8-yl]methanone	
6		[(3R,9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**10.9**
8		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-1H-pyrazolo[3,4-b]pyridin-5-yl)methanone	**705.2**
9		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-fluoro-3-methoxy-phenyl)methanone	**85.6**
10		(2-chloro-3-methoxy-phenyl)-[(3R,9aS)-3-[4-fluoro-3-[rac-(E)-prop-1-enyl]phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**178.6**

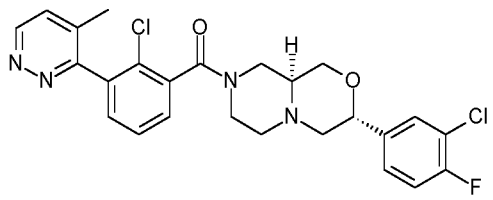
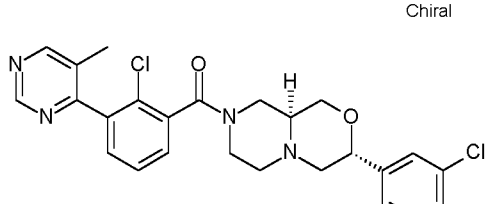
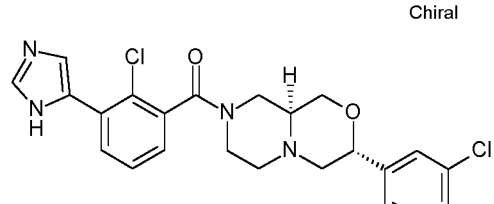
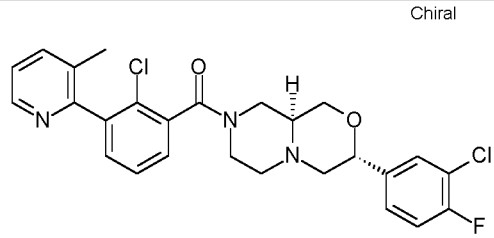
11	 Chiral	[(3R,9aS)-3-(4-fluoro-3-phenyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**259**
12	 Chiral	[(3S,9aS)-3-(4-fluoro-3-phenyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**575.3**
13		[(3R,9aS)-3-(4-fluoro-3-prop-1-ynyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**237.9**
14	 Chiral	[(3,9aS)-3-(3-cyano-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**153.5**
16	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-3-quinolyl)methanone	**131.5**

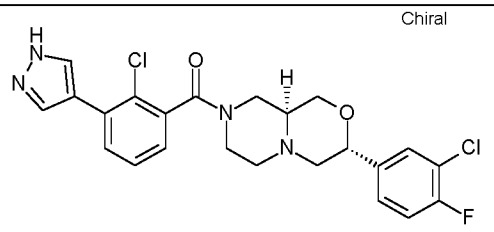
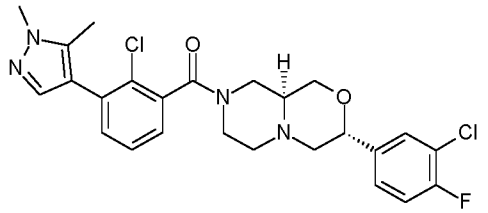
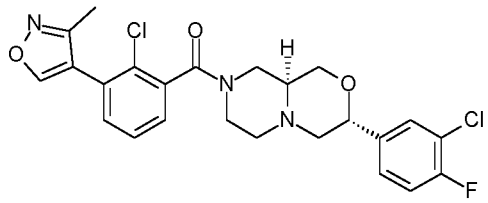
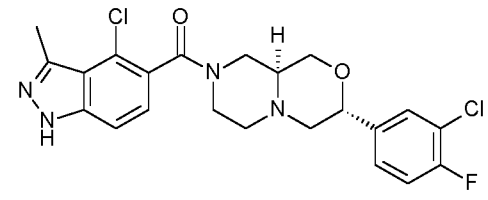
17	 Chiral	[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,5-dimethoxy-phenyl)methanone	**4567.8**
18	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,5-dimethoxy-phenyl)methanone	**51.2**
19	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3,4-dimethoxy-phenyl)methanone	**304.7**
20	 Chiral	2-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-xahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-6-methyl-benzonitrile	**120.6**
21	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-	**746.3**

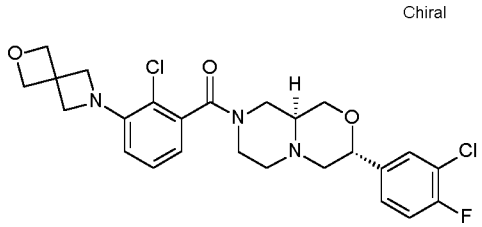
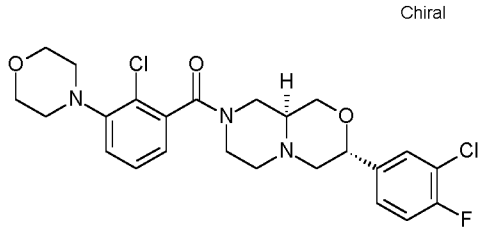
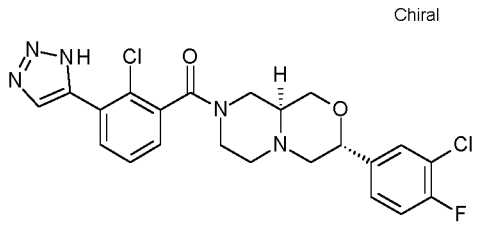
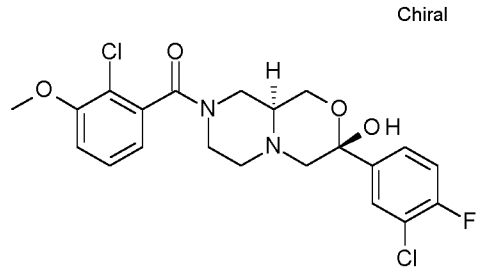
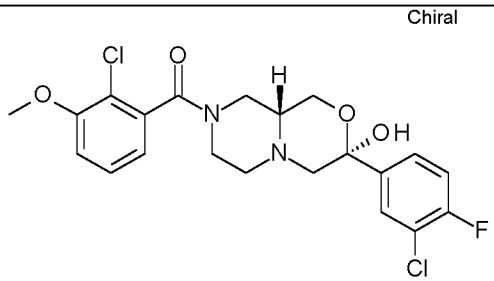
		(trifluoromethoxy)phenyl]methanone	
22		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-phenyl-phenyl)methanone	**16.1**
23		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-methoxyphenyl)phenyl]methanone	**26.3**
24		[(3R,9aS)-3-(3-cyclopropyl-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**94.8**
25		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(difluoromethoxy)phenyl]methanone	**131.1**

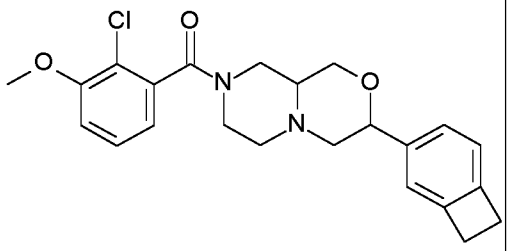
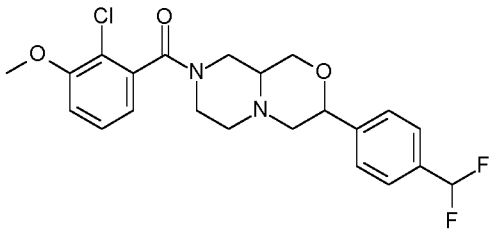
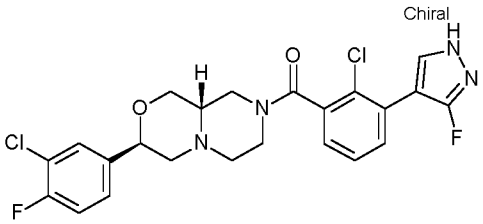
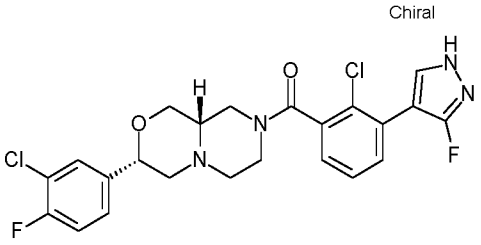
26	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(5-methyl-1H-pyrazol-4-yl)phenyl]methanone	**10.6**
27	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(4-methyl-3-pyridyl)phenyl]methanone	**210**
28	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methyl-4-pyridyl)phenyl]methanone	**32.6**
29	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-pyridazin-4-yl-phenyl)methanone	**202**

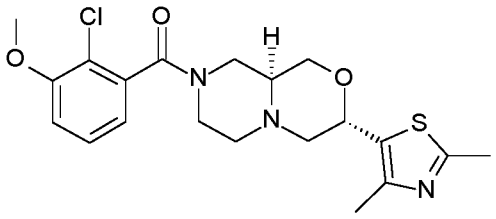
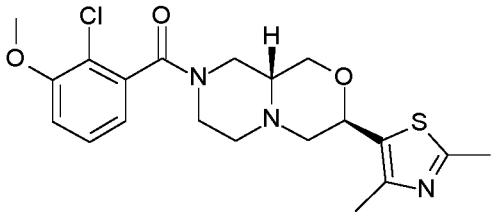
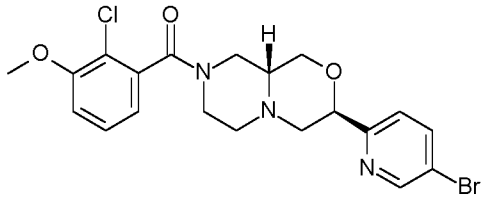
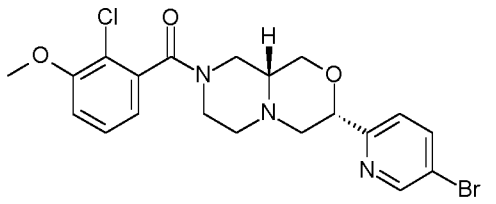
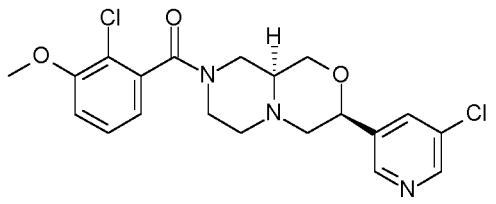
30	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-pyridyl)phenyl]methanone	**49.2**
31	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-pyridazin-3-yl-phenyl)methanone	**173.2**
32		(2-chloro-3-methoxy-phenyl)-[(rel-3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**334.5**
33	Chiral 	(2-chloro-3-methoxy-phenyl)-[(rel-3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**1912**

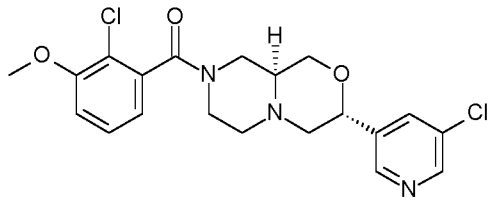
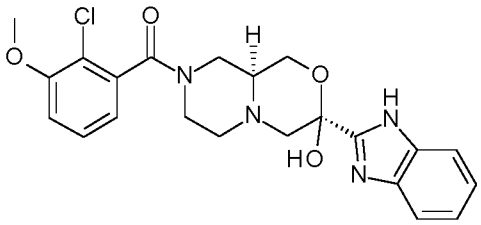
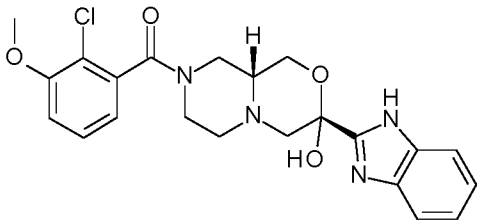
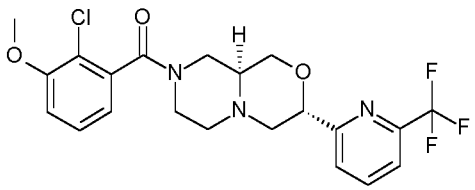
34	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(4-methylpyridazin-3-yl)phenyl]methanone	**1444.2**
35	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(5-methylpyrimidin-4-yl)phenyl]methanone	**1084.9**
36	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-imidazol-5-yl)phenyl]methanone	**7.4**
37	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methyl-2-pyridyl)phenyl]methanone	**277.4**

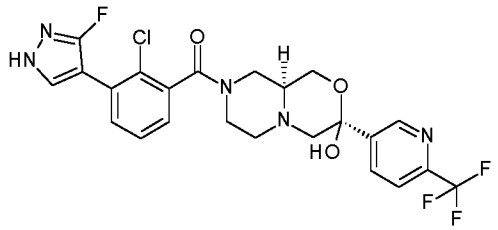
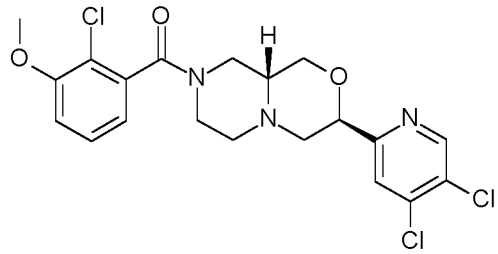
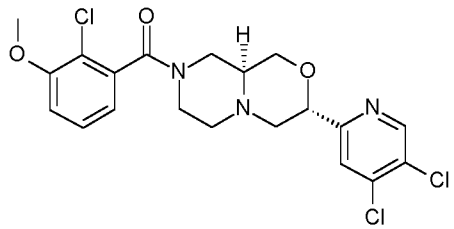
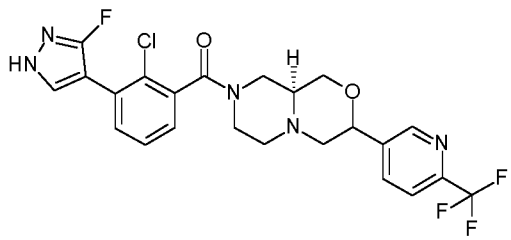
38	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone	**1.9**
39	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1,5-dimethylpyrazol-4-yl)phenyl]methanone	**49.7**
40	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-methylisoxazol-4-yl)phenyl]methanone	**160.3**
41	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(4-chloro-3-methyl-1H-indazol-5-yl)methanone	**63.8**

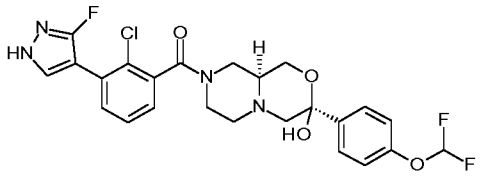
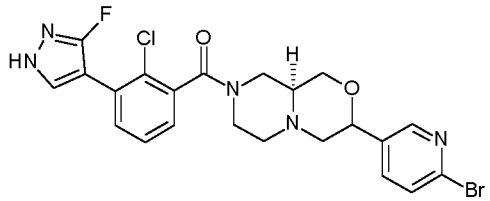
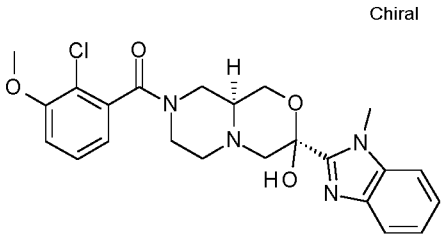
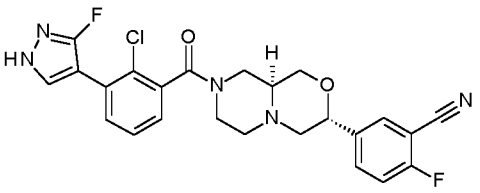
42	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl]methanone	**48.6**
43	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-morpholino-phenyl)methanone	**119.7**
44	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-triazol-5-yl)phenyl]methanone	**50**
45	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**19.4**
46	 Chiral	[(3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-	**177.5**

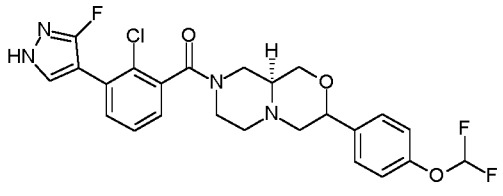
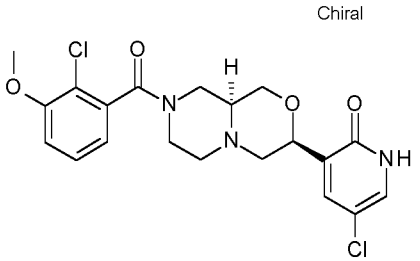
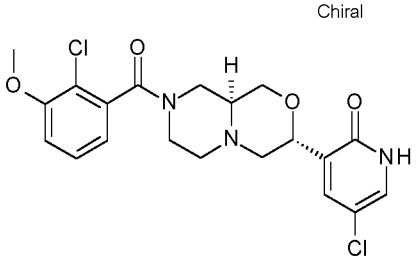
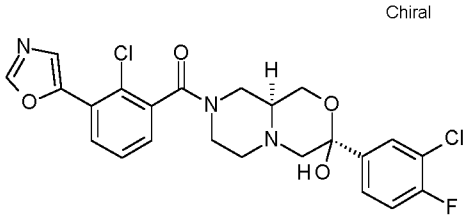
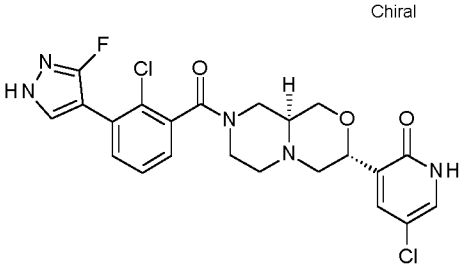
		chloro-3-methoxy-phenyl)methanone	
47		[3-(3-bicyclo[4.2.0]octa-1,3,5-trienyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**133.7**
48		(2-chloro-3-methoxy-phenyl)-[3-[4-(difluoromethyl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**146.2**
49		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**1**
50		[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**417.6**

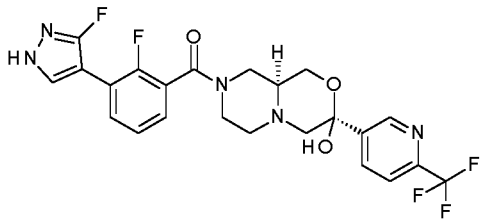
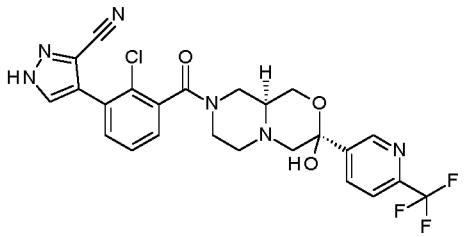
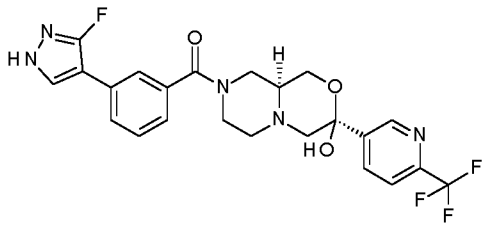
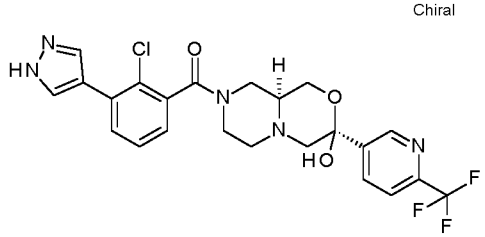
51		(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**4984.9**
52		(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**1383.2**
53		(2-chloro-3-methoxy-phenyl)-[rac-(3R,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**76**
54		(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**975.4**
58		(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-	**2221.6**

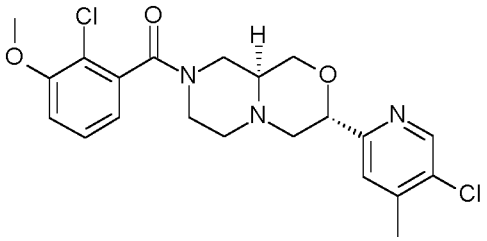
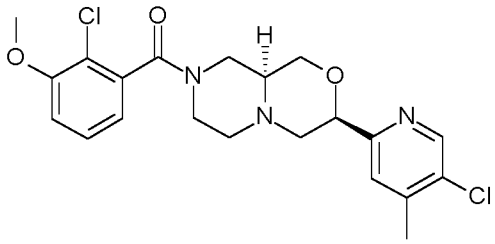
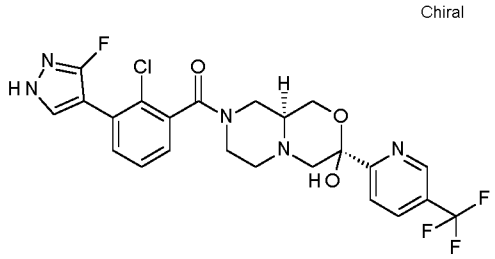
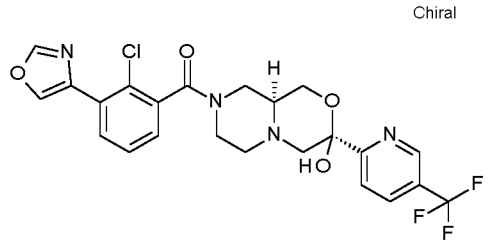
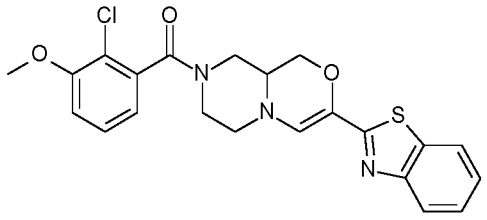
		c][1,4]oxazin-8-yl]methanone	
59		(2-chloro-3-methoxy-phenyl)-[rac-(3R,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**543.6**
60		(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**951.1**
61		(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**294.4**
63		(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-[6-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**1309.0**

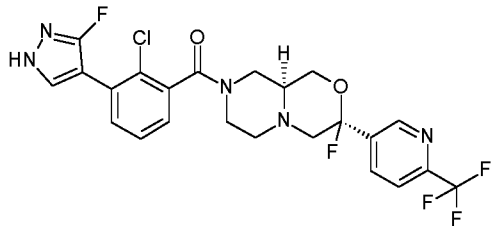
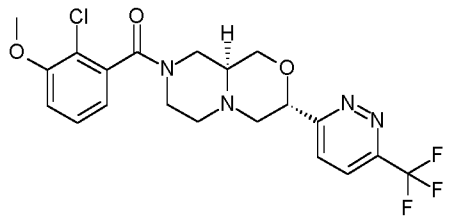
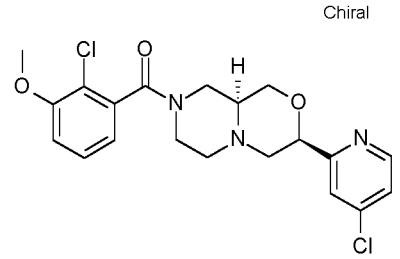
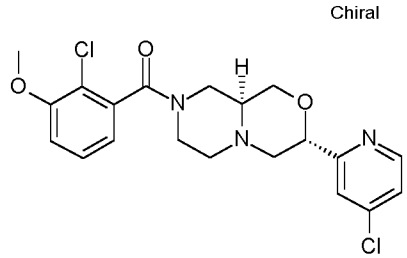
65		[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)pyridin-3-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**13.8**
66		(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**531.1**
67		(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**8.4**
68		[(9aS)-3-[6-(trifluoromethyl)-3-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**15.8**

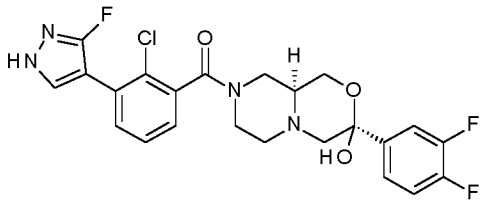
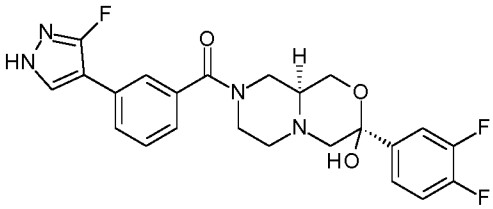
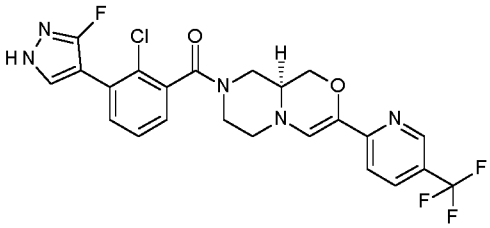
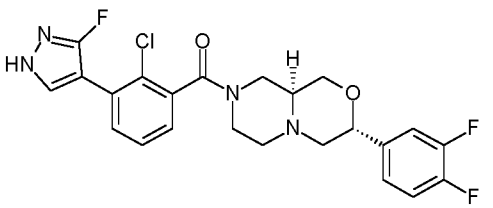
69		[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3R,9aS)-3-[4-(difluoromethoxy)phenyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**51.8**
70		[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(9aS)-3-(6-bromo-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**44.6**
71		[(3S,9aS)-3-hydroxy-3-(1-methylbenzimidazol-2-yl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**4026.0**
72		5-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-2-fluoro-benzonitrile	**61.4**

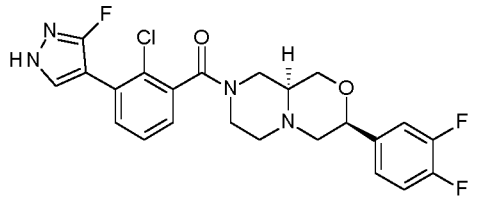
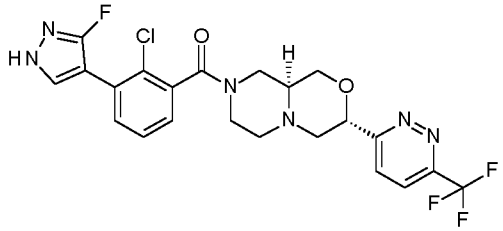
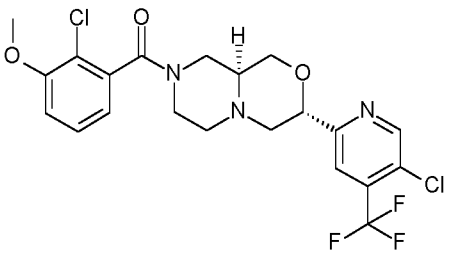
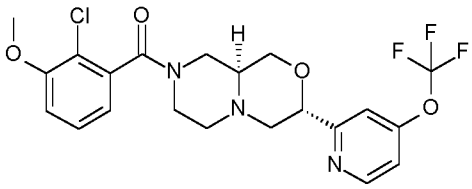
73		(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)((9aS)-3-(4-(difluoromethoxy)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone	**53.3**
74		3-[(3S,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one	**2211.9**
75		3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one	**850.4**
76		[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-5-yl-phenyl)methanone	**15.5**
77		3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one	**46.3**

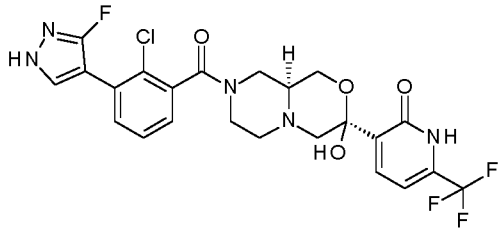
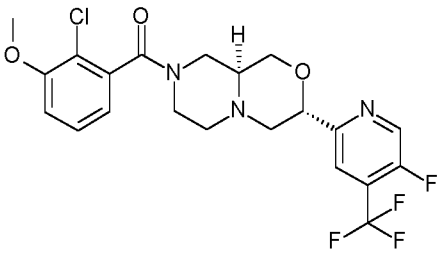
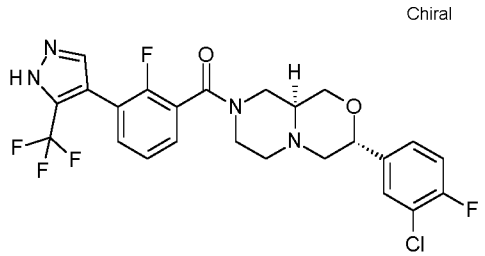
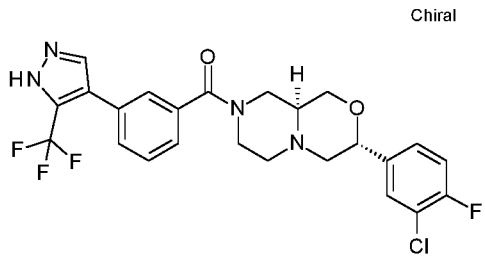
78	Chiral 	[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**129.7**
80	Chiral 	4-[3-[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrazole-3-carbonitrile	**26.2**
81	Chiral 	[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**80.4**
82	Chiral 	[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone	**15.9**

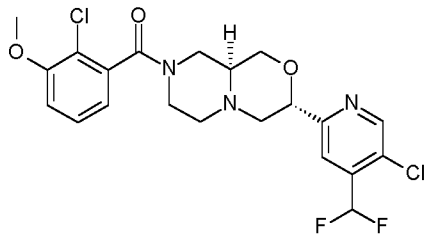
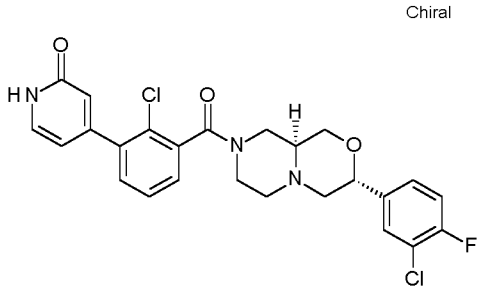
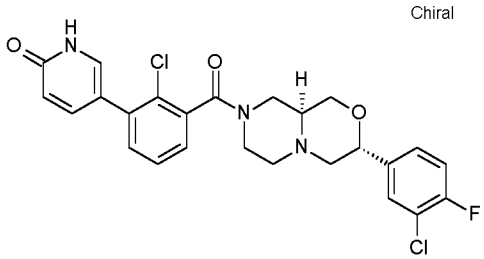
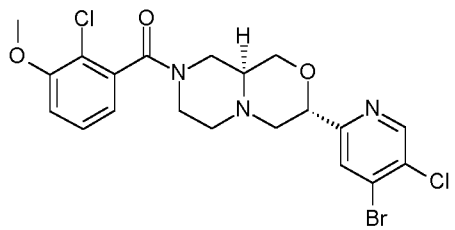
83		(2-chloro-3-methoxyphenyl)((3S,9aS)-3-(5-chloro-4-methylpyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone	**94.4**
84		(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(5-chloro-4-methylpyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone	**332.7**
85	 Chiral	[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**38.2**
86	 Chiral	[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-4-yl-phenyl)methanone	**237.3**
87		[3-(1,3-benzothiazol-2-yl)-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**983.2**

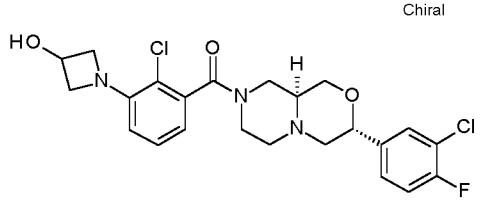
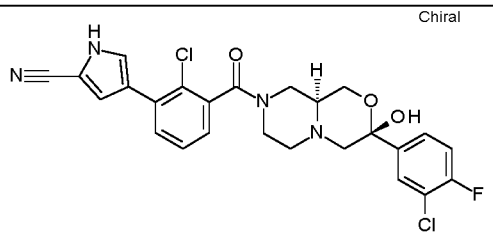
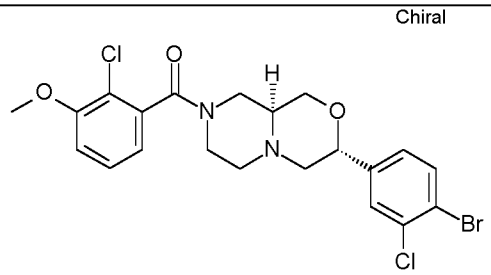
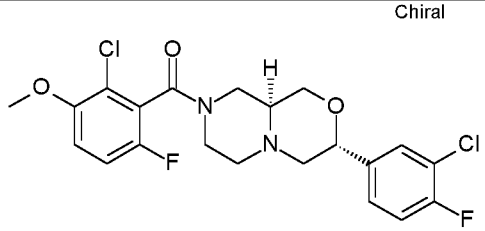
88		[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3S,9aS)-3-fluoro-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**10.7**
89		(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**2030.6**
90		[(3R,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**2311.4**
91		[(3S,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**232.5**

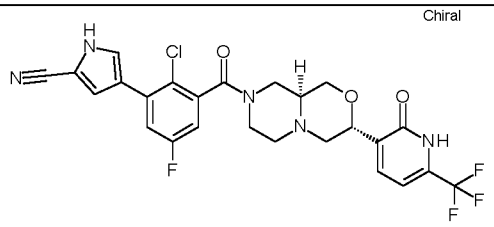
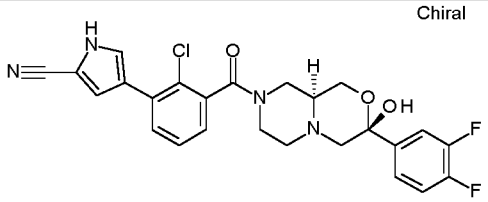
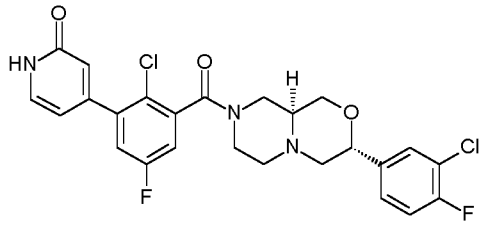
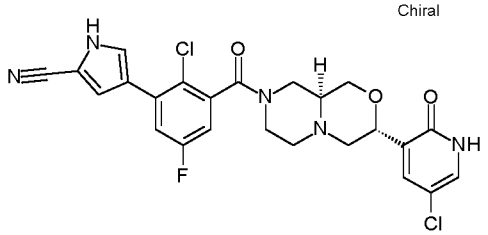
92	Chiral 	[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**9.1**
93	Chiral 	[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**81.9**
94	Chiral 	[(9aS)-3-[5-(trifluoromethyl)-2-pyridyl]-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**219.7**
95	Chiral 	[(3R,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**7.6**

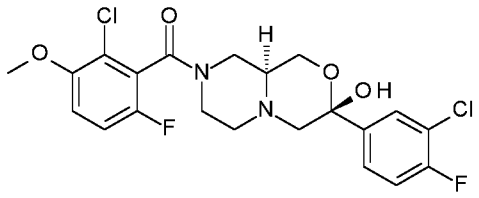
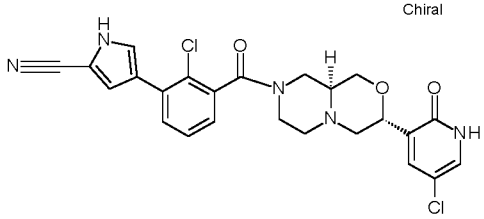
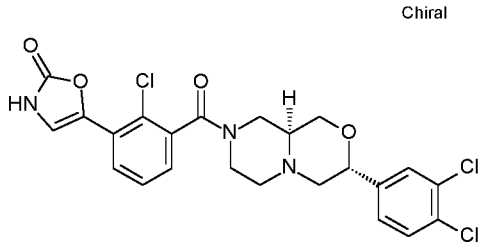
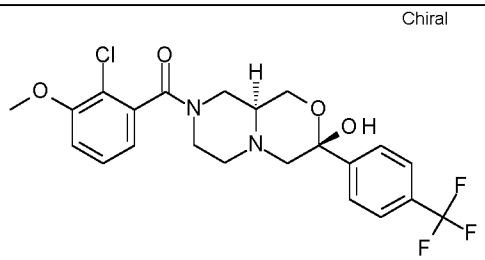
96	Chiral 	[(3S,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**1242.7**
97	Chiral 	[(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone	**439.4**
98		(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**30.7**
99		(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[4-(trifluoromethoxy)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**284.1**

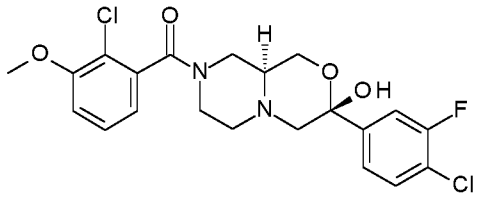
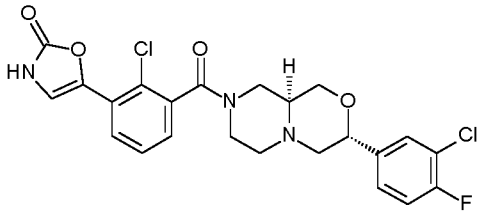
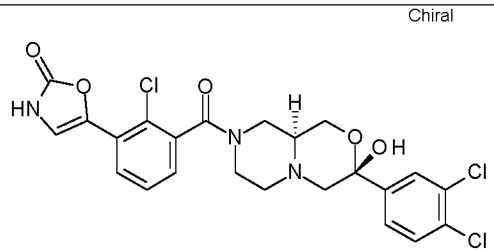
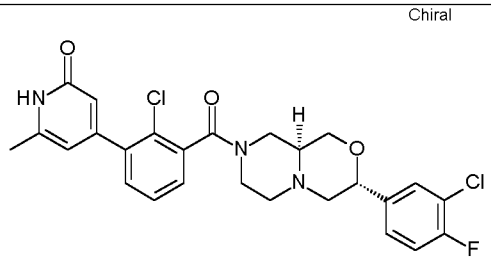
100	Chiral 	3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one	**55.3**
101		(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-fluoro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**133.2**
102	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone	**20.7**
103	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone	**28.2**

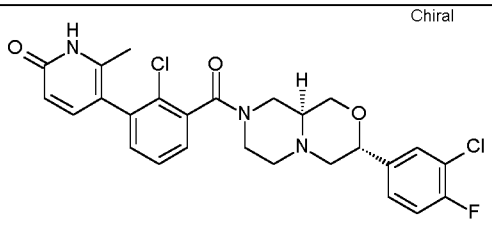
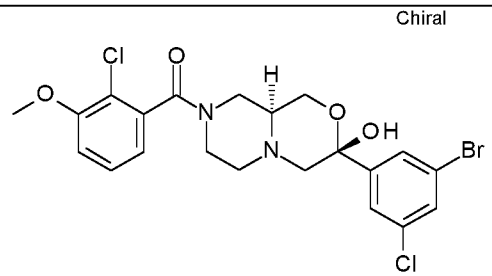
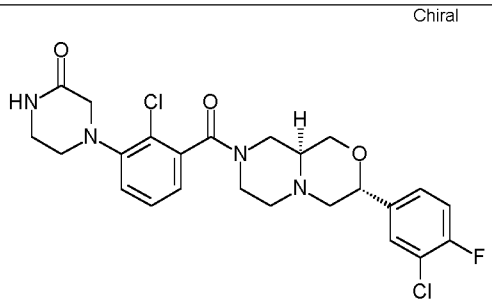
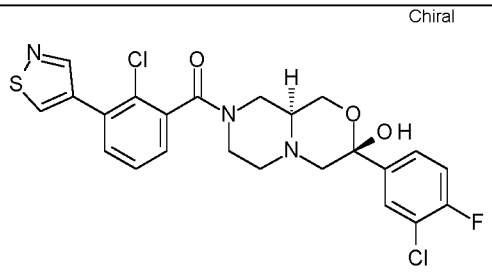
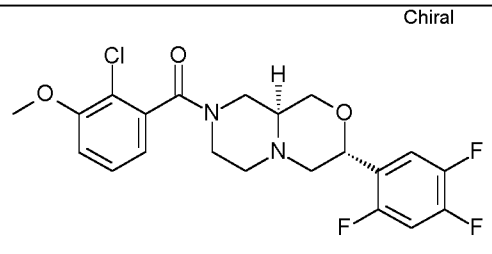
104		(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[4-(difluoromethyl)-5-fluoro-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**89.5**
105		4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one	**8.9**
106		5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one	**14.3**
107		(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-bromo-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone	**12.6**

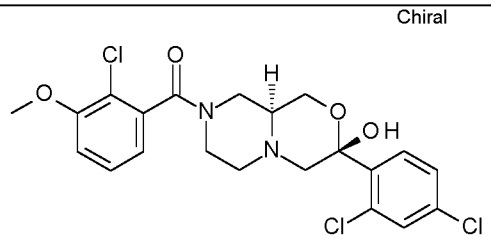
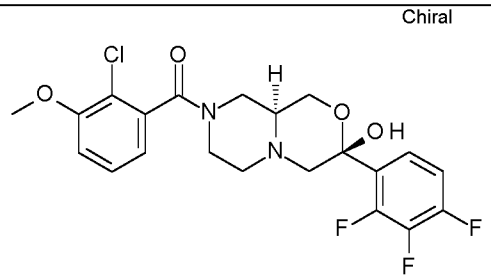
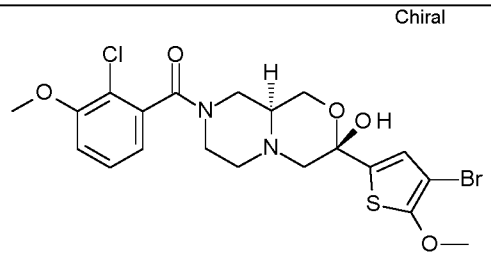
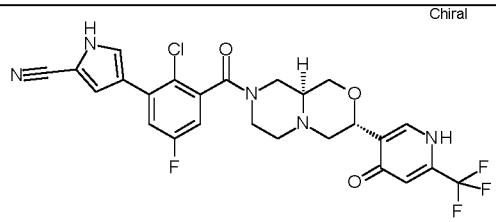
108	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-hydroxyazetidin-1-yl)phenyl]methanone	**10.5**
109	Chiral 	4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile	**1.6**
110	Chiral 	[(3R,9aS)-3-(4-bromo-3-chloro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**5.0**
111	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-6-fluoro-3-methoxy-phenyl)methanone	**5.8**

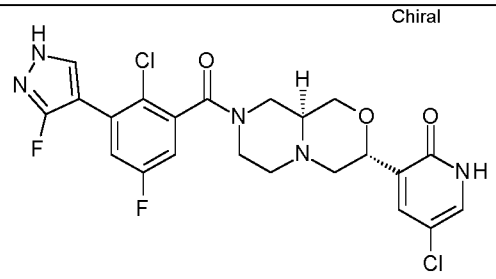
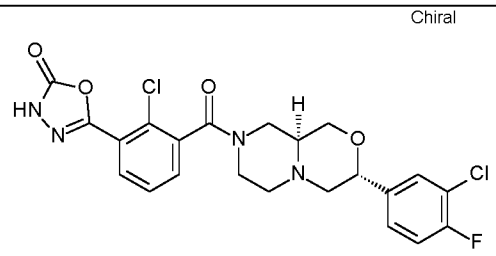
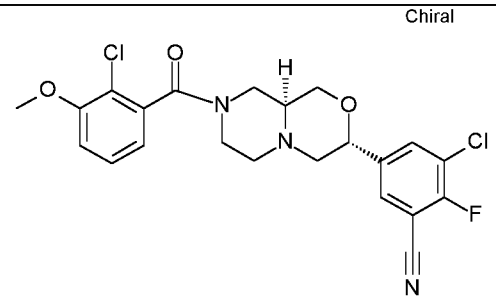
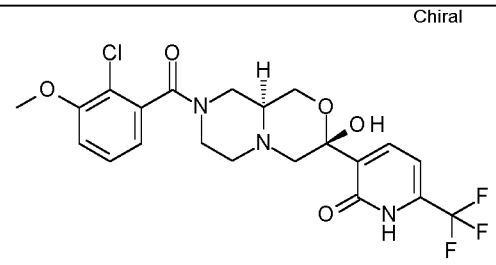
112	 Chiral	4-[3-[(3R,9aS)-3-[2-oxo-6-(trifluoromethyl)-1H-pyridin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile	**6.5**
113	 Chiral	4-[3-[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile	**7.6**
114	 Chiral	4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyridin-2-one	**10.8**
115	 Chiral	4-[3-[(3R,9aS)-3-(5-chloro-2-oxo-1H-pyridin-3-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile	**13.5**

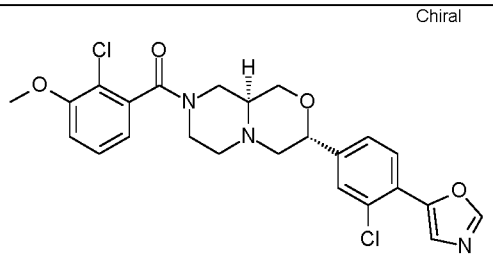
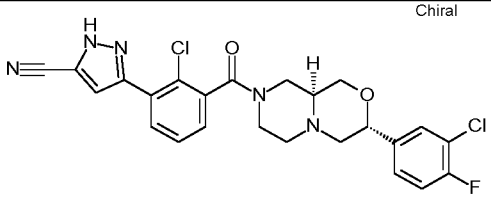
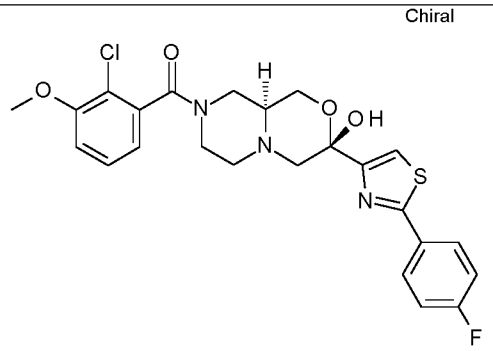
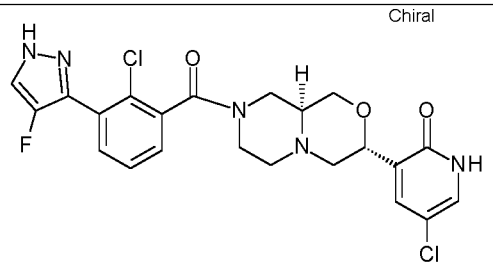
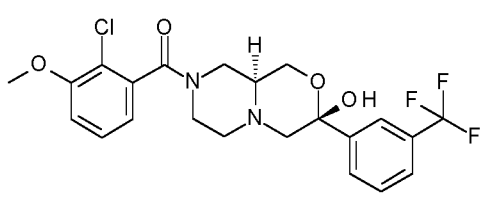
116	Chiral 	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-6-fluoro-3-methoxy-phenyl)methanone	**15.9**
117	Chiral 	4-[3-[(3R,9aS)-3-(5-chloro-2-oxo-1H-pyridin-3-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile	**17.4**
118	Chiral 	5-[3-[(3R,9aS)-3-(3,4-dichlorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-oxazol-2-one	**33.1**
119	Chiral 	[(3R,9aS)-3-hydroxy-3-[4-(trifluoromethyl)phenyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**34.7**

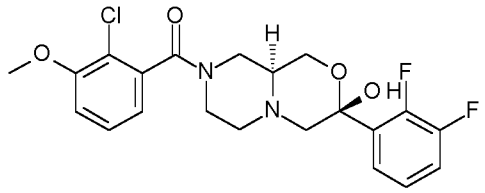
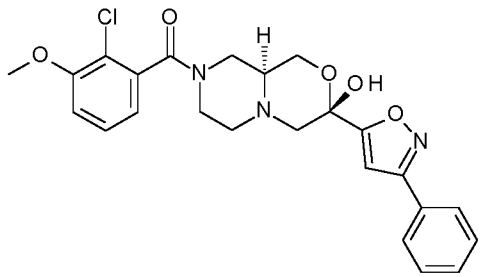
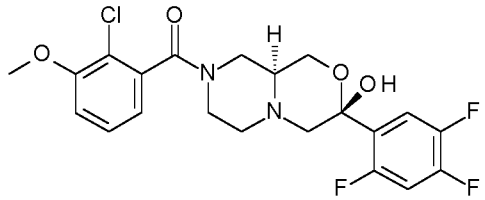
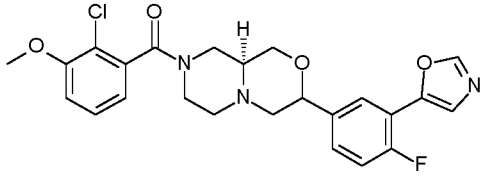
120	Chiral 	[(3R,9aS)-3-(4-chloro-3-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**42.4**
121	Chiral 	5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-oxazol-2-one	**46.4**
122	Chiral 	5-[3-[(3R,9aS)-3-(3,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-oxazol-2-one	**48.6**
123	Chiral 	4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-6-methyl-1H-pyridin-2-one	**55.7**

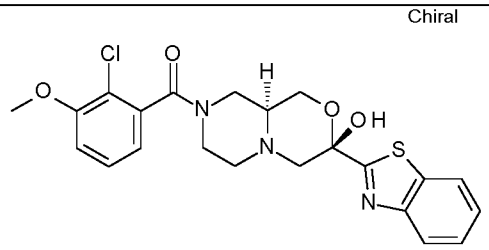
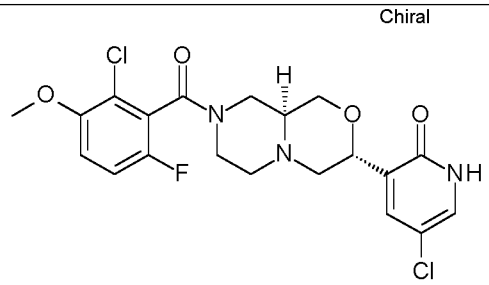
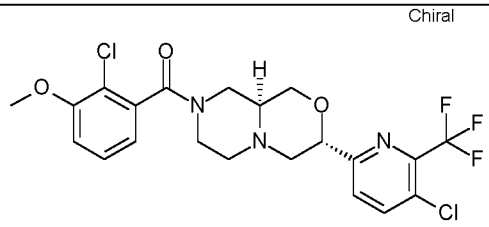
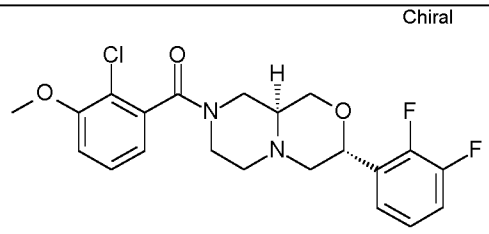
124	 Chiral	5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-6-methyl-1H-pyridin-2-one	**57.6**
125	 Chiral	[(3R,9aS)-3-(3-bromo-5-chloro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**82.8**
126	 Chiral	4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]piperazin-2-one	**96.2**
127	 Chiral	[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-isothiazol-4-yl-phenyl)methanone	**97.7**
128	 Chiral	[(3R,9aS)-3-(2,4,5-trifluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-	**102.6**

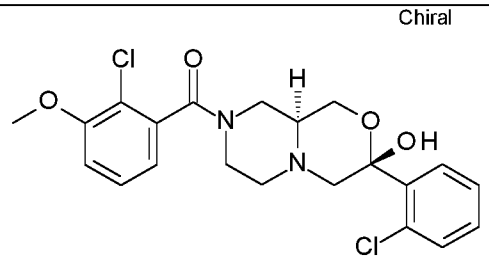
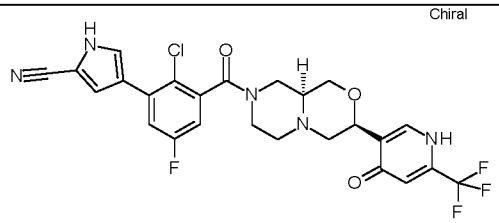
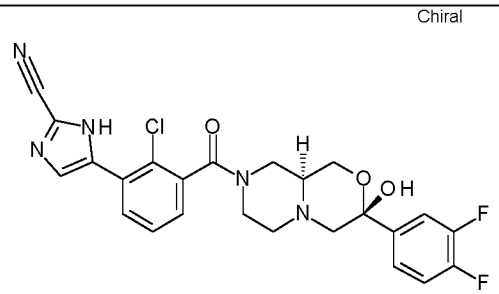
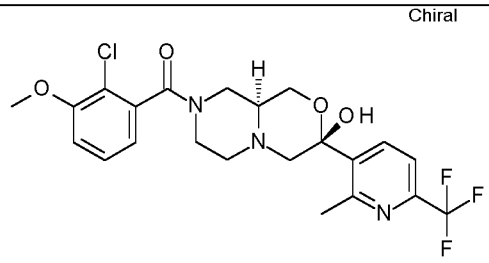
		chloro-3-methoxy-phenyl)methanone	
129		[(3R,9aS)-3-(2,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**112.9**
130		[(3R,9aS)-3-hydroxy-3-(2,3,4-trifluorophenyl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**117.1**
131		[(3S,9aS)-3-(4-bromo-5-methoxy-2-thienyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**118.1**
132		4-[3-[(3R,9aS)-3-[4-oxo-6-(trifluoromethyl)-1H-pyridin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile	**131.1**

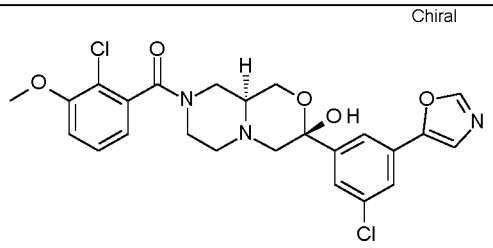
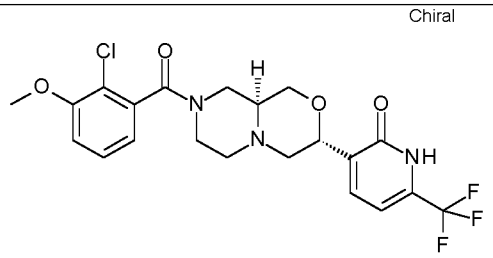
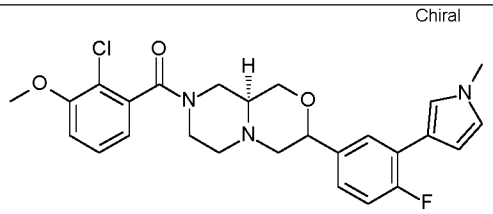
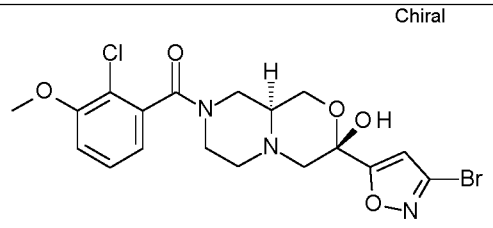
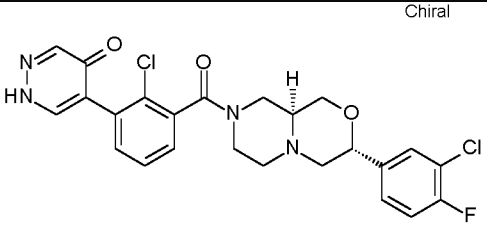
133	Chiral 	3-[(3R,9aS)-8-[2-chloro-5-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one	**141.8**
134	Chiral 	5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-3H-1,3,4-oxadiazol-2-one	**144.1**
135	Chiral 	5-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-3-chloro-2-fluoro-benzonitrile	**145.5**
136	Chiral 	3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one	**152.1**

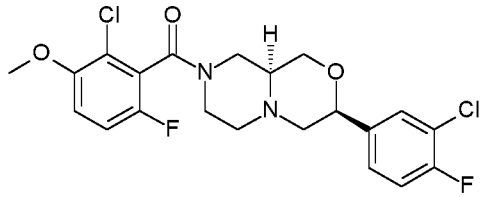
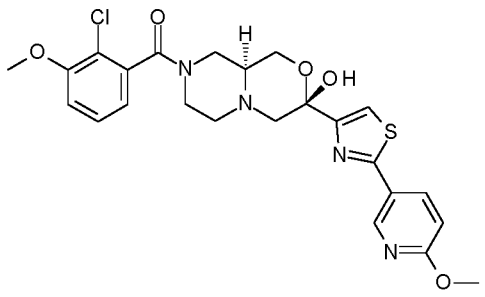
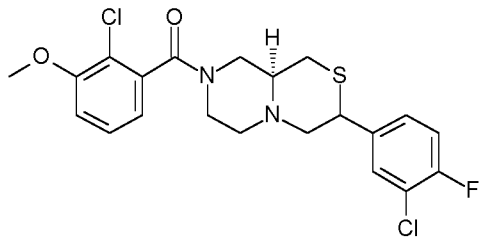
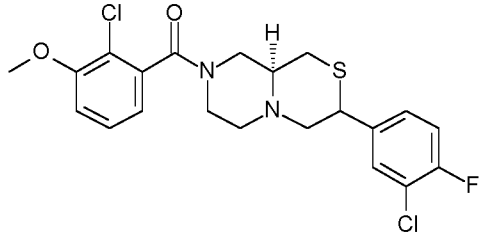
137	 Chiral	[(3R,9aS)-3-(3-chloro-4-oxazol-5-yl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**182.4**
138	 Chiral	3-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrazole-5-carbonitrile	**190.3**
139	 Chiral	[(3S,9aS)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**254.4**
140	 Chiral	3-[(3R,9aS)-8-[2-chloro-3-(4-fluoro-1H-pyrazol-3-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one	**277.0**
141	 Chiral	[(3R,9aS)-3-hydroxy-3-[3-(trifluoromethyl)phenyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-	**288.3**

		chloro-3-methoxy-phenyl)methanone	
142	Chiral 	[(3R,9aS)-3-(2,3-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**332.0**
143	Chiral 	[(3S,9aS)-3-hydroxy-3-(3-phenylisoxazol-5-yl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**348.3**
144	Chiral 	[(3R,9aS)-3-hydroxy-3-(2,4,5-trifluorophenyl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**354.8**
145	Chiral 	[(9aS)-3-(4-fluoro-3-oxazol-5-yl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**363.0**

146	 Chiral	[(3S,9aS)-3-(1,3-benzothiazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**378.0**
147	 Chiral	3-[(3R,9aS)-8-(2-chloro-6-fluoro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one	**384.9**
148	 Chiral	[(3S,9aS)-3-[5-chloro-6-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**426.1**
149	 Chiral	[(3R,9aS)-3-(2,3-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**467.8**

150	Chiral 	[(3R,9aS)-3-(2-chlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**546.3**
151	Chiral 	4-[3-[(3S,9aS)-3-[4-oxo-6-(trifluoromethyl)-1H-pyridin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyrrole-2-carbonitrile	**575.4**
152	Chiral 	5-[3-[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-imidazole-2-carbonitrile	**580.6**
153	Chiral 	[(3R,9aS)-3-hydroxy-3-[2-methyl-6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**704.7**

154	Chiral 	[(3R,9aS)-3-(3-chloro-5-oxazol-5-yl-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**769.0**
155	Chiral 	3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one	**780.1**
156	Chiral 	[(9aS)-3-[4-fluoro-3-(1-methylpyrrol-3-yl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**814.7**
157	Chiral 	[(3S,9aS)-3-(3-bromoisoxazol-5-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**849.3**
158	Chiral 	5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-	**1016.3**

		phenyl]-1H-pyridazin-4-one	
159	Chiral 	[(3S,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-6-fluoro-3-methoxy-phenyl)methanone	**1481.3**
160	Chiral 	[(3S,9aS)-3-hydroxy-3-[2-(6-methoxy-3-pyridyl)thiazol-4-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**1600.4**
161	Chiral 	[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**3.1**
162	Chiral 	[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone	**21.6**

In one aspect, the present invention provides compounds of formula (I) and their pharmaceutically acceptable salts or esters as described herein, wherein said compounds of formula (I) and their pharmaceutically acceptable salts or esters have IC_{50}'s for MAGL inhibition below 25 µM, preferably below 10 µM, more preferably below 5 µM as measured in the MAGL assay described herein.

In one embodiment, compounds of formula (I) and their pharmaceutically acceptable salts or esters as described herein have IC_{50} (MAGL inhibition) values between 0.000001 µM and 25 µM, particular compounds have IC_{50} values between 0.000005 µM and 10 µM, further particular compounds have IC_{50} values between 0.00005 µM and 5 µM, as measured in the MAGL assay described herein.

Using the Compounds of the Invention

In one aspect, the present invention provides compounds of formula (I) as described herein for use as therapeutically active substance.

In a further aspect, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of cancer in a mammal.

In one aspect, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

In a preferred embodiment, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal.

In a particularly preferred embodiment, the present invention provides the use of compounds of formula (I) as described herein for the treatment or prophylaxis of multiple sclerosis in a mammal.

In one aspect, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

In one embodiment, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of cancer in a mammal.

In one embodiment, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of neurodegenerative diseases in a mammal.

In one aspect, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

In a preferred embodiment, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal.

In a particularly preferred embodiment, the present invention provides compounds of formula (I) as described herein for use in the treatment or prophylaxis of multiple sclerosis in a mammal.

In one aspect, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of neurodegenerative diseases in a mammal.

In one embodiment, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of cancer in a mammal.

In a further aspect, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

In a preferred embodiment, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal.

In a particularly preferred embodiment, the present invention provides the use of compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis in a mammal.

In one aspect, the present invention provides a method for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a

mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or prophylaxis of neuroinflammation and/or neurodegenerative diseases in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

In one embodiment, the present invention provides a method for the treatment or prophylaxis of neurodegenerative diseases in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

In one aspect, the present invention provides a method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression and/or pain in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

In a preferred embodiment, the present invention provides a method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease and/or Parkinson's disease in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

In a particularly preferred embodiment, the present invention provides a method for the treatment or prophylaxis of multiple sclerosis in a mammal, which method comprises administering an effective amount of a compound of formula (I) as described herein to the mammal.

Pharmaceutical Compositions and Administration

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

The compounds of formula (I) and their pharmaceutically acceptable salts and esters can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or

suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

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

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

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

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

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

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

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

Examples

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

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

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

Abbreviations

AcOH = acetic acid, ACN = acetonitrile , Bn = benzyl, BINAP = (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), Boc = tert-butyloxycarbonyl, CAS RN = chemical abstracts registration number, Cbz = benzyloxycarbonyl, Cs_2CO_3 = cesium carbonate, CO = carbon monoxide, CuCl = copper(I) chloride, CuCN = copper(I) cyanide, CuI = copper(I) iodide, DAST = (diethylamino)sulfur trifluoride, DBU = 1,8-diazabicyclo[5,4,0]undec-7-ene, DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, DME = dimethoxyethane, DMEDA = N,N'-dimethylethylenediamine, DMF = N,N-dimethylformamide, DIPEA = N,N-diisopropylethylamine, dppf = 1,1 bis(diphenyl phosphino)ferrocene, EDC·HCl = N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride, EI = electron impact, ESI = electrospray ionization, EtOAc = ethyl acetate, EtOH = ethanol, h = hour(s), FA = formic acid, H_2O = water, H_2SO_4 = sulfuric acid, HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate, HBTU = O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate, HCl = hydrogen chloride, HOBt = 1-hydroxy-1H-benzotriazole, HPLC = high performance liquid chromatography, iPrMgCl = isopropylmagnesium chloride, I_2 = iodine, IPA = 2-propanol, ISP = ion spray positive (mode), ISN = ion spray negative (mode), K_2CO_3 = potassium carbonate, $KHCO_3$ = potassium bicarbonate, KI = potassium iodide, KOH = potassium hydroxide, K_3PO_4 = potassium phosphate tribasic, $LiAlH_4$ or LAH = lithium aluminium hydride, LiHMDS = lithium bis(trimethylsilyl)amide, LiOH = lithium hydroxide, mCPBA = meta-chloroperoxybenzoic acid, $MgSO_4$ = magnesium sulfate, min = minute(s), mL = milliliter,

MPLC = medium pressure liquid chromatography, MS = mass spectrum, nBuLi = n-butyllithium, $NaBH_3CN$ = sodium cyanoborohydride, NaH = sodium hydride, NBS = N-bromosuccinimide, $NaHCO_3$ = sodium hydrogen carbonate, $NaNO_2$ = sodium nitrite, $NaBH(OAc)_3$ = sodium triacetoxyborohydride, NaOH = sodium hydroxide, Na_2CO_3 = sodium carbonate, Na_2SO_4 = sodium sulfate, $Na_2S_2O_3$ = sodium thiosulfate, NBS = N-bromosuccinimide, nBuLi = n-butyllithium, NEt_3 = triethylamine (TEA), NH_4Cl = ammonium chloride, NMP = N-methyl-2-pyrrolidone, OAc = Acetoxy, T_3P = propylphosphonic anhydride, PE = petroleum ether, PG = protective group, Pd-C = palladium on activated carbon, $PdCl_2(dppf)$-CH_2Cl_2 = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0), $Pd(OAc)_2$ = palladium(II) acetate, $Pd(OH)_2$ = palladium hydroxide, $Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0), PTSA = p-toluenesulfonic acid, R = any group, RP = reverse phase, RT = room temperature, SFC = Supercritical Fluid Chromatography, S-PHOS = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TBAI = tetra butyl ammonium iodine, TEA = triethylamine, TES = triethylsilane, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMEDA = N,N,N',N'-tetramethylethylenediamine, T3P = 1-propanephosphonic anhydride, $ZnCl_2$ = zinc chloride, Hal = halogen.

Intermediate 1

(2-chloro-3-methoxy-phenyl)-[3-(hydroxymethyl)piperazin-1-yl]methanone

tert-butyl 4-(2-chloro-3-methoxybenzoyl)-2-(hydroxymethyl)piperazine-1-carboxylate (2.5 g, 6.5 mmol) was dissolved in 25 ml 4M HCl in dioxane and stirred for 90 min at room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in 0.1 M HCl(aq), extracted with ethylacetate, basified with 4M NaOH(aq) and extracted again with EtOAC to get the product. Due to the high polarity of the product, an excess of ethyl acetate was used and the extraction was done several times to get the product out of the basic aqueous phase. The organic fractions were combined, dried over Na2SO4 and concentrated *in vacuo* to yield 1.295 g Intermediate 1. No further purification. ESI(MS) m/z = 285.3 $[M+H]^+$

a) tert-butyl 4-(2-chloro-3-methoxybenzoyl)-2-(hydroxymethyl)piperazine-1-carboxylate

A mixture of 2-chloro-3-methoxybenzoic acid (1.29 g, 6.94 mmol), tert-butyl 2-(hydroxymethyl)piperazine-1-carboxylate (1500 mg, 6.94 mmol) and HATU (2.51 g, 6.59 mmol) was dissolved in 25 ml ethyl acetate. DIPEA (1.79 g, 2.42 ml, 13.9 mmol) was added to the solution and the reaction mixture was stirred at rt for 2 hr. The reaction mixture was washed twice with sat. $NaHCO_3$, dried over Na_2SO_4, filtered, evaporated and further dried on the high vacuum. The resultant crude residue was purified by flash column chromatography (silica 50g, 40 ml/min EtOAc/Heptan 0-100%). The product fractions were combined and evaporated to yield 2.5 g of the desired product. ESI(MS) m/z = 329.2 $[M-56]^+$

Intermediate 1S

(2-chloro-3-methoxy-phenyl)-[(3S)-3-(hydroxymethyl)piperazin-1-yl]methanone

Intermediate 1S was synthesized as described for Intermediate 1, starting from enantiopure tert-butyl (S)-2-(hydroxymethyl)piperazine-1-carboxylate.

Intermediate 2

(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazine

tert-butyl (3R,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (2.52 g, 6.8 mmol) was dissolved in HCl 4M in dioxan (17 ml, 68 mmol) and the solution was stirred overnight at room temperature. The solvents were removed *in vacuo*, the residue was dissolved in 1M aq. HCl and washed with EtOAc. The aq. phase was basified with 4M NaOH, became turbid and extracted with EtOAc. The organic phases were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. 1.52 g of Intermediate 2 were obtained as a waxy yellow solid and used directly for the next step. ESI(MS) m/z = 271.2 $[M+H]^+$

a) 2-(3-chloro-4-fluoro-phenyl)oxirane

2-chloro-1-fluoro-4-vinylbenzene (2.97 g, 19 mmol) was dissolved in DCM (100 ml) at 0 °C then 3-chlorobenzoperoxoic acid (4.91 g, 28.5 mmol) was added and the mixture was slowly warmed up to room temperature overnight. The reaction mixture was then washed once each with saturated aq. Na2S2O3, NaHCO3, and brine. The organic layer was dried over MgSO4, filtered, and evaporated to dryness. The crude material was purified by flash

chromatography (silica gel, 100 g, 0% to 70% EtOAc in heptane) to yield in the product as a colorless liquid (2.57 g). The compound did not ionize on ESI(MS).

b) tert-butyl (3S)-4-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

2-(3-chloro-4-fluorophenyl)oxirane (1.285 g, 7.45 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (2.42 g, 11.2 mmol) were dissolved in ethanol (20 mL) then placed in a sealed tubes and heated in the microwave at 150°C for 40min. The solvent was evaporated, the crude material was purified by flash chromatography (silica gel, 100 g, 10% to 100% EtOAc (+10% EtOH) in Heptane) to yield 2.57 g of desired product as a light yellow oil. ESI(MS) m/z = 389.2 $[M+H]^+$

c) tert-butyl (3R,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl (3S)-4-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (5.14 g, 13.2 mmol) was dissolved in toluene anhydrous (50 ml) , the solution was transferred to a argon-purged, flame dried flask and the solution was further degassed with argon, subsequently 2-(tributyl-l5-phosphaneylidene)acetonitrile (5.58 g, 6.07 ml, 23.1 mmol) was added in one portion. The reaction mixture was heated for 1.5 h at 100°C. The reaction mixture was extracted with EtOAc / sat. $NaHCO_3$, combined organic layers washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 100 g, 0% to 100% EtOAc in heptane) 2 times. The product fractions were combined and evaporated to yield 2.53g of the desired product as a light brown oil. ESI(MS) m/z = 371.2 $[M+H]^+$. The desired trans isomer (3R,9aS) was the major product (ratio 4:1)

Intermediate 3

(9aS)-3-(3-bromo-4-fluoro-phenyl)-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazine

tert-butyl (S)-3-(3-bromo-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (1.78 g, 4.29 mmol) was dissolved in 21.4 ml 4M HCl in dioxane and stirred for 120 min at room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in 0.1 M HCl(aq), extracted with ethylacetate, basified with 4M NaOH(aq) and extracted again with EtOAC to get the product. The organic fractions were combined,

dried over Na_2SO_4 and concentrated *in vacuo* to yield 1.3 g Intermediate 3. No further purification. ESI(MS) m/z = 315.1 $[M+H]^+$

a) tert-butyl (S)-4-(2-(3-bromo-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

2-(3-bromo-4-fluorophenyl)oxirane (1.0 g, 4.6 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1.49 g, 6.91 mmol) were dissolved in ethanol (17 mL) then placed in a sealed tubes and heated in the microwave at 130°C for 80 min and for 25 min at 150°C to complete the reaction. The solvent was evaporated, the crude material was purified by flash chromatography (silica gel, 120 g, 0% to 60% EtOAc (+10% EtOH) in Heptane) to yield 1.57 g of desired product as a colorless oil. ESI(MS) m/z = 433.1 $[M+H]^+$

b) tert-butyl (S)-3-(3-bromo-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl (S)-4-(2-(3-bromo-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (3.2 g, 7.38 mmol) was dissolved in toluene anhydrous (50 ml) , the solution was transferred to a argon-purged, flame dried flask and the solution was further degassed with argon, subsequently 2-(tributyl-l5-phosphaneylidene)acetonitrile (3.12 g, 3.39 ml, 12.9 mmol) was added in one portion. The reaction mixture was heated for 1.5 h at 100°C. The reaction mixture was extracted with EtOAc / sat. $NaHCO_3$, combined organic layers washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 100 g, 0% to 60% EtOAc in heptane). The product fractions were combined and evaporated to yield 1.8 g of the desired product as a waxy yellow solid. ESI(MS) m/z = 415.2 $[M+H]^+$

Intermediate 4

(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazine

tert-butyl 3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (350 mg, 944 µmol) was dissolved in 4.72 ml 4M HCl in dioxane and stirred for 120 min at room temperature. The solvent was removed *in vacuo*, and the residue was

dissolved in 0.1 M HCl(aq), extracted with ethylacetate, basified with 4M NaOH(aq) and extracted again with EtOAC to get the product. The organic fractions were combined, dried over Na_2SO_4 and concentrated *in vacuo* to yield 243 mg Intermediate 4 as a waxy, orange solid. No further purification. ESI(MS) m/z = 285.2 $[M+H]^+$

a) tert-butyl 4-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)-3-methylpiperazine-1-carboxylate

2-(3-chloro-4-fluorophenyl)oxirane (843 mg, 3.91 mmol) and tert-butyl 3-(hydroxymethyl)-3-methylpiperazine-1-carboxylate (1 g, 3.91 mmol) were dissolved in Ethanol (17 ml) then placed in a sealed tubes and microwaved at 140°C for 115 min and 150°C for 20 min. Almost complete conversion. The solvent was evaporated and the residue was purified by flash chromatography (120g SiO_2, 0%-80% ethyl acetate in heptane).). The product fractions were combined and evaporated to yield 950 mg of desired product as a colorless, waxy solid. ESI(MS) m/z = 403.4 $[M+H]^+$

b) tert-butyl 3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl 4-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)-3-methylpiperazine-1-carboxylate (950 mg, 2.36 mmol was dissolved in toluene anhydrous (14.3 ml) , the solution was transferred to a argon-purged, flame dried flask and the solution was further degassed with argon, subsequently 2-(tributyl-l5-phosphaneylidene)acetonitrile (1.14 g, 1.24 ml, 4.72 mmol) was added in one portion. The reaction mixture was heated for 5 h at 100°C. The reaction mixture was extracted with EtOAc / sat. $NaHCO_3$, combined organic layers washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 70% EtOAc in heptane). The product fractions were combined and evaporated to yield 340 mg of the desired product as a viscous, yellow oil. ESI(MS) m/z = 385.3 $[M+H]^+$

Intermediate 5

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3S)-3-(hydroxymethyl)piperazin-1-yl]methanone

tert-butyl (S)-4-(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl)-2-(hydroxymethyl)piperazine-1-carboxylate (0.151 g, 344 µmol) was combined with 4 M HCl in dioxane (1.29 ml, 5.16 mmol) to give a colorless solution. The reaction mixture was stirred at room temperature for 2 hr. It was then concentrated, dissolved in 10 ml sat. $NaHCO_3$ and extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield in the target compound as a colorless oil (117 mg). ESI(MS) m/z = 339.1 $[M+H]^+$

a) methyl 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoate

Methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (849 mg, 2.86 mmol), 4-bromo-3-fluoro-1H-pyrazole (350 mg, 2.12 mmol), $(APhos)_2PdCl_2$ (150 mg, 212 µmol) and K_2CO_3 (880 mg, 6.36 mmol) were dispersed in 15 ml dioxane and 4 ml water and degassed with argon. It was then reacted in the microwave (90 °C, 30 min) before it was poured into sat. $NaHCO_3$ and extracted into EtOAc twice, dried over Na_2SO_4 and concentrated in vacuo. The crude was then purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in heptane). The product fractions were combined and evaporated to yield 201 mg of the desired product as a yellow solid. ESI(MS) m/z = 255.1 $[M+H]^+$

b) 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid

To a solution of methyl 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoate (326 mg, 1.28 mmol) in THF (10 ml) was added 1 M aq. LiOH (3.84 ml, 3.84 mmol) and the resulting mixture was stirred at room temperature overnight. The mixture was then acidified with 1 M aq. HCl and extracted with 2-MeTHF twice, dried over Na_2SO_4, filtered and concentrated *in vacuo* to result in 304 mg the desired product as a yellow solid. ESI(MS) m/z = 241.1 $[M+H]^+$

c) tert-butyl (S)-4-(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl)-2-(hydroxymethyl)piperazine-1-carboxylate

2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (300 mg, 1.25 mmol), tert-butyl (S)-2-(hydroxymethyl)piperazine-1-carboxylate (200 mg, 0.925 mmol) and HATU (527 mg, 1.39 mmol) were dissolved in DMF (5 ml). DIPEA (359 mg, 2.77 mmol) was added and the reaction stirred at room temperature for 2.5 hr. Then the reaction mixture was diluted with EtOAc, washed twice with sat. $NaHCO_3$ and the aq. phase was backexracted twice with EtOAc. The combined org. phases were dried over Na_2SO_4, filtered, mixed with silica

gel and concentrated *in vacuo*. It was then purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in DCM) and then reverse phase column chromatography (HPLC Prep Method F). The product was obtained as a white solid (151 mg). ESI(MS) m/z = 437.3 $[M-H]^-$

Intermediate 6

(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol

tert-butyl (3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (1 eq, 2.356 g) was mixed with 27 ml 4 M HCl in dioxane and 10 ml dioxane and the resulting greenish slurry stirred at room temperature. After 2.5 hr, the mixture was basified with 4 M aq. NaOH and extracted twice into EtOAc, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a yellow-white foam (1.75 g) and used without further purification for the next step. ESI(MS) m/z = 287.1 $[M+H]^+$

a) *tert-butyl (3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate*

tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1 eq, 1.52 g) and DIPEA (1.3 eq, 1.6 ml) were dissolved in 25 ml THF. 2-bromo-1-(3-chloro-4-fluorophenyl)ethan-1-one (1 eq, 1.77 g) in 5 ml THF was added dropwise over 10 min at room temperature. After 20 hr, the crude was filtered and then adsorbed on silica, concentrated *in vacuo* and purified by silica column chromatograhy (two times 70 g, EtOAc in Hept 0% to 70%). The product was obtained as a white-yellow foam (2.356 g). ESI(MS) m/z = 387.2 $[M+H]^+$

Intermediate 7

2-fluoro-5-[rac-(9aS)-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazin-3-yl]benzonitrile

tert-butyl (9aS)-3-(3-cyano-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (0.294 g, 813 µmol, impure) was dissolved in 0.5 mL 4 M HCl in dioxane and stirred at room temperature for one hour. Subsequently, it was concentrated *in vacuo* and used directly in the next step without further purification. ESI(MS) m/z = 262.2 $[M+H]^+$

a) *2-fluoro-5-vinylbenzonitrile*

5-bromo-2-fluorobenzonitrile (500 mg, 2.5 mmol), potassium trifluoro(vinyl)borate (402 mg, 3 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (102 mg, 125 µmol) and triethylamine (253 mg, 2.5 mmol) were dispersed in 12 ml ethanol, degassed with argon and reacted in the microwave (120 °C, 20 min). The mixture was then concentraed *in vacuo*, diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* before it was purified by silica column chromatography (50 g, EtOAc in Hept 0% to 50%). The product was obtained as a white solid (312 mg). Product confirmed by 1H-NMR.

b) *2-fluoro-5-(oxiran-2-yl)benzonitrile*

2-fluoro-5-vinylbenzonitrile (0.15 g, 1.02 mmol) was dispersed in 2 ml water and 1 ml dioxane under heavy stirring. NBS (218 mg, 1.22 mmol) was dissolved in 2 ml water and 1 ml dioxane and added to the mixture dropwise over 15 min. The reaction mixture was stirred at room temperature overnight. Then, the mixture was cooled to 0 °C and 4 M aq. NaOH (765 µl, 3.06 mmol) was added dropwise. After one hour, the reaction mixture was poured into 15 ml sat. aq. $NaHCO_3$ and extracted with EtOAc (2 x 25 mL). The organic layers were combined, washed with water and then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The target molecule was obtained as a yellow oil (153 mg) and used directly for the next step. Product confirmed by 1H-NMR.

c) *tert-butyl (3R)-4-(2-(3-cyano-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate*

2-fluoro-5-(oxiran-2-yl)benzonitrile (153 mg, 938 µmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (223 mg, 1.03 mmol) were dissolved in MeOH (4 ml) and reacted in the microwave (60 min, 120 °C). It was then concentrated *in vacuo* and purified by silica column chromatography (20 g, MeOH in DCM 0% to 10%) to yield in 264 mg of the target compound as a yellow oil. ESI(MS) m/z = 380.2 $[M+H]^+$

d) *tert-butyl (9aR)-3-(3-cyano-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate*

tert-butyl (3S)-4-(2-(3-cyano-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (0.260 g, 685 µmol) and

(cyanomethylene)tributylphosphorane (331 mg, 1.37 mmol were dissolved in dry toluene (5 ml), degassed with argon and then reacted at 100 °C for 2 hr. The solution was then concentrated *in vacuo* and purified by silica column chromatography (20 g, MeOH in DCM 0% to 10%). The desired product was obtained as a light brown oil together with residual tributylphosphine oxide (301 mg). It was used in the next step without further purification ESI(MS) m/z = 362.2 $[M+H]^+$

Intermediate 8

(3R,9aS)-3-[6-(trifluoromethyl)-3-pyridyl]-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol

tert-butyl (7R,9aR)-7-hydroxy-7-(6-(trifluoromethyl)pyridin-2-yl)octahydro-2H-pyrido[1,2-a]pyrazine-2-carboxylate (150 mg, 0.372 mmol) was mixed with 6 ml 4 M HCl in dioxane and 5 ml dioxane and stirred at room temperature. After 4 hr, the mixture was concentrated *in vacuo*, basified with 4 M aq. NaOH, diluted with brine and extracted into excess EtOAc and then 2-MeTHF. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as an impure orange oil (165 mg). It was used in the next step without further purification. ESI(MS) m/z = 304.2 $[M+H]^+$

a) *2-bromo-1-(6-(trifluoromethyl)pyridin-2-yl)ethan-1-one*

1-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-on (224 mg, 1.19 mmol), bromine (61 ul, 1.19 mmol) and acetic acid (1.2 ml) were mixed in a pressure tube and reacted at 75 °C for one hour upon which the red solution turned into a yellow suspension. It was concentrated *in vacuo* and purified by silica column chromatography (20 g, EtOAc in Heptane 0% to 40%). The target compound was isolated as a white solid (240 mg). ESI(MS) m/z = 270.0 $[M+H]^+$

b) tert-butyl (7R,9aR)-7-hydroxy-7-(6-(trifluoromethyl)pyridin-2-yl)octahydro-2H-pyrido[1,2-a]pyrazine-2-carboxylate

tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (97 mg, 0.45 mmol) and DIPEA (97 ul, 0.55 mmol) were dissolved in 2 ml THF and cooled to 0 °C. 2-bromo-1-(6-(trifluoromethyl)pyridin-2-yl)ethan-1-one (114 mg, 0.425 mmol) in 1.5 mL THF was added dropwise over 10 min. After 30 min, the solution was warmed up to room

temperature and after 4 hr, it was diluted with water and extracted into EtOAc. The aq. phase was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica column chromatography (20 g, EtOAc in Hept 0% to 70%). The product was obtained as a white solid (150 mg). ESI(MS) m/z = 404.2 $[M+H]^+$

Intermediate 9

(3S,9aS)-3-[5-(trifluoromethyl)-2-pyridyl]-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol

Synthesis according to intermediate 8. ESI(MS) m/z = 304.2 $[M+H]^+$

a) *tert-butyl (3S,9aS)-3-hydroxy-3-(5-(trifluoromethyl)pyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate*

2-chloro-1-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-one (473 mg, 2.12 mmol), tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (503 mg, 2.33 mmol) and DIPEA (480 ul, 2.75 mmol) were dissolved in 10 mL dry THF and stirred at 50 °C overnight and then at 60 °C for 24 hr. Subsequently, it was concentrated *in vacuo*, diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* again. The crude was purified by silica column chromatography (50 g, EtOAc in Hept 0% to 80%). The target compound was obtained as an off-white solid (437 mg). ESI(MS) m/z = 404.2 $[M+H]^+$

Intermediate 10

(3R,9aS)-3-(3,4-difluorophenyl)-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol hydrochloride

Synthesis according to Intermediate 8 starting from 2-bromo-1-(3,4-difluorophenyl)ethan-1-one (500 mg, 2.13 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (506 mg, 2.34 mmol). Intermediate 10 was obtained as a light blue solid (596 mg, 1.94 mmol). ESI(MS) m/z = 271.2 $[M+H]^+$

Intermediate 11

(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazine

tert-butyl (9aS)-3-(6-(trifluoromethyl)pyridazin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (266 mg, ca. 50% purity, 0.34 mmol) was dissolved in 1.5 mL dioxane and 3 mL 4 M HCl in dioxane and stirred at room temperature. After 90 min, the red mixture was concentrated *in vacuo* and purified by reverse phase column chromatography (HPLC Prep Method E). The desired diastereomer was obtained as a white solid (50 mg). ESI(MS) m/z = 289.2 $[M+H]^+$

a) *3-(trifluoromethyl)-6-vinylpyridazine*

Synthesis according to Intermediate 7 a), starting from 3-chloro-6-(trifluoromethyl)pyridazine (800 mg, 4.38 mmol). ESI(MS) m/z = 175.0 $[M+H]^+$

b) *3-(oxiran-2-yl)-6-(trifluoromethyl)pyridazine*

3-(trifluoromethyl)-6-vinylpyridazine (592 mg, 3.4 mmol) was dispersed in 6 ml dioxane and 6 ml water and cooled to 0 °C. NBS (726 mg, 4.08 mmol) dissolved in 6 ml dioxane and 12 ml water was added dropwise over 15 min and the flask was warmed up to room temperature and 2 hr later, it was cooled down to 0 °C again and NaOH (2.55 mL of a 4 M aq. solution, 10.2 mmol) was added dropwise and after 30 min it was warmed up to room temperature. After another 30 min, the mixture was diluted with sat. aq. $NaHCO_3$ solution containing additional NaCl and was extracted three times into EtOAc before being dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by silica column chromatography (50 g, EtOAc in heptane, 0% to 50%) to yield in 272 mg of the product as a light brown solid. ESI(MS) m/z = 191.0 $[M+H]^+$

c) *tert-butyl (3S)-4-(2-hydroxy-2-(6-(trifluoromethyl)pyridazin-3-yl)ethyl)-3-(hydroxymethyl)piperazine-1-carboxylate*

Synthesis according to Intermediate 7 c). ESI(MS) m/z = 407.2 $[M+H]^+$

d) *tert-butyl (9aS)-3-(6-(trifluoromethyl)pyridazin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate*

Synthesis according to Intermediate 7 d). ESI(MS) m/z = 389.2 $[M+H]^+$

Intermediate 12

3-[(3R,9aS)-3-hydroxy-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one

tert-butyl (3R,9aS)-3-hydroxy-3-(2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (527 mg, 70% purity, 0.88 mmol) was mixed with 1.6 ml dioxane and 4.4 ml 4 M HCl in dioxane and stirred at room temperature for two hours. The mixture was concentrated *in vacuo*, basified with 4 M aq. NaOH, diluted with brine and extracted into excess EtOAc, dried over sodium sulfate, filtered and concentrated *in vacuo*. It was then purified by reverse phase column chromatography (HPLC Prep Method E). The product was obtained as a light yellow solid (22.3 mg). ESI(MS) m/z = 320.1 $[M+H]^+$

a) *tert-butyl (3R,9aS)-3-hydroxy-3-(2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate*

Synthesis according to Intermediate 8 b), starting from 3-(2-bromoacetyl)-6-(trifluoromethyl)pyridin-2(1H)-one (400 mg, 1.41 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (335 mg, 1.55 mmol). ESI(MS) m/z = 420.3 $[M+H]^+$

Intermediate 13

2-chloro-3-(5-methyl-1H-pyrazol-4-yl)benzoic acid

i) In a microwave vial, methyl 3-bromo-2-chlorobenzoate (400 mg, 1.6 mmol), 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 2.4 mmol) and K_3PO_4 (4.81 ml of an 1 M aqueous solution, 4.81 mmol) in THF (3.2 ml) was degassed with argon. XPhos-Pd-G2 (126 mg, 160 µmol) was added and the mixture was heated at 100 °C for 2 hr before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 35-90% in 40 min) to yield the desired product as an orange waxy solid (122 mg, 30%). ESI(MS) m/z = 251.2 $[M+H]^+$

ii) To a solution of methyl 2-chloro-3-(5-methyl-1H-pyrazol-4-yl)benzoate (167 mg, 666 µmol) in THF (3.5 ml) was added a 1 M aqueous solution of LiOH (1.33 ml, 1.33 mmol), and the resulting mixture was stirred at 22 °C overnight. It was then acidified with 1 M HCl and the aqueous layer extracted with 2-MeTHF, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as an orange viscouos oil (142 mg, 90%). ESI(MS) m/z = 237.2 $[M+H]^+$

Intermediate 14

2-chloro-3-(4-methyl-3-pyridyl)benzoic acid

i) In a microwave vial, methyl 3-bromo-2-chlorobenzoate (200 mg, 802 µmol), (4-methylpyridin-3-yl)boronic acid (137 mg, 1 mmol) and K_2CO_3 (276 mg, 2.4 mmol) were mixed with dioxane (6 ml) and degassed with argon. (A-^{ta}Phos)$_2PdCl_2$ (56.8 mg, 80.2 µmol) was added and the mixture heated at 80 °C for 15 hr. After concentration *in vacuo*, the residue was purified via flash chromatography (SiO_2, Hep/EtOAc 30-90% in 30 min) to yield the desired product as a yellow waxy solid (105 mg, 50%). ESI(MS) m/z = 262.2 $[M+H]^+$

ii) To a solution of methyl 2-chloro-3-(4-methylpyridin-3-yl)benzoate (120 mg, 459 µmol) in THF (2.5 ml) was added a 1 M aqueous solution of LiOH (923 µl, 923 µmol) and the resulting mixture was stirred at 22 °C overnight. 3 mL toluene were added and the mixture concentrated *in vacuo*. No yield was calculated and it was used for the next step without further purification. ESI(MS) m/z = 248.1 $[M+H]^+$

Intermediate 15

2-chloro-3-(3-methyl-4-pyridyl)benzoic acid

Synthesis according to intermediate 14. ESI(MS) m/z = 248.1 $[M+H]^+$

Intermediate 16

2-chloro-3-(pyridazin-4-yl)benzoic acid

Synthesis according to intermediate 14. ESI(MS) m/z = 235.2 $[M+H]^+$

Intermediate 17

2-chloro-3-(pyridin-2-yl)benzoic acid

i) In a microwave vial, methyl 3-bromo-2-chlorobenzoate (200 mg, 802 µmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (329 mg, 1.6 mmol), Cs_2CO_3 (522 mg, 1.6 mmol) and copper (I) chloride (79.4 mg, 802 µmol) were dissolved in DMF (8.02 ml) and degassed with argon. XPhos Pd G2 (44.2 mg, 56.1 µmol) was added and the mixture was reacted at 100 °C for 16 hr before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 30-90% in 30 min) to yield the desired product as a light yellow waxy solid (35 mg, 18%). ESI(MS) m/z = 248.2 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 234.1 $[M+H]^+$

Intermediate 18

2-chloro-3-(pyridazin-3-yl)benzoic acid

i) In a microwave vial, methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (215 mg, 725 µmol), 3-chloropyridazine hydrochloride (230 mg, 1.52 mmol) and K_2CO_3 (411 mg, 2.97 mmol) were mixed with dioxane (4.5 ml) and degassed with argon. (A-taPhos)$_2$PdCl$_2$ (51.3 mg, 72.5 µmol) was added and the mixture reacted at 80 °C for 80 min before it was concentrated *in vacuo* and and purified via flash chromatography (SiO_2, Hep/EtOAc 30-100% in 30 min) to yield the desired product as a light yellow waxy solid (24 mg, 13%). ESI(MS) m/z = 249.1 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 235.1 $[M+H]^+$

Intermediate 19

2-chloro-3-(4-methylpyridazin-3-yl)benzoic acid

i) In a microwave vial, methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (219 mg, 739 µmol), 3-chloro-4-methylpyridazine (95 mg, 739 µmol) and K_2CO_3 (204 mg, 1.48 mmol) was mixed with toluene (2.1 ml) and water (0.23 mL) and degassed with argon. (A-taPhos)$_2$PdCl$_2$ (52.3 mg, 73.9 µmol) was added and the mixture was reacted at 120 °C for 30 min before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 30-100% in 35 min) to yield the desired product as a yellow waxy solid (30 mg, 16%). ESI(MS) m/z = 263.2 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 249.1 $[M+H]^+$

Intermediate 20

2-chloro-3-(5-methylpyrimidin-4-yl)benzoic acid

i) A microwave vial was charged with methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (200 mg, 674 µmol), 4-chloro-5-methylpyrimidine (104 mg, 809 µmol) and K_2CO_3 (186 mg, 1.35 mmol), toluene (2.25 ml) and was degassed with argon. (A-^{ta}Phos)$_2$PdCl$_2$ (47.8 mg, 67.4 µmol) was added and the mixture was heated at 120° C for 30 min. The mixture was concentrated *in vacuo*. The residue was purified via

flash chromatography (SiO_2, DCM, 0-10% MeOH) resulting in not completely pure product. Repurification with gradient of Hep/EtOAc 0-60% lead to the the desired product as a yellow oil (130 mg, 73%). ESI(MS) m/z = 263.2 $[M+H]^+$

ii) According to intermediate 13. ESI(MS) m/z = 249.1 $[M+H]^+$

Intermediate 21

2-chloro-3-(1H-imidazol-4-yl)benzoic acid

i) In a microwave vial, methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (300 mg, 1.01 mmol), 4-iodo-1H-imidazole (196 mg, 1.01 mmol) and K_2CO_3 (2.53 ml, 3.03 mmol) were mixed with dioxane (7.5 ml) and water (2.5 ml) and degassed with argon. $(APhos)_2PdCl_2$ (71.6 mg, 101 µmol) was added and the mixture reacted at 115 °C for 30 min before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, DCM/MeOH 0-10% in 35 min) and then reverse phase column chromatography to yield the desired product as a white solid (60.1 mg, 25%). ESI(MS) m/z = 237.2 $[M+H]^+$

ii) According to intermediate 13. ESI(MS) m/z = 223.1 $[M+H]^+$

Intermediate 22

2-chloro-3-(3-methylpyridin-2-yl)benzoic acid

i) According to intermediate 19 i). ESI(MS) m/z = 262.2 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 248.2 $[M+H]^+$

Intermediate 23

2-chloro-3-(1H-pyrazol-4-yl)benzoic acid

i) In a microwave vial, methyl 3-bromo-2-chlorobenzoate (300 mg, 1.2 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (350 mg, 1.8 mmol) and K_2CO_3 (3.01 ml, 3.61 mmol) were mixed with dioxane (9 ml) and water (3 ml) and degassed with argon. $(APhos)_2PdCl_2$ (85.1 mg, 120 µmol) was added and the mixture was reacted at 115 °C for 30 min before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, DCM/MeOH 0-8% in 35 min) and then reverse phase column chromatography to yield the desired product as a white solid (34 mg, 12%). ESI(MS) m/z = 237.2 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 223.1 $[M+H]^+$

Intermediate 24

2-chloro-3-(1,5-dimethyl-1H-pyrazol-4-yl)benzoic acid

i) In a microwave vial, methyl 2-chloro-3-(5-methyl-1H-pyrazol-4-yl)benzoate (as described in intermediate 13 i), 70 mg, 279 µmol) and Cs_2CO_3 (136 mg, 419 µmol) were dissolved in DMF (2 ml), treated with methyl iodide (198 mg, 1.4 mmol) and then reacted at 100 °C for 15 min. The reaction was subsequently diluted with saturated aqueous ammonium chloride solution and extracted into ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 0-100%) to yield the desired product as a yellow oil (23 mg, 31%). ESI(MS) m/z = 265.2 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 251.2 $[M+H]^+$

Intermediate 25

2-chloro-3-(3-methylisoxazol-4-yl)benzoic acid

i) In a microwave vial, methyl 3-bromo-2-chlorobenzoate (200 mg, 802 µmol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (251 mg, 1.2 mmol) and K_3PO_4 (1.6 ml of a 1 M aqueous solution, 1.6 mmol) were mixed with THF (1.6 ml) and degassed with argon. XPhos-Pd-G2 (44.2 mg, 56.1 µmol) was added and the mixture reacted at 60 °C for 1 hr before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 0-40% in 35 min) to yield the desired product as a yellow oil (171 mg, 85%). ESI(MS) m/z = 252.1 $[M+H]^+$

ii) According to intermediate 13 ii). ESI(MS) m/z = 238.1 $[M+H]^+$

Intermediate 26

2-chloro-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzoic acid

i) In a pressure vial, methyl 3-bromo-2-chlorobenzoate (250 mg, 1 mmol), 2-oxa-6-azaspiro[3.3]heptane (199 mg, 2 mmol), K_3PO_4 (425 mg, 2 mmol), $Pd_2(dba)_3$ (91.8 mg, 100 µmol) and DavePhos (59.2 mg, 150 µmol) were mixed with toluene (4 ml) and then degassed with argon. It was then reacted at 100 °C for 16 hr before it was concentrated *in*

vacuo and purified via flash chromatography (SiO_2, Hep/EtOAc 0-45%) to yield the desired product as a dark red oil (210 mg, 78%). ESI(MS) m/z = 268.3 $[M+H]^+$

ii) To a solution of methyl 2-chloro-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzoate (210 mg, 784 µmol) in THF (5 ml) was added a 1 M aqueous solution of LiOH (1.57 ml, 1.57 mmol), and the resulting mixture was stirred at 22 °C overnight and then at 50 °C for 4 hr. The mixture was acidified with 1 M HCl and the aqueous layer extracted with 2-MeTHF, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as light yellow solid, 233 mg (94%, 80% purity). Used directly in the next step. ESI(MS) m/z = 254.2 $[M+H]^+$

Intermediate 27

2-chloro-3-morpholinobenzoic acid

i) According to intermediate 26, i). ESI(MS) m/z = 256.2 $[M+H]^+$

ii) According to intermediate 26, ii). ESI(MS) m/z = 242.2 $[M+H]^+$

Intermediate 28

2-chloro-3-(1H-1,2,3-triazol-4-yl)benzoic acid

Ester cleavage was performed according to intermediate 13, ii). ESI(MS) m/z = 224.1 $[M+H]^+$

a) methyl 2-chloro-3-((trimethylsilyl)ethynyl)benzoate

Methyl 3-bromo-2-chlorobenzoate (800 mg, 3.21 mmol), $PdCl_2$(DPPF) (262 mg, 321 µmol) and copper (I) iodide (30.5 mg, 160 µmol) were dissolved in dry DMF (2 ml) upon which diethylamine (11.7 g, 160 mmol) was added. The reaction mixture was degassed with argon and after the addition of ethynyltrimethylsilane (472 mg, 4.81 mmol) it was reacted at 120 °C for 30 min under microwave irradiation. It was then concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 0-20%) to yield the desired product as a yellow liquid (580 mg, 68%). Product confirmed by 1H-NMR.

b) methyl 2-chloro-3-ethynylbenzoate

Methyl 2-chloro-3-((trimethylsilyl)ethynyl)benzoate (270 mg, 1.01 mmol) was dissolved in THF (4 ml) and MeOH (4 ml) upon which potassium carbonate (559 mg, 4.05 mmol)

was added and the reaction was stirred at room temperature for 2 hr, then the residual potassium carbonate was removed by filtration and the solvent was removed under reduced pressure. The light red solid crude (200 mg, 100%) was used for the next step without further purification. ESI(MS) m/z = 195.0 $[M+H]^+$

c) methyl 2-chloro-3-(1H-1,2,3-triazol-4-yl)benzoate

In a microwave vial, copper (I) iodide (9.79 mg, 51.4 µmol), methyl 2-chloro-3-ethynylbenzoate (200 mg, 1.03 mmol) and azidotrimethylsilane (317 mg, 2.57 mmol) were suspended in DMF (3.6 ml) and MeOH (0.6 ml). The mixture was degassed with argon and then stirred at 100 °C for 7 hr before it was concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 10-70%) to yield the desired product as a light yellow solid (185 mg, 76%). ESI(MS) m/z = 238.2 $[M+H]^+$

Intermediate 29

2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid

i) According to intermediate 21, i). ESI(MS) m/z = 255.2 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 241.1 $[M+H]^+$

Intermediate 30

2-chloro-2'-methoxy-[1,1'-biphenyl]-3-carboxylic acid

i) In a microwave vial, methyl 3-bromo-2-chlorobenzoate (150 mg, 601 µmol), (2-methoxyphenyl)boronic acid (119 mg, 782 µmol) and K_3PO_4 (255 mg, 1.2 mmol) in THF (1.2 ml) was degassed with argon. XPhos-Pd-G2 (23.7 mg, 30.1 µmol) was added and the mixture reacted at 60 °C for 35 min before it was was diluted with water, extracted into EtOAc, dried and concentrated *in vacuo* and purified via flash chromatography (SiO_2, Hep/EtOAc 0-30%) to yield the desired product as a brown oil (131 mg, 79%). ESI(MS) m/z = 277.1 $[M+H]^+$

ii) According to intermediate 13, ii). ESI(MS) m/z = 263.1 $[M+H]^+$

Intermediate 31

Lithium 2-chloro-3-(3-hydroxyazetidin-1-yl)benzoate

i) In a sealed tube, methyl 3-bromo-2-chlorobenzoate (CAS RN 871224-19-0, 0.1 g, 0.401 mmol), cesium carbonate (0.261 g, 0.802 mmol), $Pd_2(dba)_3$ (0.037 g, 0.040 mmol) and Xantphos (23.2 mg, 40.1 µmol) were mixed in dioxane (1 mL). The mixture was degassed with argon, then azetidin-3-ol (CAS RN 45347-82-8, 0.059 g, 0.802 mmol) was added and the reaction mixture was heated to 100 °C for 16 hours. The mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (EtOAc in heptane, 0% to 50%) to give Methyl 2-chloro-3-(3-hydroxyazetidin-1-yl)benzoate (0.034 g, 35%) as an orange viscous oil; MS (ESI): m/z = 242.1 $[M+H]^+$.

ii) To a solution of methyl 2-chloro-3-(3-hydroxyazetidin-1-yl)benzoate (0.035 g, 0.145 mmol) in THF (0.35 mL) was added a 1 M LiOH aq. solution (0.29 mL, 290 mmol) and the reaction mixture was stirred at room temperature for 5 hours. The mixture was concentrated *in vacuo* and the residue triturated in diisopropylether, filtered off and further dried on the high vacuum to give the crude title compound (0.032 g, 82%) as a light brown solid as lithium salt; MS (ESI): m/z = 228.1 $[M+H]^+$.

Intermediate 32

2-chloro-3-(oxazol-5-yl)benzoic acid

i) Methyl 3-bromo-2-chlorobenzoate (300 mg, 1.2 mmol), oxazole (166 mg, 2.4), palladium acetate (13.5 mg, 0.06 mmol), potassium carbonate (500 mg, 3.61 mmol), pivalic acid (49 mg, 0.48 mmol) and di-tert-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphane (58 mg, 0.12 mmol) were dispersed in 6.6 mL DMA, degassed with argon and reacted for 15 hours at 110 °C. After reaction completion, the mixture was diluted with water and extracted into EtOAc twice. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (EtOAc/heptane 0% to 50%). The product was obtained as a light yellow solid (89 mg, ca. 75% purity, 23% yield). MS (ESI): m/z = 238.1 $[M+H]^+$

ii) According to intermediate 14, ii). ESI(MS) m/z = 224.0 $[M+H]^+$

Intermediate 33

2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid

i) According to Intermediate 21 i), starting from 4-bromo-3-fluoro-1H-pyrazole and methyl 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate, yielding methyl 2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoate as a yellow solid, 49%. MS (ESI): m/z = 239.1 $[M+H]^+$

ii) According to Intermediate 14 ii). MS (ESI): m/z = 225.1 $[M+H]^+$

Intermediate 34

2-chloro-3-(3-cyano-1H-pyrazol-4-yl)benzoic acid

i) i) According to Intermediate 21 i), starting from 4-bromo-1H-pyrazole-3-carbonitrile and methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate, yielding methyl 2-chloro-3-(3-cyano-1H-pyrazol-4-yl)benzoate as a red solid. m/z = 260.1 $[M-H]^-$

ii) According to Intermediate 14 ii). m/z = 246.1 $[M-H]^-$

Intermediate 35A / 35B

[(3R,9aS)-3-(2-benzyloxy-5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone and [(3S,9aS)-3-(2-benzyloxy-5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

((3S)-4-(2-(2-(benzyloxy)-5-chloropyridin-3-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)(2-chloro-3-methoxyphenyl)methanone (197 mg, 361 umol) and 2-(tributyl-l5-phosphaneylidene)acetonitrile (174 mg, 721 umol) were dissolved in 2.5 mL dry toluene, degassed and heated to 110 °C. After 5 h, it was concentrated *in vacuo* and purified by silica column chromatography (EA in Heptane). Both diastereomers could be separated

Intermediate 35A (first eluting diastereomer) was obtained as a brown oil (44.7 mg, 23.5%) ESI(MS) m/z = 528.2 $[M+H]^+$

Intermediate 35B (second eluting diastereomer) was obtained as a brown oil (31.6 mg, 16.6%) ESI(MS) m/z = 528.2 $[M+H]^+$

a) 2-(benzyloxy)-3-bromo-5-chloropyridine

3-bromo-5-chloropyridin-2(1H)-one (600 mg, 2.88 mmol), silver carbonate (1.06 g, 3.84 mmol) and benzyl bromide (591 mg, 3.45 mmol) were weighed in the dark into an aluminium-wrapped round bottom flask, mixed with 5 ml toluene and reacted at 50 °C. After 28 h, the mixture was cooled down to room temperature, filtered and washed with aqueous sat. bicarbonate solution and then water twice. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica column chromatography (EtOAc/heptane 0% to 50%) and the target compound was isolated as a white solid (895 mg, 95%). MS (ESI): m/z = 300.0 [M+H]+.

b) 2-(benzyloxy)-5-chloro-3-vinylpyridine

2-(benzyloxy)-3-bromo-5-chloropyridine (595 mg, 1.99 mmol), potassium trifluoro(vinyl)borate (320 mg, 2.39 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (82 mg, 0.1 mmol) and triethylamine (202 mg, 1.99 mmol) were dispersed in 15 ml EtOH and degassed with argon. It was reacted in the microwave (120 °C, 20 min) and then then concentraed *in vacuo*, diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered, adsorbed on silica and concentrated *in vacuo*. It was purified by silica column chromatography (EtOAc/heptane 0% to 10%). The product was isolated as a colorless oil which turned into a white solid upon standing (443 mg, 91%). MS (ESI): m/z = 246.1 [M+H]+.

c) 2-(benzyloxy)-5-chloro-3-(oxiran-2-yl)pyridine

According to Intermediate 7, step b). MS (ESI): m/z = 262.1 [M+H]+.

d) ((3S)-4-(2-(2-(benzyloxy)-5-chloropyridin-3-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)(2-chloro-3-methoxyphenyl)methanone

2-(benzyloxy)-5-chloro-3-(oxiran-2-yl)pyridine (365 mg, 1.39 mmol) and (S)-(2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**intermediate 1S**, 437 mg, 1.53 mmol) were dissolved in 2.5 mL THF and 2.5 mL EtOH and reacted in the microwave (120 °C, 70 min) and then again (130 °C, 30 min). It was then concentrated *in vacuo* and purified by silica column chromatography (MeOH in DCM 0% to 10%). ((3S)-4-(2-(2-(benzyloxy)-5-chloropyridin-3-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)(2-chloro-3-methoxyphenyl)methanone was isolated as a yellow oil (197 mg, 26%). ESI(MS) m/z = 546.2 $[M+H]^+$

Intermediate 36

2-(3-bicyclo[4.2.0]octa-1(6),2,4-trienyl)oxirane

3-vinylbicyclo[4.2.0]octa-1,3,5-triene (170 mg, 1.31 mmol) was dissolved in 2.4 ml DCM. Methyltrioxorhenium (3.2 mg, 0.013 mmol) and 1H-pyrazole (10.7 mg, 0.157 mmol) were added. The purple solution was cooled to 0 °C and upon addition of hydrogen peroxide (225 ul of a 35% aq. solution, 2.61 mmol) the solution turned yellow. It was stirred vigorously for 60 min. A few grains of manganese dioxide were added and after no bubbling was observed anymore the reaction mixture was diluted with sat. aqueous bicarbonate solution and extracted into DCM twice. It was then dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by silica column chromatography (EtOAc/heptane 0% to 10%). The product was isolated as a colorless oil (132 mg, 69%). Structure confirmed by 1H-NMR.

Intermediate 37

4,5-dichloro-2-(oxiran-2-yl)pyridine

According to Intermediate 7, step b), starting from 4,5-dichloro-2-vinylpyridine ESI(MS): m/z = 190.0 $[M+H]^+$

a) 4,5-dichloro-2-vinylpyridine

2-Bromo-4,5-dichloropyridine (500 mg, 2.2 mmol), potassium vinyl trifluoroborate (1.2 eq, 354 mg), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.05 eq, 90 mg) and TEA (307 uL, 2.2 mol) were dispersed in 12 mL ethanol in a large microvave vial. The mixture was degassed with argon and heated in the microwave (120°C, 20 min). It was then concentraed *in vacuo*, diluted with EtOAc, washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. It was purified by silica column chromatography (EA in Heptane 0% to 50%). The product was obtained as a light yellow oil (278 mg, 73%). Structure confirmed by ^{1}H-NMR.

Intermediate 38

(9aS)-3-(5-bromopyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazine hydrochloride

Boc-deprotection of tert-butyl (9aS)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxylate performed according to Intermediate 7. ESI (MS): m/z = 300.0 [M+H]+.

a) tert-butyl (3S)-4-(2-(5-bromopyridin-2-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

5-bromo-2-(oxiran-2-yl)pyridine (44 mg, 0.22 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (52 mg, 0.242 mmol) were dissolved in 1.5 ml MeOH and reacted in the microwave (60 min, 120 °C). It was then concentrated *in vacuo* and purified by silica column chromatography (MeOH/DCM 0% to 10%). The product was isolated as a slightly yellow oil (60 mg, 66%). ESI (MS): m/z = 418.2 $[M+H]^+$

b) tert-butyl (9aS)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carboxylate

tert-butyl (3S)-4-(2-(5-bromopyridin-2-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (60 mg, 0.144 mmol) and (cyanomethylene)tributylphosphorane (69 mg, 0.288 mmol) were dissolved in 1 ml dry toluene, the solution was degassed with argon and then heated to 100 °C. After 2 hours, it was concentrated *in vacuo* and purified by silica column chromatography (MeOH/DCM 0% to 10%). The product was obtained as a brown oil (39 mg, ca. 30% purity, 20% yield) and used without further purification for the next step. MS (ESI): m/z = 398.2 $[M+H]^+$

Intermediate 39

5-chloro-4-methyl-2-(oxiran-2-yl)pyridine

According to Intermediate 7, step b, starting from 5-chloro-4-methyl-2-vinyl-pyridine. MS (ESI): m/z = 170.0 $[M+H]^+$

a) 5-chloro-4-methyl-2-vinyl-pyridine

According to Intermediate 7, step a, starting from 2,5-dichloro-4-methylpyridine. MS (ESI): m/z = 154.0 [M+H]+.

Intermediate 40

5-chloro-2-(oxiran-2-yl)-4-(trifluoromethyl)pyridine

According to Intermediate 7, step b, starting from *5-chloro-4-(trifluoromethyl)-2-vinylpyridine*. Structure confirmed by 1H-NMR.

a) 5-chloro-4-(trifluoromethyl)-2-vinylpyridine

According to Intermediate 7, step a, starting from 2,5-dichloro-4-(trifluoromethyl)pyridine. Structure confirmed by 1H-NMR.

Intermediate 41

2-(oxiran-2-yl)-4-(trifluoromethoxy)pyridine

According to Intermediate 7, step b, starting from *4-trifluoromethoxy-2-vinylpyridine*. MS (ESI): m/z = 206.0 [M+H]+

a) 4-trifluoromethoxy-2-vinylpyridine

According to Intermediate 7, step a, starting from 2-chloro-*4-(trifluoromethoxy)pyridine*. MS (ESI): m/z = 190.0 [M+H]+.

Intermediate 42

5-fluoro-2-(oxiran-2-yl)-4-(trifluoromethyl)pyridine

According to Intermediate 7, step b, starting from *5-fluoro-4-(trifluoromethyl)-2-vinylpyridine*. Structure confirmed by 1H-NMR.

a) 5-fluoro-4-(trifluoromethyl)-2-vinylpyridine

According to Intermediate 7, step a, starting from 2-chloro-5-fluoro-4-(trifluoromethyl)pyridine. Structure confirmed by 1H-NMR.

Intermediate 43

5-chloro-4-(difluoromethyl)-2-(oxiran-2-yl)pyridine

According to Intermediate 7, step b, starting from 5-chloro-4-(difluoromethyl)-2-vinylpyridine MS (ESI): m/z = 206.0 $[M+H]^+$

a) 5-chloro-4-(difluoromethyl)-2-vinylpyridine

According to Intermediate 7, step a, starting from 2,5-dichloro-4-(difluoromethyl)pyridine. After the silica column chromatography, the solvent was not removed completely due to suspected volatility of the compound. MS (ESI): m/z = 189.9 $[M+H]^+$

Intermediate 44

4-bromo-5-chloro-2-(oxiran-2-yl)pyridine

According to Intermediate 7, step b, starting from 4-bromo-5-chloro-2-vinylpyridine MS (ESI): m/z = 236.0 $[M+H]^+$

a) -bromo-5-chloro-2-vinylpyridine

According to Intermediate 7, step a, starting from 2,4-dibromo-5-chloropyridine. After the silica column chromatography, the solvent was not removed completely due to suspected volatility of the compound. MS (ESI): m/z = 219.9 $[M+H]^+$

Intermediate 45

2-fluoro-3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoic acid

According to Intermediate 13, step ii), starting from Methyl 2-fluoro-3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoate. MS (ESI): m/z = 275.1 [M+H]+.

a) Methyl 2-fluoro-3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoate

Methyl 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (CAS 1638847-77-4, 292 mg with 75% purity, 0.7 mmol), 4-bromo-5-(trifluoromethyl)-1H-pyrazole (168 mg, 0.78 mmol), bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (55 mg, 0.078 mmol) and K_2CO_3 (324 mg, 2.35 mmol) were mixed with 4.5 ml dioxane and 1.5 ml water, degassed with argon and reacted in the microwave (115 °C, 30 min). It was diluted with water and extracted into EtOAc twice, dried over Na_2SO_4, filtered, adsorbed on silica, concentrated *in vacuo* and purified by silica column chromatography (20 g, EtOAc/heptane 0% to 40%). The desired product was isolated as a yellow oil (123 mg, 55%). MS (ESI): m/z = 289.1 [M+H]+.

Intermediate 46

3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoic acid

According to Intermediate 13, step ii), starting from Ethyl 3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoate. MS (ESI): m/z = 257.1 $[M+H]^+$

a) Ethyl 3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoate

According to Intermediate 45, step b, starting from with ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate. MS (ESI): m/z = 285.1 $[M+H]^+$

Intermediate 47

Lithium 2-chloro-3-(2-oxo-1,2-dihydropyridin-4-yl)benzoate

According to Intermediate 13, step ii), starting from Methyl 2-chloro-3-(2-oxo-1,2-dihydropyridin-4-yl)benzoate. The target compound was not extracted into organic solvent but the reaction mixture was lyophilized and used in the next step without further purification. MS (ESI): m/z = 250.1 $[M+H]^+$

a) Methyl 2-chloro-3-(2-oxo-1,2-dihydropyridin-4-yl)benzoate

Synthesis according to Intermediate 21, step i), starting from 4-bromopyridin-2(1H)-one. MS (ESI): m/z = 264.1 $[M+H]^+$

Intermediate 48

2-chloro-3-(6-oxo-1H-pyridin-3-yl)benzoic acid

Methyl 2-chloro-3-(6-oxo-1,6-dihydropyridin-3-yl)benzoate (120 mg, 0.455 mmol) and LiOH monohydrate (57 mg, 1.37 mmol) were dispersed in 1.4 ml water, 0.5 ml MeOH and 3.9 ml THF and stirred at 22°C. 19 hours later, it was acidified with 1 M aqueous HCl and diluted with brine. It was concentrated *in vacuo*, suspended in EtOH, stirred heavily for a few minutes and filtered. The process was repeated twice and the combined filtered solutions concentrated *in vacuo*. The target compound was obtained as a white solid together with residual NaCl and LiCl.

a) Methyl 2-chloro-3-(6-oxo-1,6-dihydropyridin-3-yl)benzoate

According to Intermediate 21, step i), starting from 5-bromopyridin-2(1H)-one. MS (ESI): m/z = 264.1 $[M+H]^+$

Intermediate 49

5-chloro-3-((3R,9aS)-octahydropyrazino[2,1-c][1,4]oxazin-3-yl)pyridin-2-ol 2,2,2-trifluoroacetate

tert-butyl (3R,9aS)-3-(2-(benzyloxy)-5-chloropyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (29.2 mg, 63.5 umol) was dissolved in 1.5 mL DCM. TFA (50 uL) was added and the yellow solution stirred at RT. After 4h, another portion of TFA (1 ml) was added slowly. 3 h later, the mixture was concentrated *in vacuo*, redissolved in toluene and concentrated *in vacuo* again to obtain a brown solid. The crude was used in the next step without furhter purification. MS (ESI): m/z = 270.2 [M+H]+.

a) tert-butyl (3S)-4-(2-(2-(benzyloxy)-5-chloropyridin-3-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

Synthesis according to Intermediate 35A / 35B, step d, starting from 2-(benzyloxy)-5-chloro-3-(oxiran-2-yl)pyridine (see Intermediate 35A / 35B for the synthesis, 208 mg, 795 umol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (189 mg, 874 umol). Product obtained as a yellow oil, 181 mg (47.6%) . MS (ESI): m/z = 478.3 $[M+H]^+$

b) tert-butyl (3R,9aS)-3-(2-(benzyloxy)-5-chloropyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl (3S)-4-(2-(2-(benzyloxy)-5-chloropyridin-3-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (132 mg, 276 umol) was dissolved in 1.7 mL dry toluene. 2-(tributyl-l5-phosphaneylidene)acetonitrile (133 mg, 552 umol) in 0.3 mL dry toluene was added and the mixture heated up to 100 °C. After 5 h another (100 mg, 414 umol) of 2-(tributyl-l5-phosphaneylidene)acetonitrile in 0.2 mL dry toluene was added. The solution was warmed up to 110 °C. After 5 h the reaction mixture was concentrated and purified by column chromatography (EA in Heptane 0% to 90%). The first eluting diastereomer was carried forward to the next step. Product obtained as a yellow oil, 29.2 mg (23%). MS (ESI): m/z = 460.3 $[M+H]^+$

Intermediate 50

(3-bromo-2-chloro-5-fluorophenyl)((3R,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone

(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazine (Intermediate 2, 1 eq, 74.6 mg), 3-bromo-2-chloro-5-fluorobenzoic acid

(1.35 eq, 105 mg) and HATU (1.35 eq, 141 mg) were mixed with 2 mL dry DMF and cooled to 0 °C. DIPEA (3 eq, 144 uL) was added upon which a yellow solution formed. After 10 min, it was warmed up to RT. 3 h later, it was diluted with EtOAc and washed with cold water and then sat. bicarbonate solution and finally brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude was purified by silica column chromatography (10 g, EtOAc in Hept 30% to 80%). The product was obtained as a white solid (102 mg, ca. 80% purity, yield ca. 59%).

Also a fraction recuperated form the waste was obtained: 19 mg, ca 80% pure, yield ca. 11%

Intermediate 51a

(3R,9aS)-3-(3,4-dichlorophenyl)-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol

According to Intermediate 52, step b, starting from tert-butyl (3R,9aS)-3-(3,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate. MS (ESI): m/z = 303.2 [M+H]+.

a) tert-butyl (3R,9aS)-3-(3,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate

Synthesis according to Intermediate 52, step a, starting from 2-bromo-1-(3,4-dichlorophenyl)ethan-1-one and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate. MS (ESI): m/z = 403.3 [M+H]+.

Intermediate 51b

(3R,9aS)-3-(3,4-dichlorophenyl)-1,3,4,6,7,8,9,9a-octahydropyrazino[2,1-c][1,4]oxazine

Synthesis according to Intermediate 53, starting from tert-butyl (3R,9aS)-3-(3,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate (product of step a, Intermediate 51a). MS (ESI): m/z = 287.2 [M+H]+.

Intermediate 52

(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)((3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone

Bis(pinacolato)diboron (327 mg, 1.29 mmol), [(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(3-bromo-2-chloro-phenyl)methanone (0.500 g, 992 µmol) and potassium acetate (292 mg, 2.98 mmol) were dispersed in Dioxane (4 ml) and degassed. 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride complex (121 mg, 149 µmol) was then added. It was reacted in the microwave (30 min, 100 °C). It was then extracted with EtOAc and water. The combined organic layers were combined, washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by silica column chromatography (EtOAc/Hept 0% to 80%). The product was obtained as a brown oil (234mg, ca. 72% purity, 42% yield) and used without further purification for the next step. MS (ESI): m/z = 551.3 $[M-H]^-$.

a) tert-butyl (3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate

tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1 eq, 1.52 g) and Hunig's base (1.3 eq, 1.6 mL) were dissolved in 25 mL THF. 2-bromo-1-(3-chloro-4-fluorophenyl)ethan-1-one (1 eq, 1.77 g) in 5 mL THF was added dropwise at 0 °C over 10 min. The reaction mixture was stirred at room temperature for 20 hours. The crude was then filtered, and the yellow mother liquor solution was concentrated in vacuo and purified by silica column chromatography (EtOAc/Hept 0% to 70%). The product was isolated as a light yellow foam (2.3g, 85%). ESI (MS): m/z = 387.1 $[M+H]^+$

b) (3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol

tert-butyl (3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate (2.3 g, 5.95 mmol) was mixed with HCl 4M in dioxane (29.7 ml, 119 mmol) and Dioxane (10 ml) and stirred at room temperature for 2.5 hours. The mixture was then diluted in EtOAc, basified with 4 M NaOH and extracted twice with EtOAc. The organic layers were combined, dried over sodium sulfate, filtered and concentrated in vacuo. The product was obtained as light yellow foam (1.7g, ca. 80% purity, 99% yield) and used without further purification for the next step. MS (ESI): m/z = 287.1 $[M+H]^+$

c) [(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(3-bromo-2-chloro-phenyl)methanone

(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-4,6,7,8,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-ol (1 g, 3.49 mmol), 3-bromo-2-chlorobenzoic acid (985 mg, 4.19 mmol) and HATU (1.59 g, 4.19 mmol) were combined with DMF (20 ml). Hunig's base (1.35 g, 1.83 ml, 10.5 mmol) was added and the reaction mixture was stirred at RT for 1 hour. It was then extracted with water and EtOAc. The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by silica column chromatography (EtOAc/Hept 0% to 100%). The product was isolated as a yellow oil (1.48g, 84%). ESI (MS): m/z = 505.1 $[M+H]^+$

Intermediate 53

(3R,9aS)-3-(4-bromo-3-chlorophenyl)octahydropyrazino[2,1-c][1,4]oxazine

tert-butyl (3R,9aS)-3-(4-bromo-3-chloro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate (0.959 g, 2.14 mmol) was mixed with triethylsilane (747 mg, 1.03 ml, 6.43 mmol) and DCM (11 ml). Trifluoroacetic acid (7.33 g, 4.92 ml, 64.3 mmol) was added and the solution heated to 45 °C for 2 hours. The crude yellow solution was concentrated in vacuo, mixed with water / 1 M HCl and washed with diethyl ether. The organic phase was backextracted with 0.5 M HCl twice. The combined aqueous phases were then basified with 4 M NaOH, supplemented with NaCl and extracted into EtOAc twice. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo to result in an yellow oil (0.643 g, 91%). The diastereomeric ratio is ca. eq/ax 8:1 as estimated by NMR. ESI (MS): m/z = 333.2 $[M+H]^+$

a) tert-butyl (3R,9aS)-3-(4-bromo-3-chloro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carboxylate

Synthesis according to Intermediate 52, step a, starting from 2-bromo-1-(4-bromo-3-chlorophenyl)ethan-1-one and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate. MS (ESI): m/z = 449.2 $[M+H]^+$

Intermediate 54

2-chloro-3-(3-oxopiperazin-1-yl)benzoic acid

To a solution of methyl 2-chloro-3-(3-oxopiperazin-1-yl)benzoate (0.175 g, 651 µmol) in THF (2 ml) was added LiOH 1M in H2O (1.95 ml, 1.95 mmol) and the resulting mixture was stirred at RT for 3 hours. The reaction mixture was poured into 1M HCl and extracted twice with EtOAc. The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated in vacuo. The product was obtained as a light yellow oil (100 mg, ca. 72% purity, 60% yield) and used without further purification for the next step. MS (ESI): m/z = 255.05 $[M+H]^+$

a) methyl 2-chloro-3-(3-oxopiperazin-1-yl)benzoate

A solution of methyl 3-bromo-2-chlorobenzoate (0.600 g, 2.4 mmol), piperazin-2-one (265 mg, 2.65 mmol), cesium carbonate (1.57 g, 4.81 mmol) in Dioxane (15 ml) was degassed with argon. $Pd(OAc)_2$ (54 mg, 240 µmol) and xantphos (139 mg, 240 µmol) were added, reaction degassed once more and the reaction was stirred at 90°C overnight. The reaction was filtered on decalite and concenrated in vacuo. The yellow oil was then dissolved in EtOAc and extracted with water. Organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by Si-Amine column chromatography (MeOH/DCM 0% to 10%). The product was isolated as a yellow oil (175 mg, 27%). ESI (MS): m/z = 269.2 $[M+H]^+$

Intermediate 55

2-chloro-3-(5-cyano-1H-pyrrol-3-yl)benzoic acid

Saponification according to Intermediate 54, starting from methyl 2-chloro-3-(5-cyano-1H-pyrrol-3-yl)benzoate. MS (ESI): m/z = 245.1 $[M-H]^-$

a) methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Borylation according to Intermediate 52, starting from methyl 3-bromo-2-chlorobenzoate. MS (ESI): m/z = 297.2 $[M+H]^+$

b) methyl 2-chloro-3-(5-cyano-1H-pyrrol-3-yl)benzoate

methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (0.203 g, 685 µmol), 4-bromo-1H-pyrrole-2-carbonitrile (129 mg, 753 µmol), potassium carbonate (284 mg, 2.05 mmol) were combined with Dioxane (5 ml) and Water (850 µl). The reaction mixture was degassed and Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)

dichloropalladium(II) (48.5 mg, 68.5 µmol) was added. The reaction mixture was heated at 80°C for 2 hours, and then extracted with saturated $NaHCO_3$ solution / EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by silica column chromatography (MeOH/DCM 0% to 10%). The product was isolated as a yellow oil (177mg, 99%). ESI (MS): m/z = 259.1 $[M-H]^-$

Intermediate 56

2-chloro-3-(2-cyano-1H-imidazol-5-yl)benzoic acid

Saponification according to Intermediate 54, starting from methyl 2-chloro-3-(2-cyano-1H-imidazol-5-yl)benzoate. MS (ESI): m/z = 248.1 $[M+H]^+$

a) methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Borylation according to Intermediate 52, starting from methyl 3-bromo-2-chlorobenzoate. MS (ESI): m/z = 297.2 $[M+H]^+$

b) methyl 2-chloro-3-(2-cyano-1H-imidazol-5-yl)benzoate

Cross coupling according to Intermediate 55, step b, starting from methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate and 5-bromo-1H-imidazole-2-carbonitrile. MS (ESI): m/z = 262.1 $[M+H]^+$

Intermediate 57

2-chloro-3-(2-oxo-3H-1,3,4-oxadiazol-5-yl)benzoic acid

5-(3-bromo-2-chloro-phenyl)-3H-1,3,4-oxadiazol-2-one (1 eq, 138 mg) was dissolved in 3 mL dry THF at 0 °C upon which isopropyl magnesium chloride LiCl complex (1.1 eq, 425 uL of a 1.3 M solution in THF) was added dropwise upon which the solution turned orange and then dark red. After the addition, the mixture was allowed to warm up to RT. The transmetallation was monitored by LCMS. After 20 min, ca. 30% transmetallation was observed which did not change 40 min later, so another 400 uL isopropyl magnesium chloride LiCl complex was added upon which precipitation formed. 20 min later, LCMS confirmed complete transmetallation. Through the suspension, gaseous CO_2 was bubbled via a balloon, and after 5 min 5 mL more dry THF was added to the flask to ensure good bubbling and stirring. It was diluted with 1 N NaOH and washed with EtOAc twice. The

aq. phase was acidified with 1 M HCl, a bit of NaCl was added and then extracted into EtOAc twice. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The product was obtained as an off-white solid (68 mg). MS (ESI): m/z = 241.1 $[M+H]^+$

a) 3-bromo-2-chloro-benzohydrazide

methyl 3-bromo-2-chlorobenzoate (1 eq, 500 mg) and hydrazine hydrate (5 eq, 490 uL) were dissolved in 15 mL EtOH and heated to 80 °C for 2.5 days. It was then concentrated in vacuo and purified by silica column chromatography (50 g, EtOAc in n-heptane 40% to 100%). The product was isolated as a white solid (315 mg, 63%). MS (ESI): m/z = 251.0 $[M+H]^+$

5-(3-bromo-2-chloro-phenyl)-3H-1,3,4-oxadiazol-2-one

3-bromo-2-chlorobenzohydrazide (1 eq, 271 mg) and TEA (1.4 eq, 212 uL) were dispersed in 4 mL dry THF at 0 °C and then Carbonyldiimidazole (1.1 eq, 194 mg) in 2 mL dry THF was added dropwise and the mixture slowly warmed to RT upon which a clear yellow solution formed. Even though the reaction had not gone to full completion, it was diluted with EtOAc and washed with 1 M HCl, sat. bicarbonate solution and then brine before it was dried over sodium sulfate, filtered and concentrated in vacuo to result in a shiny crystalline white solid (236 mg, 79%). MS (ESI): m/z = 274.9 $[M-H]^-$

Intermediate 58

2-chloro-3-(2-oxo-2,3-dihydrooxazol-5-yl)benzoic acid

5-(3-bromo-2-chloro-phenyl)-3H-oxazol-2-one (1 eq, 71 mg) was dissolved in 1.2 mL dry THF with the aid of sonication and cooled to 0 °C. Isopropyl magnesium chloride LiCl complex (1.3 eq, 233 uL of a 1.3 M solution in THF) was slowly added upon which the mixture turned dark. 15 min later, it was slowly warmed to RT. An orange-red mixture had formed. 30 min after the addition, 8% transmetallation was observed and another 120 uL isopropyl magnesium chloride LiCl complex was added at 0 °C and the mixture then warmed up to RT. 30 min later, ca. 50% transmetallation was observed. Even though the transmetallation was not complete gaseous CO_2 (1 balloon) was bubbled trough at ca. 10 °C. Another 2 mL dry THF were added and another balloon CO_2 was bubbled through at RT in the sonicator. A yellowish suspension formed, it was diluted with ca. 0.5 M NaOH

and washed with diethyl ether twice. The aqueous phase was acidified with 1 M HCl and treated with NaCl and then extracted into EtOAc twice. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. The impure product was obtained as an orange solid (61 mg). MS (ESI): m/z = 238.1 $[M-H]^-$

a) 2-bromo-1-(3-bromo-2-chloro-phenyl)ethanone

1-(3-bromo-2-chlorophenyl)ethan-1-one (1 eq, 340 mg), NBS (1.05 eq, 272 mg) and pTsOH monohydrate (0.11 eq, 30 mg) were mixed with 12 mL dry DCM and reacted in the microwave (90 °C, 80 min) and then again (90 °C, 40 min). The mixture was diluted with DCM and washed with sat. bicarbonate solution, water and then brine. The combined aq. phases were backextrated into DCM, the combined organic layers dried over sodium sulfate, filtered and concentrated in vacuo to result in a crude yellow oil (460 mg). It was purified by silica column chromatography (50 g, EtOAc in Hept 0-30%). The target was obtained as a yellow oil (429 mg, ca. 80% pure, 75% yield). Confirmed by ^{1}H-NMR.

b) 3-(2-(3-bromo-2-chloro-phenyl)-2-oxo-ethyl)thiazolidine-2,4-dione

2-bromo-1-(3-bromo-2-chloro-phenyl)ethanone (1 eq, 226 mg), thiazolidine-2,4-dione (1 eq, 68 mg), postassium carbonate (1.05 eq, 84 mg) and TBAI (0.1 eq, 21 mg) were mixed with 3 mL DMF and the yellow solution stirred at RT. After 20 min, the mixture had turned slightly orange and after 1 h, an orange suspension had formed. After 70 min, the mixture was diluted with EtOAc and washed with ice water (2x) and then brine, dried over sodium sulfate, filtered and concentrated in vacuo to give the desired compound as a red solid (249 mg, ca. 100%). MS (ESI): m/z = 346.1 $[M-H]^-$

c) 5-(3-bromo-2-chloro-phenyl)-3H-oxazol-2-one

3-(2-(3-bromo-2-chloro-phenyl)-2-oxo-ethyl)thiazolidine-2,4-dione (1 eq, 248 mg of ca. 80% purity) and triethylamine (2.5 eq, 200 uL) were mixed with 2.8 mL EtOH in a pressure vial and heated to 80 °C in a sandbath. After a reaction time of 15 h, 70% conversion was observed (UV). The reaction mixture was diluted with EtOAc and washed with half-saturated ammonium chloride solution and then brine, dried over sodium sulfate, filtered and concentrated in vacuo to a red/white solid (241 mg). The residuewas adsorbed on silica and purified by silica column chromatography (20 g, EtOAc in n-heptane 20% to 60%). The product was isolated as an white solid with also some red parts (123 mg, ca. 90% purity, 71% yield). MS (ESI): m/z = 274.0 $[M+H]^+$

Intermediate 59

2-chloro-3-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)benzoic acid

Saponification according to Intermediate 54, starting from methyl 2-chloro-3-(2-methyl-6-oxo-1H-pyridin-4-yl)benzoate. MS (ESI): m/z = 264.2 $[M+H]^+$

a) methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

In a microwave vial, 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.3 eq, 1.32 g), methyl 3-bromo-2-chlorobenzoate (1 eq, 1 g), $PdCl_2$(DPPF) (0.1 eq, 327 mg) and potassium acetate (3 eq, 1.18 g) were dispersed in 17 mL dioxane and degassed. It was reacted in the microwave (80 °C, 25 min. The mixture was filtered into an extraction funnel, washed with water and and then brine, backextracted in some EtOAc, dried over sodium sulfate, filtered, adsorbed on silica and concentrated in vacuo. It was purified by silica column chromatography (70 g, EtOAc in n-heptane 0% to 10%). The product was isolated together with tetramethyloxirane as a white solid (1.41 g, impure, 36% yield). MS (ESI): m/z = 297.2 $[M+H]^+$

b) methyl 2-chloro-3-(2-methyl-6-oxo-1H-pyridin-4-yl)benzoate

4-bromo-6-methylpyridin-2(1H)-one (1 eq, 125 mg), methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.1 eq, 361 mg of ca. 60% purity), $(APhos)_2PdCl_2$ (0.1 eq, 47 mg) and potassium carbonate (3 eq, 276 mg) were mixed with 3 mL dioxane and 1 mL water and degassed with argon. The mixture was then reacted in the microwave (115 °C, 30 min) and then diluted with EtOAc and washed with brine. The aqueous phase was backextracted an the combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. The crude was purified by silica column chromatography (20 g, MeOH in DCM 0% to 10%). The product was isolated as a a green-white solid (206 mg, 112%, impurities). MS (ESI): m/z = 278.2 $[M+H]^+$

Intermediate 60

2-chloro-3-(2-methyl-6-oxo-1,6-dihydropyridin-3-yl)benzoic acid

methyl 2-chloro-3-(6-methoxy-2-methyl-3-pyridyl)benzoate (1 eq, 106 mg) was mixed with 4 mL 7.6 M aq. HCl and the colorless mixture heated to 120 °C in a pressure vial and sandbath. After 22 h, complete monodemethylation and partial dimethylation was

observed. After 30 h, the reaction was at ca. 80% conversion (UV), cooled down to RT, the flasks rinsed with some water/MeCN and the solvents evaporated with the aid of toluene to an off-white solid (56mg, 58%) MS (ESI): m/z = 264.1 $[M+H]^+$

a) methyl 2-chloro-3-(6-methoxy-2-methyl-3-pyridyl)benzoate

methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1 eq, 232 mg of ca. 60% purity), 3-bromo-6-methoxy-2-methylpyridine (1.35 eq, 128 mg), Pd dppf DCM complex (0.1 eq, 38 mg) and potassium carbonate (3 eq, 195 mg) were suspended in 3 mL dioxane and 1mL water, degassed with argon and reacted in the microwave (115 °C, 30 min). Colling to RT the mixture was diluted with EtOAc and washed with brine. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The crude was then purified by silica column chromatography (20 g, EtOAc in n-heptane 0% to 50%). The product eluted at ca. 25% EtOAc partly together with impurities and was isolated as a light yellow oil (119 mg, 71% yield combined). MS (ESI): m/z = 292.2 $[M+H]^+$

Intermediate 61

2-chloro-3-(4-oxo-1H-pyridazin-5-yl)benzoic acid

The crude 3-(5-benzyloxypyridazin-4-yl)-2-chloro-benzoic acid (1 eq, 45 mg) was dissolved in 2.5 mL MeOH in a 25 mL flask. The flask was purged with argon/vacuum three times. Palladium on carbon (0.1 eq, 14 mg) was added and the flask purged with argon three times again. A hydrogen balloon was added and purged three times and then stirred at RT. After 100 min, ca. 60% (by LC-UV) conversion was visible. The next morning it was filtered over celite and concentrated in vacuo to yield a green crude solid (40 mg),which was used without purification for the next step. MS (ESI): m/z = 251.1 $[M+H]^+$

a) 4-benzyloxy-5-chloro-pyridazine

Work in dark. In an aluminium foil wrapped flask, 5-chloropyridazin-4(1H)-one (1 eq, 300 mg), benzyl bromide (1.2 eq, 330 uL) and silver carbonate (1.2 eq, 760 mg) were dispersed in 5 mL dry toluene and heated to 85 °C for 30 min and then to 50 °C for 1 h. It was then diluted with half-saturated brine and extracted into EtOAc three times. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. It was

purified by silica column chromatography (50 g, EtOAc in n-heptane 30% to 100%). The product was obtained as yellow solid (85 mg, 17%). MS (ESI): m/z = 221.1 $[M+H]^+$

b) methyl 3-(5-benzyloxypyridazin-4-yl)-2-chloro-benzoate

methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.05 eq, 122 mg of ca. 60% purity), 4-benzyloxy-5-chloro-pyridazine (1 eq, 52 mg), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.1 eq, 19 mg) and potassium carbonate (3 eq, 98 mg) were mixed with 2.4 mL dioxane and 0.8 mL water, degassed and reacted in the microwave (115 °C, 30 min). It was purified by silica column chromatography (20 g, EtOAc in n-heptane 0% to 80%). The product was obtained as an orange oil (47 mg, 34%). MS (ESI): m/z = 355.1 $[M+H]^+$

c) 3-(5-benzyloxypyridazin-4-yl)-2-chloro-benzoic acid

methyl 3-(5-benzyloxypyridazin-4-yl)-2-chloro-benzoate (1 eq, 47 mg) was mixed with 1.5 mL 7.6 M aq. HCl and heated to 120 °C in a sandbath and pressure vial for 16h. Cooloing to RT and acetonitrile was added to give a homogenous solution and LCMS showed full ester hydrolysis. It was concentrated in vacuo to a yellow/orange oil and was used in the next step without further purification (45mg, 100%). MS (ESI): m/z = 341.1 $[M+H]^+$

Intermediate 62

2-chloro-3-(5-cyano-1H-pyrazol-3-yl)benzoic acid

Saponification according to Intermediate 54, starting from methyl 2-chloro-3-(5-cyano-1H-pyrazol-3-yl)benzoate. MS (ESI): m/z = 248.1 $[M+H]^+$

a) 5-bromo-1H-pyrazole-3-carboxamide

methyl 5-bromo-1H-pyrazole-3-carboxylate (1 eq, 140 mg) was dissolved in 3 mL MeOH. Aq. ammonium hydroxide solution (10 eq, 1 ml of a 25% solution) was added and the solution heated to 60 °C. After 40 min, ca. 20% re-esterification to the methyl ester but no amide bond formation was visible. After 1 h, the temperature was raised to 80 °C. 18 h later, it was concentrated in vacuo to remove excess ammonia. A white solid was obtained (120mg, 100%). MS (ESI): m/z = 251.1 $[M+H]^+$

b) 5-bromo-1H-pyrazole-3-carbonitrile

5-bromo-1H-pyrazole-3-carboxamide (crude, 1 eq, 120 mg) was dissolved in 3.5 ml pyridine and cooled to 0 °C. Trifluoroacetic anhydride (4 eq, 360 uL) was added dropwise. White smoke emerged immediately. 40 min later, it was diluted with EtOAc, washed with sat. aq. bicarbonate solution twice and then 1 M HCl twice, dried over sodium sulfate and concentrated in vacuo to a light brown solid (121 mg). It was purified by silica column chromatography (10 g, EtOAc in n-heptane 0% to 50%). The product was obtained as a white solid (56mg, 51%) MS (ESI): m/z = 172.0 $[M+H]^+$

c) methyl 2-chloro-3-(5-cyano-1H-pyrazol-3-yl)benzoate

5-bromo-1H-pyrazole-3-carbonitrile (1 eq, 56 mg), methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.3 eq, 209 mg of ca. 60% purity), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.1 eq, 26 mg) and potassium carbonate (3 eq, 135 mg) were mixed with 1.8 ml dioxane and 600 ul water, degassed and reacted in the microwave (30 min, 115 °C). Another 40 mg (0.3 eq) of methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate and a pinch of Pd cat was added, degassed and reacted again (120 °C, 30 min). The reaction was cooled to RT and diluted with EtOAc, washed with water and then brine, dried over sodium sulfate, filtered and concentrated in vacuo. It was then purified by silica column chromatography (10 g, EtOAc in n-heptane 0% to 50%). The product was isolated as an orange/yellow oil (24 mg, 28%). MS (ESI): m/z = 262.2 $[M+H]^+$

Intermediate 63

3-((3R,9aS)-octahydropyrazino[2,1-c][1,4]oxazin-3-yl)-6-(trifluoromethyl)pyridin-2(1H)-one hydrobromide

tert-butyl (3R,9aS)-3-(2-methoxy-6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (0.160 g, 383 µmol) was dissolved in AcOH (1.92 ml) and 33% HBr in AcOH (7 mL) was added. The reaction mixture was stirred at 100 °C for 2 hrs. Then it wasconcentrated under vaccum and co-evaporated twice with toluene. No further purification, product was obtained as a brown powder (182 mg, crude, 100%). MS (ESI): m/z = 304.1 $[M+H]^+$

a) 2-methoxy-6-(trifluoromethyl)-3-vinylpyridine

3-bromo-2-methoxy-6-(trifluoromethyl)pyridine (1 g, 3.91 mmol), potassium trifluoro(vinyl)borate (628 mg, 4.69 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (159 mg, 195 µmol) and triethylamine (395 mg, 544 µl, 3.91 mmol) were dispersed in degassed Ethanol (29.4 ml). The reation mixture was then heated up to 130 °C for 1 hour in a scealed tube. It was then concentrated in vacuo, diluted with EtOAc, washed with water, dried over sodium sulfate, filtered, adsorbed on silica and concentrated in vacuo. It was purified by silica column chromatography (50 g, EA in Hept 0% to 15 %). Product obtained as a colourless oil, 610 mg, 77%. MS (ESI): m/z = 204.0 $[M+H]^+$

b) 2-methoxy-3-(oxiran-2-yl)-6-(trifluoromethyl)pyridine

2-methoxy-6-(trifluoromethyl)-3-vinylpyridine (0.61 g, 3 mmol) was dispersed in 70 mL water and 70 mL dioxane. 1-bromopyrrolidine-2,5-dione (641 mg, 3.6 mmol) in 70 mL water and 70 mL dioxane was added dropwise. It was stirred at RT for 7 hours. According to LCMS all starting material was consumed and bromohydrin was formed. The reaction mixture was cooled down to 0 °C and 4 M NaOH solution (2.25 ml) was added dropwise. The ice-bath was removed and the RM was stirred overnight at RT. LC-MS showed complete reaction and formation of desired product. It was mixed with sat. bicarbonate solution and extracted into EtOAc twice. The combined org. phases were washed with water, brine and then dried over sodium sulfate, filtered and concentrated in vacuo. Product obtained as a colourless oil, 620 mg, 94%. ^{1}H-NMR complies.

c) tert-butyl (3S)-4-(2-hydroxy-2-(2-methoxy-6-(trifluoromethyl)pyridin-3-yl)ethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

2-methoxy-3-(oxiran-2-yl)-6-(trifluoromethyl)pyridine (0.62 g, 2.83 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (673 mg, 3.11 mmol) were dissolved in ethanol (10.7 ml) and tetrahydrofuran (10.7 ml) and heated up to 130 °C overnight in a scealed tube. It was then concentrated in vacuo and purified by silica column chromatography (20 g, MeOH in DCM 0% to 5%). Product obtained as a colourless oil, 750 mg, 61%. MS (ESI): m/z = 436.2 $[M+H]^+$

d) tert-butyl (3R,9aS)-3-(2-methoxy-6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl (3S)-4-(2-hydroxy-2-(2-methoxy-6-(trifluoromethyl)pyridin-3-yl)ethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (0.75 g, 1.72 mmol) was dissolved in dry toluene (12.5 ml). 2-(tributyl-l5-phosphaneylidene)acetonitrile (831 mg, 904 µl, 3.44 mmol) in dry Toluene (12.5 ml) was added and the mixture heated up to 105 °C. Toluene was evaporated and the residue was purified by silica column chromatography (20 g, EA in Hept 0% to 50 %). The first eluting diastereomer (less polar) was isolated and is expected to be the more active conformation and was used in the next steps. Product was obtained as a dark brown oil, 160 mg, 22%. MS (ESI): m/z = 418.2 $[M+H]^+$

Intermediate 64

2-chloro-3-(5-cyano-1H-pyrrol-3-yl)-5-fluorobenzoic acid

To a solution of methyl 2-chloro-3-(5-cyano-1H-pyrrol-3-yl)-5-fluorobenzoate (1.2 g, 4.31 mmol) in THF (21.5 ml) was added aq solution of lithium hydroxide 0.5M (11.2 ml, 5.6 mmol) dropwise and the reaction was heated up to 70 °C for 2 hrs. The solvent was removed under vaccum and the residue was acidifed with HCl 1 M (pH=2). It was then extracted twice with EtOAc, dried, filtered and concentrated under vaccum to get the desired product as a orange solid. MS (ESI): m/z = 263.0 $[M+H]^+$

a) methyl 2-chloro-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

In a MW vial, methyl 3-bromo-2-chloro-5-fluorobenzoate (4.0 g, 15 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.56 g, 17.9 mmol and potassium acetate (4.4 g, 44.9 mmol) were dispersed in dioxane (59.6 ml) and degassed. 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.83 g, 2.24 mmol) was then added. The red suspension was reacted in the heating plate (105 °C, 2 hrs). The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 20 % EtOAc in heptane in 40 min). Product obtained as white solid, 3.52 g, 75%. ^{1}H-NMR complies.

b) methyl 2-chloro-3-(5-cyano-1H-pyrrol-3-yl)-5-fluorobenzoate

methyl 2-chloro-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3.5 g, 9.12 mmol), 4-bromo-1H-pyrrole-2-carbonitrile (1.72 g, 10 mmol), $(APhos)_2PdCl_2$ (646 mg, 912 µmol) and K_2CO_3 (3.78 g, 27.4 mmol) were dispersed in dioxane (50.8 ml) and Water (9.24 ml) and degassed with argon. It was then heated at 80°C for 2 hrs. The

mixture was poured into sat. $NaHCO_3$ and extracted with EtOAc twice. The organic layers were combined , washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude orange oil was purified by silica gel chromatographie (20 g, DCM/MeOH 0 to 10% in 30 min). Product was obtained as a yellow solid, 1.2 g, 47%. MS (ESI): m/z = 277.1 $[M-H]^-$

Intermediate 65

2-chloro-5-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid

Saponification was carried out as described for intermediate 64, starting from methyl 2-chloro-5-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoate (80 mg, 293 umol). Product obtained as white solid, 20 mg, 26%. MS (ESI): m/z = 259.1 $[M+H]^+$

a) methyl 2-chloro-5-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoate

methyl 2-chloro-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (732 mg, 2.33 mmol), 4-bromo-3-fluoro-1H-pyrazole (320 mg, 1.94 mmol), $(APhos)_2PdCl_2$ (137 mg, 194 µmol) and K_2CO_3 (804 mg, 5.82 mmol) were dispersed in dioxane (9.57 ml) and Water (3.19 ml) and degassed with argon.(yellow suspension). It was then heated at 60°C for 30 min and at 110°C for 3 hours. The mixture was poured into sat. $NaHCO_3$ and extracted with EtOAc twice. The organic layers were combined , washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude yellow oil was purified by silica gel chromatography (n-heptane and EtOAc 0 to 70% in 40 min) to get the desired product as a light yellow oil (80 mg, 15%). MS (ESI): m/z = 273.1 $[M+H]^+$

Intermediate 66

3-chloro-2-fluoro-5-((3R,9aS)-octahydropyrazino[2,1-c][1,4]oxazin-3-yl)benzonitrile trifluoroacetate

tert-butyl (3R,9aS)-3-(3-chloro-5-cyano-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (0.160 g, 404 µmol) was dissolved in DCM (8.79 ml). Trifluoroacetic acid (1.38 g, 928 µl, 12.1 mmol) was added and the orange solution stirred at RT. The mixture was concentrated in vacuo, redissolved in toluene and concentrated in vacuo again to obtain an orange oil. The crude was used in the next step without further purification. (200 mg, 100%). MS (ESI): m/z = 290.2 $[M+H]^+$

a) tert-butyl (3S)-4-(2-(3-chloro-5-cyano-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

3-chloro-2-fluoro-5-(oxiran-2-yl)benzonitrile (1.3 g, 6.58 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1.57 g, 7.24 mmol) were dissolved in EtOH (15 ml) and THF (15 ml) and heated up to 130 °C overnight in a scealed tube. It was then concentrated in vacuo and purified by silica column chromatography (50 g, MeOH in DCM 0% to 5%). Product obtained as a yellow oil, 1.68 g, 62%. MS (ESI): m/z = 414.3 $[M+H]^+$

b) tert-butyl (3R,9aS)-3-(3-chloro-5-cyano-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl (3S)-4-(2-(3-chloro-5-cyano-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.68 g, 4.06 mmol) was dissolved in dry toluene (29.4 ml). 2-(tributyl-l5-phosphaneylidene)acetonitrile (1.96 g, 8.12 mmol) in dry Toluene (29.4 ml) was added dropwise and the mixture heated up to 110 °C overnight. Toluene was evaporated and the residue was purified by silica column chromatography (50 g, EA in Hept 0% to 50 %). The 2 diastereomers came out as a single spot and were collected together. Product obtained as red oil (160 mg, 10%). MS (ESI): m/z = 396.2 $[M+H]^+$

Intermediate 67

5-((3R,9aS)-octahydropyrazino[2,1-c][1,4]oxazin-3-yl)-2-(trifluoromethyl)pyridin-4(1H)-one hydrobromide

tert-butyl (3R,9aS)-3-(4-methoxy-6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (0.674 g, 1.61 mmol) was dissolved in AcOH (8.07 ml) and 33% HBr in AcOH (28 mL) was added. The mixture was stirred at 100 °C for 3 hrs.Then it was concentrated under vaccum and co-evaporated twice with toluene. Used without any further purification, product obtained as a dark brown foam (1 g, crude, 100%). MS (ESI): m/z = 304.1 $[M+H]^+$

a) 4-methoxy-2-(trifluoromethyl)-5-vinylpyridine

5-bromo-4-methoxy-2-(trifluoromethyl)pyridine (1.3 g, 5.08 mmol), potassium trifluoro(vinyl)borate (816 mg, 6.09 mmol), 1,1'-bis(diphenylphosphino)ferrocene-

palladium(II)dichloride dichloromethane complex (207 mg, 254 µmol, Eq) and triethylamine (514 mg, 708 µl, 5.08 mmol) were dispersed in degassed Ethanol (38.2 ml). The reation mixture was then heated up to 130 °C for 1 hour in a scealed tube. It was then concentraed in vacuo, diluted with EtOAc, washed with water, dried over sodium sulfate, filtered, adsorbed on silica and concentrated in vacuo. It was purified by silica column chromatography (50 g, EA in Hept 0% to 15 %). Product obtained as a light yellow oil (838 mg, 81%). MS (ESI): m/z = 204.0 $[M+H]^+$

b) 4-methoxy-5-(oxiran-2-yl)-2-(trifluoromethyl)pyridine

4-methoxy-2-(trifluoromethyl)-5-vinylpyridine (0.838 g, 4.12 mmol) was dispersed in 8 mL water and 8 mL dioxane. 1-bromopyrrolidine-2,5-dione (881 mg, 4.95 mmol) in 8 mL water and 8 mL dioxane was added dropwise. It was stirred at RT for 4 hours (and then cooled down to 0 °C and 4 M NaOH solution was added dropwise. The ice-bath was removed, the mixture was stirred overnight at RT and mixed with sat. bicarbonate solution and extracted into EtOAc twice. The combined org. phases were washed with water, brine and then dried over sodium sulfate, filtered and concentrated in vacuo. It was purified by silica column chromatography (20 g, EA in Hept 0% to 50 %). Product obtained as a colorless oil (554 mg, 61%). MS (ESI): m/z = 220.1 $[M+H]^+$

c) tert-butyl (3S)-4-(2-hydroxy-2-(4-methoxy-6-(trifluoromethyl)pyridin-3-yl)ethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

4-methoxy-5-(oxiran-2-yl)-2-(trifluoromethyl)pyridine (0.550 g, 2.51 mmol,) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (597 mg, 2.76 mmol) were dissolved in Ethanol (9.51 ml) and Tetrahydrofuran (9.51 ml)) and heated up to 130 °C overnight in a scealed tube. It was then concentrated in vacuo and purified by silica column chromatography (20 g, MeOH in DCM 0% to 5%). Product was obtained as a colorless oil (1.05 g, 96%). MS (ESI): m/z = 436.3 $[M+H]^+$

d) tert-butyl (3R,9aS)-3-(4-methoxy-6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

tert-butyl (3S)-4-(2-hydroxy-2-(4-methoxy-6-(trifluoromethyl)pyridin-3-yl)ethyl)-3-(hydroxymethyl)piperazine-1-carboxylate (1.05 g, 2.41 mmol) was dissolved in dry Toluene (17.5 ml). 2-(tributyl-l5-phosphaneylidene)acetonitrile (1.16 g, 4.82 mmol) in dry Toluene (17.5 ml) was added and the mixture heated up to 100 °C. Toluene was

evaporated and the residue was purified by silica column chromatography (50 g, EA in Heptane 0% to 90 %). Yield 734 mg, 73%, mixture of both diastereomers. MS (ESI): m/z = 418.2 $[M+H]^+$

Intermediate 68

(3S,9aS)-3-(5-chloro-6-(trifluoromethyl)pyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazine trifluoroacetate

Boc-deprotection as described for example 66, starting from tert-butyl (3S,9aS)-3-(5-chloro-6-(trifluoromethyl)pyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate (200 mg, 474 umol). Product was obtained as a orange oil (274 mg, crude, 100%). MS (ESI): m/z = 322.1 $[M+H]^+$

a) 3-chloro-2-(trifluoromethyl)-6-vinylpyridine

Vinylation as described for intermediate 67, step a, starting from 3,6-dichloro-2-(trifluoromethyl)pyridine (2 g, 9.26 mmol). Product was obtained as a colorless oil (1.28 g, 67%). MS (ESI): m/z = 207.9 $[M+H]^+$

b) 3-chloro-6-(oxiran-2-yl)-2-(trifluoromethyl)pyridine

Epoxidation as described for intermediate 67, step b, starting from 3-chloro-2-(trifluoromethyl)-6-vinylpyridine (1.28 g, 6.17 mmol). Product was obtained as a colorless oil (0.5 g, 36%). MS (ESI): m/z = 224.2 $[M+H]^+$

c) tert-butyl (3S)-4-(2-(5-chloro-6-(trifluoromethyl)pyridin-2-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-carboxylate

Reaction of 3-chloro-6-(oxiran-2-yl)-2-(trifluoromethyl)pyridine (0.53 g, 2.37 mmol) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (564 mg, 2.61 mmol) as described for Intermediate 66, step a. Product was obtained as a light yellow oil (1.04 g, 99%). MS (ESI): m/z = 440.3 $[M+H]^+$

d) tert-butyl (3S,9aS)-3-(5-chloro-6-(trifluoromethyl)pyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazine-8(1H)-carboxylate

Ring closure as described for Intermediate 66, step b, starting from tert-butyl (3S)-4-(2-(5-chloro-6-(trifluoromethyl)pyridin-2-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazine-1-

carboxylate (1.05 g, 2.39 mmol). Product was obtained as a red oil (200 mg, 20%). MS (ESI): m/z = 422.3 $[M+H]^+$

Intermediate 69

2-chloro-3-(4-fluoro-1H-pyrazol-3-yl)benzoic acid

Saponification was carried out as described for intermediate 64, starting from methyl 2-chloro-3-(4-fluoro-1H-pyrazol-3-yl)benzoate (227 mg, 891 umol). Product obtained as yellow oil, 193 mg, 90%. MS (ESI): m/z = 241.0 $[M+H]^+$

a) methyl 2-chloro-3-(4-fluoro-1H-pyrazol-3-yl)benzoate

Cross coupling as described for intermediate 65, step a, starting from methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (420 mg, 1.42 mmol) and 3-bromo-4-fluoro-1H-pyrazole (100 mg, 1.56 mmol). Product obtained as yellow oil, 227 mg, 63%. ^{1}H-NMR complies.

Intermediate 70

2-bromo-1-(2-(6-methoxypyridin-3-yl)thiazol-4-yl)ethan-1-one

Intermediate 70 was synthesized starting from 6-Methoxypyridine-carbothioamide and 1,4-Dibromo-2,3-butanedione, The reactants were dissolved in DMF and 2,6-di-tert.butylpyridin was added. The mixture was stirred at room temperature before the product was isolated.

General methods and columns used for reversed phase HPLC and SFC purifications:

HPLC Prep Method A:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, gradient 30-50-65-100 ACN in water + 0.1% HCOOH

HPLC Prep Method B:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, gradient 20-40-55-100 ACN in water + 0.1% HCOOH

HPLC Prep Method C:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, 40 ml/min, gradient 30-80 ACN in water + 0.1% HCOOH

HPLC Prep Method D:

YMC-Triart C18, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, gradient 20-40-60-100 ACN in water + 0.1% HCOOH

HPLC Prep Method E:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, 40 ml/min, gradient 30-80 ACN in water + 0.1% TEA

HPLC Prep Method F:

YMC-Triart C18, 12 nm, 5 µm, 100 x 30 mm, 11 min run time, gradient 30-50-65-100 ACN in water + 0.1% HCOOH

HPLC Prep Method G:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 11 min run time, gradient 10-25-40-100 ACN in water + 0.1% HCOOH

HPLC Prep Method H:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 11 min run time, gradient 15-35-50-100 ACN in water + 0.1% HCOOH

HPLC Prep Method J:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, gradient 20-40-55-100 ACN in water + 0.1% TEA

HPLC Prep Method K:

YMC-Triart C18, 12 nm, 5 µm, 100 x 30 mm, 11 min run time, gradient 20-98 ACN in water + 0.1% TEA

HPLC Prep Method L:

Gemini NX, 12 nm, 5 µm, 100 x 30 mm, 15 min run time, gradient 5-50-100 ACN in water + 0.1% HCOOH

SFC Method A

ChiralPak IB, 12 nm, 5 µm, 250 x 4.6 mm, 25% MeOH

SFC Method B

ChiralPak AY-H, 12 nm, 5 µm, 250 x 4.6 mm, Gradient 30-40% EtOAC

SFC Method C

ChiralPak OD-H, 12 nm, 5 µm, 250 x 4.6 mm, 35% MeOH

SFC Method D

ChiralPak IC, 12 nm, 5 µm, 250 x 4.6 mm, 40% MeOH + 0.2% Diethylamine

SFC Method E

ChiralPak AY-H, 12 nm, 5 µm, 250 x 4.6 mm, 25% MeOH

Example 47

[3-(3-bicyclo[4.2.0]octa-1,3,5-trienyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

i) (2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**Intermediate 1**, 695 umol, 198 mg , dissolved in 2 mL MeOH) was added to 2-(3-bicyclo[4.2.0]octa-1(6),2,4-trienyl)oxirane (**Intermediate 36**, 94 mg, 580 umol) in a microwave vial. The vial was sealed and the mixture was heated in a 100 min at 120 °C. It was concentrated *in vacuo* and purified by silica column chromatography (0% to 20% MeOH in DCM). The product eluted together with an impurity. It was purified again in EtOAc/Heptanes and the product eluted as a very broad peak at 100% EtOAc. The product was obtained as a colorless oil (45 mg, 18%). ESI(MS) m/z = 431.3 $[M+H]^+$

ii) (4-(2-(bicyclo[4.2.0]octa-1,3,5-trien-3-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)(2-chloro-3-methoxyphenyl)methanone (104 umol, 45 mg) was dissolved in 0.9 ml dry Toluene and 0.2 ml dry THF to aid solution, cyanomethylenetributylphosphorane (125 umol, 36 mg) in 100 uL dry Toluene was added to the microwave vial. The vial was capped, degassed with argon and heated at 100 °C under argon while stirring. LCMS showed only little conversion to product, therefore 3

additional portions of cyanomethylenetributylphosphorane (in total 90 mg, 208 umol) were added over the next 30 hours while stirring at 100°C continued. The solvent was partly evaporated and the orange-brown solution was subjected to silica column purification (0% - 15% MeOH in DCM). Additional SFC purification to remove the co-eluting Tributylphosphinoxid yielded the pure product as a colorless oil (mixture of all four stereoisomers, 3.7 mg, 7.8%) ESI(MS) m/z = 413.3 $[M+H]^+$

Example 48

(2-chloro-3-methoxy-phenyl)-[3-[4-(difluoromethyl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 48 was obtained from **Intermediate 1** (104 mg, 365 umol) and 2-(4-(difluoromethyl)phenyl)oxirane (CAS 1546906-13-1, 82 mg, 482 umol), using the same procedure as described for Example 47. Colorless oil, mixture of all four stereoisomers 6.9 mg (18%). ESI(MS) m/z = 437.3 $[M+H]^+$

Example 9

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-fluoro-3-methoxy-phenyl)methanone

A mixture of (9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine (**Intermediate 2**, 0.080 g, 295 µmol), 2-fluoro-3-methoxybenzoic acid (55.3 mg, 325 µmol) and HATU (124 mg, 325 µmol) was dissolved in DMF (2 ml) and then DIPEA (115 mg, 155 µl, 886 µmol) was added to the solution. The reaction mixture was stirred at RT for 1 hour. The crude product was purified by prep. HPLC (method C) to get the pure product as a white, lyophilized powder. 41 mg (32.8%). ESI(MS) m/z = 423.13 $[M+H]^+$

The following examples were prepared following the same procedure as described for Example 9:

Ex.	**Building Blocks**	**ESI(MS)**
17	Intermediate 2 2-chloro-3,5-dimethoxybenzoic acid	m/z = 469.1 $[M+H]^+$

	Minor isomer (cis, major: Example 18) , separated with HPLC (Method A)	
18	Intermediate 2 2-chloro-3,5-dimethoxybenzoic acid Major isomer (trans), separated with HPLC (Method A)	m/z = 469.1 $[M+H]^+$
19	Intermediate 2 2-chloro-3,4-dimethoxybenzoic acid Major isomer (trans), separated with HPLC (Method B)	m/z = 469.1 $[M+H]^+$
20	Intermediate 2 2-cyano-3-methylbenzoic acid Major isomer (trans), separated with HPLC (Method B)	m/z = 414.1 $[M+H]^+$
21	Intermediate 2 2-fluoro-3-trifluoromethoxybenzoic acid Major isomer (trans), separated with HPLC (Method A)	m/z = 477.1 $[M+H]^+$
25	Intermediate 2 2-chloro-3-difluoromethoxybenzoic acid Major isomer (trans), separated with HPLC (Method C)	m/z = 475.1 $[M+H]^+$
26	Intermediate 2 Intermediate 13 Major isomer (trans), separated with HPLC (Method D)	m/z = 489.1 $[M+H]^+$
27	Intermediate 2 Intermediate 14	m/z = 500.1 $[M+H]^+$

	Major isomer (trans), separated with HPLC (Method B)	
28	Intermediate 2 Intermediate 15 Major isomer (trans), separated with HPLC (Method B)	m/z = 500.1 $[M+H]^+$
29	Intermediate 2 Intermediate 16 Major isomer (trans), separated with HPLC (Method B)	m/z = 487.1 $[M+H]^+$
30	Intermediate 2 Intermediate 17 Major isomer (trans), separated with HPLC (Method E)	m/z = 486.1 $[M+H]^+$
31	Intermediate 2 Intermediate 18 Major isomer (trans), separated with HPLC (Method E)	m/z = 487.1 $[M+H]^+$
34	Intermediate 2 Intermediate 19 Major isomer (trans), separated with HPLC (Method B)	m/z = 501.1 $[M+H]^+$
35	Intermediate 2 Intermediate 20 Major isomer (trans), separated with HPLC (Method B)	m/z = 501.1 $[M+H]^+$
36	Intermediate 2 Intermediate 21 Major isomer (trans), separated with HPLC (Method B)	m/z = 475.1 $[M+H]^+$

37	Intermediate 2 Intermediate 22 Major isomer (trans), separated with HPLC (Method B)	m/z = 500.1 $[M+H]^+$
38	Intermediate 2 Intermediate 23 Major isomer (trans), separated with HPLC (Method B)	m/z = 475.1 $[M+H]^+$
39	Intermediate 2 Intermediate 24 Major isomer (trans), separated with HPLC (Method B)	m/z = 503.1 $[M+H]^+$
40	Intermediate 2 Intermediate 25 Major isomer (trans), separated with HPLC (Method B)	m/z = 490.3 $[M+H]^+$
41	Intermediate 2 CAS: 1895008-64-6 Major isomer (trans), separated with HPLC (Method D) and subsequent SFC (Method A)	m/z = 463.1 $[M+H]^+$
42	Intermediate 2 Intermediate 26 Major isomer (trans), separated with HPLC (Method B)	m/z = 506.3 $[M+H]^+$
43	Intermediate 2 Intermediate 27 Major isomer (trans), separated with HPLC (Method B)	m/z = 494.3 $[M+H]^+$

44	Intermediate 2 Intermediate 28 Major isomer (trans), separated with HPLC (Method B)	m/z = 476.3 $[M+H]^+$
49	Intermediate 2 Intermediate 29 Major isomer (trans), separated with HPLC (Method F)	m/z = 493.3 $[M+H]^+$
50	Intermediate 2 Intermediate 29 Minor isomer (cis, major: example 49), separated with HPLC (Method F)	m/z = 493.3 $[M+H]^+$
1	Intermediate 2 CAS: 33234-36-5 Major isomer (trans), separated by flash column chromatography (SiO_2, EtOAc/Heptan 0-100%). Contains ca. 25% cis isomer.	m/z = 439.1 $[M+H]^+$
2	Intermediate 2 CAS: 88377-29-1 Major isomer (trans), separated by flash column chromatography (SiO_2, EtOAc/Heptan 0-100%). Contains ca. 25% cis isomer.	m/z = 485.1 $[M+H]^+$
5	Intermediate 2 CAS: 700844-19-5 Major isomer (trans), separated with HPLC (Method C)	m/z = 466.1 $[M+H]^+$
8	Intermediate 2 CAS: 1780768-22-0	m/z = 450.1 $[M+H]^+$

	Major isomer (trans), separated with HPLC (Method E) and subsequent SFC (Method B)	
16	Intermediate 2 CAS: 179024-66-9 Major isomer (trans), separated with HPLC (Method C)	m/z = 460.1 $[M+H]^+$
22	Intermediate 2 CAS: 19240-62-1 Major isomer (trans), separated with HPLC (Method C)	m/z = 485.1 $[M+H]^+$
23	Intermediate 2 Intermediate 30 Major isomer (trans), separated with HPLC (Method C)	m/z = 515.1 $[M+H]^+$
72	Intermediate 7 Intermediate 29 Isomer (trans), separated with HPLC (Method B)	m/z = 482.3 $[M-H]^-$
76	Intermediate 6 Intermediate 32 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 492.2 $[M+H]^+$
108	Intermediate 2 Intermediate 31 Major isomer (trans), separated with HPLC (Method B)	m/z = 480.2 $[M+H]^+$

110	Intermediate 53 CAS: 33234-36-5 Purified by flash chromatography (SiO_2, EtOAc in Heptane 0% to 100%)	m/z = 501.2 $[M+H]^+$
111	Intermediate 2 CAS: 886499-40-7 Major diastereomer (trans), purified by HPLC (Method B)	m/z = 457.2 $[M+H]^+$
112	Intermediate 63 Intermediate 64 Purified by preparative HPLC (Method D).	m/z = 550.2 $[M+H]^+$
113	Intermediate 10 Intermediate 55 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 499.1 $[M+H]^+$
115	Intermediate 49 Intermediate 64 Major diastereomer (trans), purified by HPLC (Method B)	m/z = 516.2 $[M+H]^+$
116	Intermediate 6 CAS: 886499-40-7 Major diastereomer (trans), purified by HPLC (Method F)	m/z = 473.1 $[M+H]^+$
117	Intermediate 49 Intermediate 55	m/z = 498.2 $[M+H]^+$

	Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	
118	Intermediate 51b Intermediate 58 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 508.3 $[M+H]^+$
121	Intermediate 2 Intermediate 58 Major isomer (trans), separated with HPLC (Method H)	m/z = 492.3 $[M+H]^+$
122	Intermediate 51a Intermediate 58 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 526.3 $[M+H]^+$
123	Intermediate 2 Intermediate 59 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 516.5 $[M+H]^+$
124	Intermediate 2 Intermediate 60 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 516.3 $[M+H]^+$
126	Intermediate 2 Intermediate 54	m/z = 507.3 $[M+H]^+$

	Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	
132	Intermediate 67 Intermediate 64 Trans diastereomer, isolated with HPLC (Method D). Second diastereomer is Example 151	m/z = 550.2 $[M+H]^+$
133	Intermediate 49 Intermediate 65 Major isomer (trans), separated with HPLC (Method B)	m/z = 510.2 $[M+H]^+$
134	Intermediate 2 Intermediate 57 Major isomer (trans), separated with HPLC (Method H)	m/z = 493.2 $[M+H]^+$
135	Intermediate 66 CAS 33234-36-5 Diastereomer (trans), isolated by HPLC (Method B)	m/z = 464.3 $[M+H]^+$
138	Intermediate 2 Intermediate 62 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 500.3 $[M+H]^+$
140	Intermediate 49 Intermediate 69 Purified by preparative HPLC (Method L)	m/z = 492.2 $[M+H]^+$

147	Intermediate 49 CAS 886499-40-7 Purified by preparative HPLC (Method K)	m/z = 456.1 $[M+H]^+$
148	Intermediate 68 CAS 33234-36-5 Major diastereomer, isolated by preparative HPLC (Method A)	m/z = 490.2 $[M+H]^+$
151	Intermediate 67 Intermediate 64 Cis diastereomer, isolated with HPLC (Method D). Second diastereomer is Example 132	m/z = 550.2 $[M+H]^+$
152	Intermediate 10 Intermediate 56 Purified by flash chromatography (SiO_2, MeOH in DCM 0% to 10%)	m/z = 500.3 $[M+H]^+$
155	Intermediate 63 CAS 33234-36-5 Purified by preparative HPLC (Method B)	m/z = 472.2 $[M+H]^+$
158	Intermediate 2 Intermediate 61 Major isomer (trans), separated with HPLC (Method H)	m/z = 503.3 $[M+H]^+$
159	Intermediate 2 CAS: 886499-40-7	m/z = 457.2 $[M+H]^+$

	Minor diastereomer (cis), purified by HPLC (Method B) (Major isomer is example 111)	

Example 6

[(3R,9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

A mixture of (9aS)-3-(3-bromo-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine (**Intermediate 3**, 1.36 g, 3.87 mmol), 2-chloro-3-methoxybenzoic acid (722 mg, 3.87 mmol) and HATU (1.4 g, 3.67 mmol) was dissolved in DMF (15 ml) and then DIPEA (1.5 mg, 2.03 ml, 11.6 mmol) was added to the solution. The reaction mixture was stirred at RT for 30 minutes. The crude product was purified by prep. HPLC (method C) to get the pure product as a white, lyophilized powder. 1.46 g (78 %). ESI(MS) m/z = 485.1 $[M+H]^+$

Example 10

(2-chloro-3-methoxy-phenyl)-[(3R,9aS)-3-[4-fluoro-3-[rac-(E)-prop-1-enyl]phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

In a microwave vial [(3R,9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone (**example 6**, 54 mg, 112 µmol), sodium carbonate (29.6 mg, 279 µmol) and (E)-prop-1-en-1-ylboronic acid (14.4 mg, 167 µmol) in Dioxane (1.2 ml)/ Water (120 µl) was degassed with argon. Tetrakis(triphenylphosphine)palladium (0) (25.8 mg, 22.3 µmol) was added and the mixture was heated at 110° C for 35 min in the microwave. The mixture was diluted with water and extracted 3× with DCM. The combined organic layers were washed with sat. bicarb solution and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified via flash chromatography on silica gel to yield the desired product as an off-white powder. 26 mg (52%). ESI(MS) m/z = 445.2 $[M+H]^+$

The following examples were prepared as described for example 10:

Ex.	**Building Blocks**	**ESI(MS)**

11	**Example 6** phenylboronic acid Major isomer (trans) isolated by SFC (method C)	m/z = 481.2 $[M+H]^+$
12	**Example 6** phenylboronic acid Minor isomer (cis, major: example 11), isolated by SFC (Method C)	m/z = 481.2 $[M+H]^+$

Example 13

[(3R,9aS)-3-(4-fluoro-3-prop-1-ynyl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

In a microwave vial [(3R,9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone (**example 6**, 43 mg, 88.9 µmol), TEA (27 mg, 37.2 µl, 267 µmol), trimethyl(prop-1-yn-1-yl)silane (39.9 mg, 52.7 µl, 356 µmol), PdCl2(DPPF)-CH2Cl2 adduct (7.26 mg, 8.89 µmol), copper(I) iodide (2.5 mg, 13.3 umol) in DMF (0.75 ml) was degassed with argon. Subsequently TBAF 1M in THF (133 µl, 133 µmol) was added. Reaction mixture was then heated in the microwave at 120 °C for 2.5 h. The mixture was diluted with water and extracted 3× with DCM. The combined organic layers were washed with sat. bicarb solution and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by SFC (method C). 5 mg (10.5%). ESI(MS) m/z = 443.2 $[M+H]^+$

Example 14

[(3R,9aS)-3-(3-cyano-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

A microwave vial was charged with [(3R,9aS)-3-(3-bromo-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone (**example 6**, 62 mg, 128 µmol), dicyanozinc (10.1 mg, 85.9 µmol), TMEDA (4.47 mg, 5.8 µl, 38.4 µmol) and was placed under argon. DMF anhydrous (1 ml) was added and the mixture was degassed for 5 min. Pd2(dba)3 (11.7 mg, 12.8 µmol) and xantphos (11.1 mg,

19.2 µmol) were added and the mixture was degassed for 5 min. The vial was sealed and irradiated at 110 °C in the microwave for 40 min. The reaction mixture was diluted with DCM, poured into 5%$NaHCO_3$ and extracted thrice with DCM. The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. This was then purified by prep.HPLC (method C) to get the final compound as a white lyoph powder (34 mg, 59.2%). ESI(MS) m/z = 430.1 $[M+H]^+$

Example 24

[(3R,9aS)-3-(3-cyclopropyl-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

A microwave vial was charged with ((3R,9aS)-3-(3-bromo-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (**example 6**, 67 mg, 138 µmol), potassium cyclopropyltrifluoroborate (26.6 mg, 180 µmol) and cesium carbonate (135 mg, 415 µmol) in toluene (1.0 ml)/ Water (100 µl) and was degassed with argon. cataCXium A Pd G2 (9.26 mg, 13.8 µmol) was added and the mixture was heated to 100°C for 16 hr. Extracted with EtOAc/ water (3x), dried over Na_2SO_4, conc. *in vacuo*.Pre-purified by SiO2 flash chromatography, product isolated by preparative HPLC (method C) as a white, lyophilized powder (2 mg, 3.2%). ESI(MS) m/z = 445.2 $[M+H]^+$

Example 32 and Example 33

(2-chloro-3-methoxy-phenyl)-[(rel-3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[(rel-3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-9a-methyl-1,3,4,6,7,9-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone

A mixture of 2-chloro-3-methoxybenzoic acid (56.6 mg, 304 µmol), 3-(3-chloro-4-fluorophenyl)-9a-methyloctahydropyrazino[2,1-c][1,4]oxazine hydrochloride (**intermediate 4**, 75 mg, 233 µmol) and HATU (133 mg, 350 µmol) was dissolved in DMF (2.08 ml) and then DIPEA (151 mg, 204 µl, 1.17 mmol) was added to the solution and the reaction mixture was stirred at rt for 30 min. The reaction mixture was extracted with EtOAc/ sat. $NaHCO_3$ (3x30 ml), brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by SFC (method C) and HPLC (method A) yielded the two products.

Example 32: lyophilized, white powder (21 mg, 18%), ESI(MS) m/z = 453.1 $[M+H]^+$

Example 33: lyophilized, white powder (10 mg, 9%), ESI(MS) m/z = 453.1 $[M+H]^+$

Example 45 and Example 46

(2-chloro-3-methoxy-phenyl)-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[(3S,9aR)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone

In a 25 mL round-bottomed flask, (2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**intermediate 1**, 143 mg, 502 µmol) was combined with Tetrahydrofuran (2.5 ml) to give a colorless solution. DIPEA (84.4 mg, 114 µl, 653 µmol) and 2-bromo-1-(3-chloro-4-fluorophenyl)ethan-1-one (126 mg, 502 µmol) were added. The reaction mixture was stirred at room temperature for 2 hours. The reaction was diluted with EtOAc, washed with sat. $NaHCO_3$ solution, dried over NaSO4, filtered and concentrated. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography. (DCM / MeOH 0-20%). 222 mg of product were isolated, they were submitted to chiral SFC (method E) to separate the isomers.

Example 45 85 mg (37%), light-brown solid. ESI(MS) m/z = 455.3 $[M+H]^+$

Example 46 81 mg (35%), light-brown solid. ESI(MS) m/z = 455.3 $[M+H]^+$

Example 51 and **Example 52**

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(2,4-dimethylthiazol-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

i) (2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (intermediate 1, 164 mg, 577 umol) and 2-bromo-1-(2,4-dimethylthiazol-5-yl)ethan-1-one (135 mg, 0.577 umol) were dissolved/dispersed in 8 mL THF. DIPEA (130 uL, 750 umol) was added dropwise over 10 min. The dark green reaction mixture was stirred at room temperature. After 18 h, the reaction was diluted with EtOAc, washed with sat. $NaHCO_3$ solution, the aqueous phase backextracted with EtOAc and the combined org. phases dried

over $NaSO_4$, filtered, adsorbed on silica and concentrated *in vacuo*. The crude was purified by silica column chromatography (SiO_2, DCM:MeOH 100:0 to 90:10). rac-(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone was isolated as racemate (100 mg, 40%).

ii) rac-(2-chloro-3-methoxyphenyl)((3R,9aS)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (60 mg, 137 umol) was dissolved in 4.4 mL DCM and 2.2 mL TFA. Triethylsilane (66 uL, 411 umol) was added and the mixture stirred at 45 °C. After 48 h, additional TFA (1 mL) and silane (30 uL) was added and the mixture heated to 65 °C. After another 72 h, the mixture was concentrated *in vacuo* and purified by silica column chromatography (DCM/MeOH). Chiral SFC (method A) yielded the two separate enantiomers (1.8 mg, 2.4%; 2.1 mg, 3%). ESI(MS) m/z = 422.2 $[M+H]^+$

Example 53 and Example 54

(2-chloro-3-methoxy-phenyl)-[rac-(3R,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[rac-(3S,9aR)-3-(5-bromo-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

i) 2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**intermediate 1**, 218 mg, 765 umol) and 5-bromo-2-(oxiran-2-yl)pyridine (CAS 1335050-95-7, 153 mg, 765 umol) were dissolved in 2 mL MeOH in a microwave vial and heated in the microwave for 85 min at 120 °C. It was then purified by silica column chromatography (DCM/MeOH) to yield (4-(2-(5-bromopyridin-2-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)(2-chloro-3-methoxyphenyl)methanone as a dark red oil (262 mg, 71%). ESI(MS) m/z = 486.2 $[M+H]^+$

ii) (4-(2-(5-bromopyridin-2-yl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)(2-chloro-3-methoxyphenyl)methanone (73 mg, 151 umol) was dissolved in 1.2 mL dry toluene. 2-(tributyl-l5-phosphaneylidene)acetonitrile (127 mg, 527 umol) in 0.3 mL toluene was added and the mixture degassed with argon and then heated up to 100 °C for 4h. The mixture was concentrated *in vacuo*. It was purified by silica column chromatography (DCM/MeOH 100/0 to 90/10). The still impure compound was obtained as a brown viscous oil (66 mg) and submitted to SFC to separate the two diastereomers.

Example 53 (trans) 1.7 mg, 2.4%; ESI(MS) m/z = 468.1 $[M+H]^+$

Example 54 (cis) 4.7 mg, 6.7%; ESI(MS) m/z = 468.1 $[M+H]^+$

Example 58 and Example 59

(2-chloro-3-methoxy-phenyl)-[rac-(3S,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[rac-(3R,9aS)-3-(5-chloro-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Examples 58 and 59 was synthesized according to the procedure as described for examples 53 and 54, starting from 3-chloro-5-(oxiran-2-yl)pyridine (CAS 1335057-62-9, 72 mg, 464 umol) and **intermediate 1** (120 mg, 0.42 mmol).

Example 58 (cis), 5.4 mg, ESI(MS) m/z = 422.2 $[M+H]^+$

Example 59 (trans), 5.8 mg, ESI(MS) m/z = 422.2 $[M+H]^{+60}$

Example 60 and Example 61

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(1H-benzimidazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone

(2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**intermediate 1**, 96 mg, 337 umol) and DIPEA (65 uL, 371 umol) were dispersed in 2 mL dry THF and cooled down in an ice bath. 1-(1H-benzo[d]imidazol-2-yl)-2-chloroethan-1-one (79 mg, 405 umol) was dissolved in 1 mL dry THF and added dropwise to the solution over 10 min. It was then heated up to 70°C overnight. It was concentrated *in vacuo* and then purified by silica column chromatography (DCM:MeOH 100:0 to 90:10). The compound was obtained as a yellow solid (47 mg, 24%), the two enantiomers were separated by chiral SFC (method D).

Example 60 (enantiomer A) 10.9 mg, ESI(MS) m/z = 443.2 $[M+H]^+$

Example 61 (enantiomer B) 16.2 mg, ESI(MS) m/z = 443.2 $[M+H]^+$

Example 63

(2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-[6-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 63 was synthesized according to the procedure as described for examples 53 and 54, starting from 2-(oxiran-2-yl)-6-(trifluoromethyl)pyridine (CAS 1346534-02-8, 187 mg, 989 umol) and **intermediate 1** (262 mg, 920 umol). Purification by SFC (twice, methods C and E) yielded the 4 stereoisomers enantiopure.

Example 63 (major stereoisomer, trans, Enantiomer A), 13.8 mg (6.4%), colorless oil, ESI(MS) m/z = 456.2 $[M+H]^+$

Example 66 and Example 67

(2-chloro-3-methoxy-phenyl)-[rel-(3R,9aR)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone and (2-chloro-3-methoxy-phenyl)-[rel-(3S,9aS)-3-(4,5-dichloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Examples 66 and 67 was synthesized according to the procedure as described for examples 53 and 54, starting from 4,5-dichloro-2-(oxiran-2-yl)pyridine (**Intermediate 37**, 159 mg, 669 umol) and **intermediate 1** (170 mg, 284 umol). Product was isolated as two separate enantiomers (both trans) after chiral SFC.

Example 66 (enantiomer A) 8.7 mg, 4.6%, ESI(MS) m/z = 456.1 $[M+H]^+$

Example 67 (enantiomer B) 9.6 mg, 5.4%, ESI(MS) m/z = 456.1 $[M+H]^+$

Example 65

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)pyridin-3-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

(S)-(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**intermediate 5**, 40 mg, 118 umol) and DIPEA (16.8 mg, 130 umol) were dispersed in 0.8 mL dry THF and cooled down to 0 °C. 2-bromo-1-(6-(trifluoromethyl)pyridin-2-yl)ethan-1-one (CAS 1379332-23-6, 32 mg, 118 umol) was dissolved in 0.5 mL dry THF and added dropwise to the solution over 10 min. After 5 h the reaction was allowed to warm to RT and stirred overnight. The mixture was diluted

with water and extracted into EtOAc twice. The combined organic phases were dried over sodium sulfate, concentrated *in vacuo* and purified by silica column chromatography (MeOH in DCM 0% to 10%). The product was obtained as a white solid, 30.8 mg, 48%. ESI(MS) m/z = 526.2 $[M+H]^+$

Example 68

[(9aS)-3-[6-(trifluoromethyl)-3-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)pyridin-3-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone (**example 65**, 5.7 mg, 10.8 umol) was dissolved in 0.3 mL dry DCM and 0.15 mL TFA. TES (5.2 uL, 32.5 umol) was added to the yellowish solution and it was stirred at 60°C for 64 h upon which the solution turned red. The reaction mixture was concentrated *in vacuo* and the residual TFA coevaporated with toluene. The crude was then purified by reverse phase HPLC (method B) to obtain the target compound as a white solid (2.5 mg, 45%). Mixture of two diastereomers (trans/cis 2:1). ESI(MS) m/z = 510.2 $[M+H]^+$

Example 69

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3R,9aS)-3-[4-(difluoromethoxy)phenyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone

(S)-(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (**intermediate 5**, 37 mg, 109 umol) and DIPEA (23 uL, 131 umol) were dispersed in 1.1 mL dry THF and cooled down to 0°C. 2-bromo-1-(4-(difluoromethoxy)phenyl)ethan-1-one (CAS 141134-24-9, 32 mg, 120 umol) was dissolved in 0.3 mL dry THF and added dropwise to the solution over 10 min. After stirring overnight at RT,the reaction was cooled down again and another 6 uL DIPEA and 10 mg of 2-bromo-1-(4-(difluoromethoxy)phenyl)ethan-1-one in 0.3 mL dry THF were added. After 30 min, it was warmed up to RT. 3.5 h later, it was diluted with water and extracted into EtOAc twice. The combined organic phases were dried over sodium sulfate, concentrated *in vacuo* and purified by silica column chromatography (MeOH in DCM 0% to 10%). The product was isolated as yellow solid (28.8 mg, 50%). ESI(MS) m/z = 523.2 $[M+H]^+$

Example 73

(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)((9aS)-3-(4-(difluoromethoxy)phenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone

Example 73 was prepared as described for example 68, starting from example 69 (10.9 mg, 20.8 umol). Reaction was complete after 3 hours, yielding the product as a white solid (10.3 mg, 97%). Mixture of diastereomers trans/cis 3:1. ESI(MS) m/z = 507.2 $[M+H]^+$

Example 70

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(9aS)-3-(6-bromo-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

(9aS)-3-(5-bromopyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazine hydrochloride (intermediate 38, 25 mg, 74.7 umol), 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 24.3 mg, 101 umol) and HATU (38.3 mg, 101 umol) were dissolved in 800 uL DMF. DIPEA (46 uL, 261 umol) was added and the reaction stirred at RT. After 3 h, it was concentrated in vacuo and separated by preparative HPLC. 2.7 mg (6%) of desired product were obtained as a white, lyophilized solid. Mixture of both diastereomers. ESI(MS) m/z = 522.2 $[M+H]^+$

Example 71

[(3S,9aS)-3-hydroxy-3-(1-methylbenzimidazol-2-yl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 71 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(1-methyl-1H-benzo[d]imidazol-2-yl)ethan-1-one. Yield 203 mg, 80.1%. ESI(MS) m/z = 457.3 $[M+H]^+$

Example 74

3-[(3S,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one

((3S,9aS)-3-(2-(benzyloxy)-5-chloropyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (**intermediate 35B**, 31.6 mg, 59.8 umol) was dissolved in 1 mL dry DCM and 1 mL TFA was added dropwise. After 1.5 h, the

mixture was concentrated *in vacuo*, dissolved in EtOAc and washed with sat. bicarbonate solution. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. It was then purified by silica chromatography (MeOH in DCM 0% to 10%). The desired product was obtained as an orange-brown solid (19.3 mg, 66%). ESI(MS) m/z = 438.2 $[M+H]^+$

Example 75

3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one

((3S,9aS)-3-(2-(benzyloxy)-5-chloropyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (**intermediate 35A**, 44.7 mg, 84.6 umol) was dissolved in 1.3 mL dry DCM and 1.3 mL TFA was added dropwise. After 1.5 h, the mixture was concentrated *in vacuo*, dissolved in EtOAc and washed with sat. bicarbonate solution. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. It was then purified by silica chromatography (MeOH in DCM 0% to 10%). The desired product was obtained as a light brown solid (34.3 mg, 93%). ESI(MS) m/z = 438.2 $[M+H]^+$

Example 77

3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-3-yl]-5-chloro-1H-pyridin-2-one

Example 77 was prepared as described for **example 70**, starting from 5-chloro-3-((3R,9aS)-octahydropyrazino[2,1-c][1,4]oxazin-3-yl)pyridin-2-ol 2,2,2-trifluoroacetate (intermediate 49, 24 mg, 62.5 umol) and intermediate 29 (24.5 mg, 101 umol). Purified by preparatice HPLC (method G), product obtained as white, lyophilized solid (5.4 mg, 14.6%). ESI(MS) m/z = 492.2 $[M+H]^+$

Example 83 and Example 84

(2-chloro-3-methoxyphenyl)((3S,9aS)-3-(5-chloro-4-methylpyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone and (2-chloro-3-methoxyphenyl)((3R,9aS)-3-(5-chloro-4-methylpyridin-2-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone

Examples 83 and 84 were synthesized according to the procedure as described for examples 53 and 54, starting from 5-chloro-4-methyl-2-(oxiran-2-yl)pyridine (intermediate 39, 130 mg, 766 umol) and **intermediate 1S** (291 mg, 0.92 mmol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 83 (major stereoisomer, trans), yellow solid, 47 mg, ESI(MS) m/z = 436.2 $[M+H]^+$

Example 84 (minor stereoisomer, cis, contains ca. 30% trans), yellow solid, 25.8 mg (9.8%), ESI(MS) m/z = 436.2 $[M+H]^+$

Example 89

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 89 was synthesized according to the procedure as described for examples 53 and 54, starting from 3-(oxiran-2-yl)-6-(trifluoromethyl)pyridazine (see intermediate 11, steps a+b, 72 mg, 379 umol) and **intermediate 1S** (178 mg, 530 umol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 89 (major stereoisomer, trans), white lyophilized solid, 5.3 mg (4.0%), ESI(MS) m/z = 457.2 $[M+H]^+$

Example 90 and example 91

[(3R,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone and [(3S,9aS)-3-(4-chloro-2-pyridyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Examples 90 and 91 were synthesized according to the procedure as described for examples 53 and 54, starting from 4-chloro-2-(oxiran-2-yl)pyridine (CAS 115548-57-7, 90 mg, 578 umol) and **intermediate 1S** (220 mg, 694 umol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 90 (minor stereoisomer, cis), light brown solid, 17.2 mg, ESI(MS) m/z = 422.1 $[M+H]^+$

Example 91 (major stereoisomer, trans), light brown solid, 18.7 mg, ESI(MS) m/z = 422.1 $[M+H]^+$

Example 98

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 98 was synthesized according to the procedure as described for examples 53 and 54, starting from 5-chloro-2-(oxiran-2-yl)-4-(trifluoromethyl)pyridine (intermediate 40, 192 mg, 859 umol) and **intermediate 1S** (353 mg, 1.12 mmol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 98 (major stereoisomer, trans), white lyophilized solid, 22.8 mg (9.1%) ESI(MS) m/z = 490.2 $[M+H]^+$

Example 99

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[4-(trifluoromethoxy)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 99 was synthesized according to the procedure as described for examples 53 and 54, starting from 2-(oxiran-2-yl)-4-(trifluoromethoxy)pyridine (intermediate 41, 218 mg, 1.06 mmol) and **intermediate 1S** (403 mg, 1.28 mmol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 99 (major stereoisomer, trans), light yellow lyophilized solid, 51.1 mg (16%) ESI(MS) m/z = 472.2 $[M+H]^+$

Example 101

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-fluoro-4-(trifluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 101 was synthesized according to the procedure as described for examples 53 and 54, starting from 5-fluoro-2-(oxiran-2-yl)-4-(trifluoromethyl)pyridine (intermediate 42, 308 mg, 1.49 mmol) and **intermediate 1S** (508 mg, 1.78 mmol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 101 (major stereoisomer, trans), off-white lyophilized solid, 30.6 mg (12.8%) ESI(MS) m/z = 474.2 $[M+H]^+$

Example 104

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-(difluoromethyl)-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 104 was synthesized according to the procedure as described for examples 53 and 54, starting from 5-chloro-4-(difluoromethyl)-2-(oxiran-2-yl)pyridine (intermediate 43, 350 mg, 1.53 mmol) and **intermediate 1S** (524 mg, 1.84 mmol). Purification by preparatice HPLC yielded the two diastereomers separately.

Example 104 (major stereoisomer, trans), off-white lyophilized solid, 68.2 mg (14.1%) ESI(MS) m/z = 472.2 $[M+H]^+$

Example 107

(2-chloro-3-methoxy-phenyl)-[(3S,9aS)-3-[5-chloro-4-bromo-2-pyridyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]methanone

Example 107 was synthesized according to the procedure as described for examples 53 and 54, starting from 4-bromo-5-chloro-2-(oxiran-2-yl)pyridine (intermediate 44, 304 mg, 908 umol, 70% pure) and **intermediate 1S** (315 mg, 1.22 mmol). Purification by preparative HPLC yielded the two diastereomers separately.

Example 107 (major stereoisomer, trans), off-white lyophilized solid, 23 mg (8.4%) ESI(MS) m/z = 502.1 $[M+H]^+$

Example 102

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone

(3R,9aS)-3-(3-chloro-4-fluorophenyl)octahydropyrazino[2,1-c][1,4]oxazine (**intermediate 2**, 26.5 mg, 97.9 umol), 2-fluoro-3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoic acid (intermediate 45, 33.5 mg, 97.9 umol) and DIPEA (56 uL, 323 umol) were mixed with 1 mL dry THF and cooled to 0 °C. T3P (93 mg of a 50% wt/wt solution in EtOAc, 147 umol) in 0.2 mL dry THF was added dropwise over 10 min. After 20 min, it was warmed

to RT. 30 min later, it was diluted with EtOAc, washed with sat. bicarbonate solution and then brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a yellow solid (30.5 mg, 51%). ESI(MS) m/z = 527.2 $[M+H]^+$

Example 103

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[3-[5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]methanone

Example 103 was prepared as described for example 102, starting from **intermediate 2** (22.9 mg, 84.6 umol) and 3-(5-(trifluoromethyl)-1H-pyrazol-4-yl)benzoic acid (intermediate 46, 26 mg, 102 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a white solid (19.9 mg, 37.4%). ESI(MS) m/z = 509.2 $[M+H]^+$

Example 105

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one

Example 105 was prepared as described for example 102, starting from **intermediate 2** (40 mg, 148 umol) and lithium 2-chloro-3-(2-oxo-1,2-dihydropyridin-4-yl)benzoate (intermediate 47, 37.8 mg, 148 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a off-white solid (14.7 mg, 17.2%). ESI(MS) m/z = 502.2 $[M+H]^+$

Example 106

5-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyridin-2-one

Example 106 was prepared as described for example 102, starting from **intermediate 2** (60 mg, 222 umol) and 2-chloro-3-(6-oxo-1,6-dihydropyridin-3-yl)benzoic acid (intermediate 48, 55 mg, 222 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a white solid (12.8 mg, 10.8%). ESI(MS) m/z = 502.2 $[M+H]^+$

Example 78

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

Example 78 was prepared as described for example 102, starting from **intermediate 8** (33.8 mg, 89.2 umol) and 2-fluoro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 33, 20 mg, 89.2 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a off-white solid (14.7 mg, 29.8%). ESI(MS) m/z = 510.2 $[M+H]^+$

Example 80

4-[3-[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrazole-3-carbonitrile

Example 80 was prepared as described for example 102, starting from **intermediate 8** (23.3 mg, 68.6 umol) and 2-chloro-3-(3-cyano-1H-pyrazol-4-yl)benzoic acid (intermediate 34, 17 mg, 68.6 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a off-white solid (15.1 mg, 31 %). ESI(MS) m/z = 533.2 $[M+H]^+$

Example 81

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

Example 81 was prepared as described for example 102, starting from **intermediate 8** (188 mg, 554 umol) and 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 127 mg, 528 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). Dechlorinated example 81 was isolated as a byproduct (major product was example 65). The compound was obtained as a off-white solid (23.2 mg, 8.1 %). ESI(MS) m/z = 492.3 $[M+H]^+$

Example 85

[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

Example 85 was prepared as described for example 102, starting from **intermediate 9** (33.8 mg, 99.5 umol) and 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 22.8 mg, 94.8 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). Dechlorinated example 81 was isolated as a byproduct (major product was example 65). The compound was obtained as a off-white solid (6.9 mg, 13.8 %). ESI(MS) m/z = 526.2 $[M+H]^+$

Example 86

[(3S,9aS)-3-hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-oxazol-4-yl-phenyl)methanone

Example 86 was prepared as described for example 102, starting from **intermediate 9** (41 mg, 121 umol) and 2-chloro-3-(oxazol-5-yl)benzoic acid (intermediate 32, 27 mg, 121 umol). The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). The compound was obtained as a white solid (7 mg, 11.4 %). ESI(MS) m/z = 509.2 $[M+H]^+$

Example 97

[(3S,9aS)-3-[6-(trifluoromethyl)pyridazin-3-yl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

Example 97 was prepared as described for example 102, starting from **intermediate 11** (22 mg, 76.3 umol) and 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 27.5 mg, 91.6 umol). The crude was purified by reversed phase chromatography (Method B). The compound was obtained as a white solid (8.2 mg, 20.5 %). ESI(MS) m/z = 511.2 $[M+H]^+$

Example 82

[(3R,9aS)-3-hydroxy-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(1H-pyrazol-4-yl)phenyl]methanone

A microwave vial was charged with (2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)((3R,9aS)-3-hydroxy-3-(6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (0.064 g, 113 µmol, crude), 4-bromo-1H-pyrazole (18.2 mg, 124 µmol), K2CO3 (46.7 mg, 338 µmol) and combined with Dioxane (1.5 ml) and Water (0.5 ml). The reaction mixture was degassed and Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (7.98 mg, 11.3 µmol) was added. It was then heated at 115°C for 30 min. The reaction mixture was poured into 2 mL sat NaHCO3 and extracted with EtOAc (2 x 5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 0% to 10% MeOH in DCM) : 10mg of a mixture desired product + impurity. The yellow oil was purified by preparative HPLC (method B), to yield the product as a white lyophilized powder (2.1mg, 3%). ESI(MS) m/z = 506.31 $[M-H]^-$

a) *(3-bromo-2-chlorophenyl)((3R,9aS)-3-hydroxy-3-(6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone*

In a 25 mL two-necked flask, (3R,9aS)-3-(6-(trifluoromethyl)pyridin-3-yl)octahydropyrazino[2,1-c][1,4]oxazin-3-ol hydrochloride (intermediate 8, 0.100 g, 294 µmol), 3-bromo-2-chlorobenzoic acid (83.2 mg, 353 µmol) and HATU (134 mg, 353 µmol) were combined with DMF (3 ml) to give a yellow solution. DIPEA (114 mg, 154 µl, 883 µmol) was added. The reaction mixture was stirred at RT for 1 h.

The reaction mixture was poured into 5 mL H2O and extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 0% to 100% EtOAc in heptane). The product was obtained as a colorless oil (132 mg, 86%). ESI(MS) m/z = 522.1 $[M+H]^+$

b) (2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)((3R,9aS)-3-hydroxy-3-(6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone

In a microwave vial, Bis(pinacolato)diboron (83.7 mg, 330 µmol), (3-bromo-2-chlorophenyl)((3R,9aS)-3-hydroxy-3-(6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (0.132 g, 253 µmol) and

potassium acetate (74.6 mg, 760 µmol) were dispersed in Dioxane (1 ml) and degassed. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31.1 mg, 38 µmol) was then added. It was reacted in the MW (100, 60min). It was then mixed with water and extracted with EtOAc twice. The combined org. phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was attempted to purify by flash chromatography twice (silica gel, 50% to 100% EtOAc in heptane; silica gel, 0% to 10% MeOH in DCM) both leading to no separation. The crude product (brown oil, 64 mg, 44.5%) was used accordingly for the step directly. ESI(MS) m/z = 568.3 $[M+H]^+$

Example 87

[3-(1,3-benzothiazol-2-yl)-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

(3-(benzo[d]thiazol-2-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (150 mg, 326 umol) was dissolved in 9 mL DCM and 4.5 mL TFA. TES (420 uL, 2.61 mmol) was added and the reddish mixture stirred at RT under argon in a closed pressure vial. After 2 h, it was heated up to 60 °C. After two days, the reaction was concentrated *in vacuo*, poured into EtOAc, washed with sat. bicarbonate solution, filtered, adsorbedon silica and purified by silica column chromatography (Hept:EtOAc 80:20 to 10:90). The described product after elimination was the main product and obtained as a yellow solid (40 mg, 28%). ESI(MS) m/z = 442.2 $[M+H]^+$

a) (3-(benzo[d]thiazol-2-yl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone

(2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (intermediate 1, 96 mg, 337 umol) and DIPEA (65 uL, 371 umol) were dissolved in 2 mL dry THF and cooled down in an ice bath. 1-(benzo[d]thiazol-2-yl)-2-bromoethan-1-one (88 mg, 345 umol) was dissolved in 1 mL dry THF and added dropwise to the solution over 10 min. After 4 h, it was concentrated *in vacuo*. The red foam was dissolved in EtOAc and washed with sat. aq. bicarbonate solution and then water, dried (Na_2SO_4) and concentrated *in vacuo*. The compound was obtained as a slightly impure yellow-golden oil, 153 mg. It was used without further purification in the next step.

Example 88

[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]-[(3S,9aS)-3-fluoro-3-[6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]methanone

(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)((3R,9aS)-3-hydroxy-3-(6-(trifluoromethyl)pyridin-3-yl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (Example 65, 16.7 mg, 31.8 umol) was dissolved in 0.7 mL dry DCM and cooled to -78 °C. DAST (6.6 mg, 41.3 umol) dissolved in 0.3 mL dry DCM was added dropwise. After 40 min, the white suspension was warmed up to room temperature. After overnight stirring, ca 20-30% conversion was visible so the flask was cooled down to -78 °C again and DAST (12 mg, 64 umol) in 0.2 mL dry DCM were added. Two hours later, it was warmed up to room temperature. Not much more progress was visible, so the mixture was cooled to -78 °C again and DAST (19 mg, 95 umol) in 0.2 mL dry DCM were added. 40 min later, it was warmed up to room temperature. 2 h later, it was concentrated *in vacuo*, diluted with sat. bicarbonate solution and extracted into EtOAc twice. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo and then purified by silica column chromatography (silica gel, 0% to 10% MeOH in DCM). The product was obtained as a slightly orange solid (13.9 mg, 68%). ESI(MS) m/z = 528.2 $[M+H]^+$

Example 92 and Example 93

[(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone and [(3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-[3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

(3R,9aS)-3-(3,4-difluorophenyl)octahydropyrazino[2,1-c][1,4]oxazin-3-ol hydrochloride (intermediate 10, 134 mg, 436 µmol), 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 100 mg, 416 umol) and DIPEA (231 mg, 312 µl, 1.79 mmol) were mixed with 3.5 mL dry THF and cooled to 0 °C. T3P (410 mg, 644 µmol) dissolved in 1 mL dry THF was added dropwise over 15 min. After 20 min, it was warmed up to RT and an hour later, it was concentrated *in vacuo*, diluted with EtOAc, washed with sat. ammonium chloride solution, dried over sodium sulfate, filtered and concentrated in vacuo. The crude was purified by silica column chromatography (MeOH in DCM 0% to 10%). It was then purified by prep HPLC (method B) to separate the 2 products.

Example 92 32.2 mg (13.8%), white lyophilized powder, ESI(MS) m/z = 493.1 $[M+H]^+$

Example 93 11.4 mg (5.4%), white lyophilized powder, ESI(MS) m/z = 459.2 $[M+H]^+$

Example 94

[(9aS)-3-[5-(trifluoromethyl)-2-pyridyl]-6,7,9,9a-tetrahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

(S)-3-(5-(trifluoromethyl)pyridin-2-yl)-1,6,7,8,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine (23 mg, 80.6 umol), 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 24.2 mg, 80.6 umol) and DIPEA (42 uL, 242 umol) were dissolved in 0.6 mL DMSO-d6 and 0.2 mL dry THF and cooled to 0°C. T3P (1.5 eq, 77 mg of a 50% wt/wt solution in EtOAc) in 0.2 mL dry THF was added dropwise. After 20 min, it was warmed up to RT. It was partly solid because of the frozen DMSO, but turned into a yellow solution quickly upon removing from the ice bath. The next morning, the reaction had still not gone to completion, so another 20 uL (1.5 eq) of DIPEA and 38 mg (0.75 eq) of T3P were added. 2 h later, it was diluted with sat. bicarbonate solution, extracted twice into EtOAc, dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by reversed phase HPLC (method B) lead to the product which was obtained as a bright yellow solid (7.5 mg, 18.3 %). ESI(MS) m/z = 508.2 $[M+H]^+$

a) S)-3-(5-(trifluoromethyl)pyridin-2-yl)-1,6,7,8,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine

(3S,9aS)-3-(5-(trifluoromethyl)pyridin-2-yl)octahydropyrazino[2,1-c][1,4]oxazin-3-ol hydrochloride (intermediate 9, 130 mg, 383 umol) was dissolved in 5.3 mL TFA and 10.6 mL dry DCM upon which TES (183 uL, 1.15 mmol) were added and the yellow solution was stirred at room temperature. After heating at 70 °C for 2.5 days, the bright yellow solution was concentrated *in vacuo*, diluted with 1 M HCl and washed with diethyl ether twice. The ether phase was then backextracted with brine. The yellow aqeuous solution was basified with 4 M NaOH, treated with sodium chloride, extracted into excess EtOAc, dried over sodium sulfate, filtered and concentrated in vacuo. The product was obtained as a neon yellow solid (24 mg, 22%). In contrast to the desired dehydroxylated product, dehydratation occurred, leading to the unsaturated product. ESI(MS) m/z = 286.2 $[M+H]^+$

Example 95 and Example 96

[(3R,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone and [(3S,9aS)-3-(3,4-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl]methanone

(2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)phenyl)((3R,9aS)-3-(3,4-difluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (example 92, 18 mg, 36.5 µmol) was dissolved in 1 mL dry DCM. 2,2,2-trifluoroacetic acid (750 mg, 506 µl, 6.57 mmol) and triethylsilane (12.7 mg, 17.5 µl, 110 µmol) were added. The colorless solution was stirred at room temperature for 3 hours. The crude was diluted with EtOAc, washed with sat. $NaHCO_3$ solution, filtered and concentrated *in vacuo*. The crude material was purified by preparative HPLC (method B):

Example 95, major isomer (trans), 8.6 mg (49.4%), white lyophilized powder, ESI(MS) m/z = 477.1 $[M+H]^+$

Example 96, minor isomer (cis), 1.5 mg (8.6%) , white lyophilized powder, ESI(MS) m/z = 477.2 $[M+H]^+$

Example 100

3-[(3R,9aS)-8-[2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoyl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one

3-((3R,9aS)-3-hydroxyoctahydropyrazino[2,1-c][1,4]oxazin-3-yl)-6-(trifluoromethyl)pyridin-2(1H)-one (intermediate 12, 15 mg, 47 umol), 2-chloro-3-(3-fluoro-1H-pyrazol-4-yl)benzoic acid (intermediate 29, 12.5 mg, 51.7 umol), EDC hydrochloride (13.5 mg, 70.5 umol) and HOBT monohydrate (8 mg, 51.7 umol) were mixed with 0.6 mL dry DMF upon which DIPEA (25 uL, 141 umol) was added. The yellow mixture was stirred at room temperature. After 4.5 h the mixture was diluted with EtOAc and washed with sat. bicarbonate solution and then brine. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The yellow crude material was purified by silica column chromatography (MeOH in DCM 0% to 10%). The obtained solid was still impure and further purifiedby reversed phase HPLC (Method B).

The product was obtained as a light yellow solid (2.5 mg, 9%). , ESI(MS) m/z = 542.2 $[M+H]^+$

Example 109

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-phenyl]-1H-pyrrole-2-carbonitrile

Synthesis of example 109 was carried out as described for example 127, starting from **Intermediate 52** and 4-bromo-1H-pyrrole-2-carbonitrile. Purification by preparative HPLC (Method B). Yield 2.4 mg, 4%. ESI(MS) m/z = 515.3 $[M+H]^+$

Example 114

4-[3-[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazine-8-carbonyl]-2-chloro-5-fluoro-phenyl]-1H-pyridin-2-one

(3-bromo-2-chloro-5-fluorophenyl)((3R,9aS)-3-(3-chloro-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (**intermediate 50**, 1 eq, 50 mg), (2-oxo-1,2-dihydropyridin-4-yl)boronic acid (1.2 eq, 16.5 mg), potassium carbonate (3 eq, 41 mg) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.1 eq, 8 mg) were mixed with 0.9 ml dioxane and 0.1 ml water, degassed with argon and reacted in the microwave (115 °C, 25 min). Another 30 mg of (2-oxo-1,2-dihydropyridin-4-yl)boronic acid and 30 uL DIPEA were added and the mixture reacted again (115 °C, 30 min). The reaction was still not complete but the boronate consumed again, so another 40 mg (2-oxo-1,2-dihydropyridin-4-yl)boronic acid and 30 uL DIPEA was added and the mixture reacted again (115 °C, 30 min). The reaction was still not complete but the boronate consumed again, so another 60 mg boronic acid and 30 uL DIPEA was added and the mixture reacted again (115 °C, 30 min). The reaction was still not complete but was worked up anyway: It was diluted with EtOAc and washed with water and then sat. aq. bicarbonate solution, dried over sodium sulfate, filtered and concentrated in vacuo. It was purified by silica column chromatography (10 g, MeOH in DCM 0% to 10%). The crude product was submitted to HPLC purification (Method B) and obtained as a white solid. (10 mg, 19%). ESI(MS) m/z = 520.3 $[M+H]^+$

Example 119

[(3R,9aS)-3-hydroxy-3-[4-(trifluoromethyl)phenyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 119 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(4-(trifluoromethyl)phenyl)ethan-1-one (CAS 383-53-9). Yield 145 mg, 78%. ESI(MS) m/z = 471.3 $[M+H]^+$

Example 120

[(3R,9aS)-3-(4-chloro-3-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 120 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(4-chloro-3-fluorophenyl)ethan-1-one (CAS 63529-30-6). Yield 165 mg, 82%. ESI(MS) m/z = 455.2 $[M+H]^+$

Example 125

[(3R,9aS)-3-(3-bromo-5-chloro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 125 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(3-bromo-5-chlorophenyl)ethan-1-one (CAS 41011-01-2). Yield 119 mg, 66%. ESI(MS) m/z = 517.2 $[M+H]^+$

Example 127

[(3R,9aS)-3-(3-chloro-4-fluoro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-isothiazol-4-yl-phenyl)methanone

(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)((3R,9aS)-3-(3-chloro-4-fluorophenyl)-3-hydroxyhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (**Intermediate 52**, 0.060 g, 109 µmol), 4-bromoisothiazole (19.6 mg, 120 µmol), K_2CO_3 (45.1 mg, 327 µmol) were combined with Dioxane (1.5 ml) and Water (250 µl) in a microwave vial. The reaction mixture was degassed and bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) ($APhos_2$ $PdCl_2$, 7.71 mg, 10.9 µmol) was added. The vial was sealed and heated at 80°C for 2 hours. The reaction

mixture was poured into 2 mL sat $NaHCO_3$ and extracted with EtOAc (2 x 5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in DCM) to yield a crude product, which was further purified by preparative HPLC (Method J). Eventually the product was obtained as 4 mg (7%) of white lyophilized powder. ESI(MS) m/z = 508.1 $[M+H]^+$

Example 128

[(3R,9aS)-3-(2,4,5-trifluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

(2-chloro-3-methoxyphenyl)((3R,9aS)-3-hydroxy-3-(2,4,5-trifluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methanone (**Example 144**, 1 eq, 37 mg) was dissolved in 1 mL dry DCM and 0.5 mL TFA at room temperature. TES (3 eq, 35 uL) was added and the yellowish solution stirred at 40 °C for 5 h and then at room temperature overnight. It was then concentrated in vacuo and purified by silica column chromatography (10 g, MeOH in DCM 0% to 10%). The product was obtained as a yellow oil (28 mg, 80%). ESI(MS) m/z = 441.2 $[M+H]^+$

Example 129

[(3R,9aS)-3-(2,4-dichlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 129 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one (CAS 2631-72-3). Yield 163 mg, 82%. ESI(MS) m/z = 473.2 $[M+H]^+$

Example 130

[(3R,9aS)-3-hydroxy-3-(2,3,4-trifluorophenyl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 130 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2,3,4-trifluorophenyl)ethan-1-one (CAS 1214345-02-4). Yield 109 mg, 55%. ESI(MS) m/z = 457.3 $[M+H]^+$

Example 131

[(3S,9aS)-3-(4-bromo-5-methoxy-2-thienyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 131 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(4-bromo-5-methoxythiophen-2-yl)ethan-1-one (CAS 882748-05-2). Purification by HPLC, Method J. Yield 22.6 mg, 22%. ESI(MS) m/z = 519.2 $[M+H]^+$

Example 136

3-[(3R,9aS)-8-(2-chloro-3-methoxy-benzoyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-3-yl]-6-(trifluoromethyl)-1H-pyridin-2-one

Example 136 was synthesized as described for example 65, starting from **intermediate 1S** and 3-(2-bromoacetyl)-6-(trifluoromethyl)pyridin-2(1H)-one (CAS 1000931-76-9). Purification by HPLC, Method B. Yield 10.4 mg, 7.5%. ESI(MS) m/z = 488.3 $[M+H]^+$

Example 137

[(3R,9aS)-3-(3-chloro-4-oxazol-5-yl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

((3R,9aS)-3-(4-bromo-3-chlorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (**Example 110**, 0.075 g, 150 µmol), oxazole (20.7 mg, 300 µmol, Eq: 2), $Pd(OAc)_2$ (1.68 mg, 7.5 µmol), potassium carbonate (62.2 mg, 450 µmol) , pivalic acid (6.13 mg, 60 µmol) and di-tert-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphane (7.21 mg, 15 µmol) were dispersed in DMA (2 ml), degassed and heated to 110 °C in a thermoblock for 2 hours. It was then cooled down to RT, diluted with water and extracted with EtOAc twice. The organic phases were combined, washed with brine (x2), dried over sodium sulfate, filtered and conc. in vacuo. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in DCM). Yield 29 mg, 35%. ESI(MS) m/z = 488.3 $[M+H]^+$

Example 139

[(3S,9aS)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 139 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2-(4-fluorophenyl)thiazol-4-yl)ethan-1-one (CAS 937079-09-9). Yield 68 mg, 75%. ESI(MS) m/z = 504.3 $[M+H]^+$

Example 141

[(3R,9aS)-3-hydroxy-3-[3-(trifluoromethyl)phenyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 141 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(3-(trifluoromethyl)phenyl)ethan-1-one (CAS 2003-10-3). Yield 135 mg, 71%. ESI(MS) m/z = 471.3 $[M+H]^+$

Example 142

[(3R,9aS)-3-(2,3-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 142 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2,3-difluorophenyl)ethan-1-one (CAS 886762-77-2). Yield 150 mg, 72%. ESI(MS) m/z = 439.2 $[M+H]^+$

Example 143

[(3S,9aS)-3-hydroxy-3-(3-phenylisoxazol-5-yl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 143 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(3-phenylisoxazol-5-yl)ethan-1-one (CAS 14731-14-7). Yield 124 mg, 70%. ESI(MS) m/z = 470.3 $[M+H]^+$

Example 144

[(3R,9aS)-3-hydroxy-3-(2,4,5-trifluorophenyl)-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 144 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2,4,5-trifluorophenyl)ethan-1-one (CAS 193977-34-3). Yield 58 mg, 36%. ESI(MS) m/z = 457.2 $[M+H]^+$

Example 145

[(9aS)-3-(4-fluoro-3-oxazol-5-yl-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

((9aS)-3-(3-bromo-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (**Example 6**, 0.075 g, 155 µmol), oxazole (21.4 mg, 310 µmol), $Pd(OAc)_2$ (1.74 mg, 7.75 µmol), potassium carbonate (64.3 mg, 465 µmol), pivalic acid (6.33 mg, 7.2 µl, 62 µmol) and di-tert-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphine (tBuXPhos) (7.45 mg, 15.5 µmol) were dispersed in DMA (2 ml), degassed and heated to 110 °C in a thermoblock for 2 hours. It was then cooled down to RT, diluted with water and extracted with EtOAc twice. The organic phases were combined, washed with brine (x2), dried over sodium sulfate, filtered and concentrated in vacuo. Tphe crude material was purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in DCM). Yield 38 mg, 48%, light brown oil. ESI(MS) m/z = 472.3 $[M+H]^+$

Example 146

[(3S,9aS)-3-(1,3-benzothiazol-2-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 146 was synthesized as described for example 65, starting from **intermediate 1S** and 1-(1,3-Benzothiazol-2-yl)-2-bromoethan-1-one (CAS 54223-20-0). Yield 118 mg, 68%. ESI(MS) m/z = 460.3 $[M+H]^+$

Example 149

[(3R,9aS)-3-(2,3-difluorophenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

[(3R,9aS)-3-(2,3-difluorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone (**Example 142**, 50 mg, 114 umol) was dissolved in 575 ul dry DCM and 262 ul TFA at room temperature. TES (55 uL, 342 umol) was added and the yellowish solution stirred at 45°C for 2 h. It was then concentrated in vacuo and purified by silica column chromatography (10 g, MeOH in DCM 0% to 10%) and subsequently by preparative HPLC (Method B). The product was obtained as a yellow oil (20 mg, 39%). ESI(MS) m/z = 423.2 $[M+H]^+$

Example 150

[(3R,9aS)-3-(2-chlorophenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 150 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2-chlorophenyl)ethan-1-one (CAS 5000-66-8). Yield 128 mg, 62%. ESI(MS) m/z = 437.3 $[M+H]^+$

Example 153

[(3R,9aS)-3-hydroxy-3-[2-methyl-6-(trifluoromethyl)-3-pyridyl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 153 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2-methyl-6-(trifluoromethyl)pyridin-3-yl)ethan-1-one, bromide salt (CAS 1377962-47-4). Yield 63 mg, 67%. ESI(MS) m/z = 486.3 $[M+H]^+$

Example 154

[(3R,9aS)-3-(3-chloro-5-oxazol-5-yl-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Synthesis was performed as described for example 145, starting from [(3R,9aS)-3-(3-bromo-5-chloro-phenyl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone (**Example 125**, 91 mg, 176 umol) and oxazole (24.3 mg, 252 umol). Yellow oil, Yield 46 mg, 51%. ESI(MS) m/z = 504.3 $[M+H]^+$

Example 156

[(9aS)-3-[4-fluoro-3-(1-methylpyrrol-3-yl)phenyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

((9aS)-3-(3-bromo-4-fluorophenyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)(2-chloro-3-methoxyphenyl)methanone (**Example 6**, 0.075 g, 155 µmol),1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (32.1 mg, 155 µmol) , K_2CO_3 (64.3 mg, 465 µmol) were combined with Dioxane (1.5 ml) and Water (0.25 ml) in a microwave vial. The reaction muxture was degassed and bis(di-tert-butyl(4-

dimethylaminophenyl)phosphine)dichloropalladium(II) (11 mg, 15.5 µmol) was added. The reaction was heated at 80°C for 2 hours and then poured into 2 mL sat $NaHCO_3$ and extracted with EtOAc (2 x 5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 10% MeOH in DCM), yielding 77 mg of a crude product, which was further purified by preparative HPLC (Method B). The product was obtained as a yellow lyophilized powder. Yield 28mg, 36%. ESI(MS) m/z = 484.4 $[M+H]^+$

Example 157

[(3S,9aS)-3-(3-bromoisoxazol-5-yl)-3-hydroxy-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 157 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(3-bromoisoxazol-5-yl)ethan-1-one (CAS 76596-54-8). Yield 13.6 mg, 15%. ESI(MS) m/z = 474.2 $[M+H]^+$

Example 160

[(3S,9aS)-3-hydroxy-3-[2-(6-methoxy-3-pyridyl)thiazol-4-yl]-1,4,6,7,9,9a-hexahydropyrazino[2,1-c][1,4]oxazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

Example 160 was synthesized as described for example 65, starting from **intermediate 1S** and 2-bromo-1-(2-(6-methoxypyridin-3-yl)thiazol-4-yl)ethan-1-one (Intermediate 70). Yield 10 mg, 19%. ESI(MS) m/z = 517.3 $[M+H]^+$

Example 161 & Example 162

[(9aS)-3-(3-chloro-4-fluoro-phenyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]thiazin-8-yl]-(2-chloro-3-methoxy-phenyl)methanone

In a 25 ml glass tube under argon, S-(((2S)-1-(2-chloro-2-(3-chloro-4-fluorophenyl)ethyl)-4-(2-chloro-3-methoxybenzoyl)piperazin-2-yl)methyl) ethanethioate (100mg, 187 µmol) in THF (10 ml) was treated with sodium methoxide 25 % in methanol (121 mg, 129 µl, 562 µmol). The yellow mixture was stirred at 20-22°C under argon for 1hr. LCMS showed the formation of the desired product as a pair of diastereomers. The reaction mixture was concentrated and partitioned between ethyl acetat and water. The organic layer was separated and washed with brine, dried and evaporated to dryness get the crude product as

a yellow oil (95 mg). The crude product was purified by SFC, Reprospher 100 PEI, 10% MeOH.

Example 161, first eluting diastereomer, 23 mg (26%), ESI(MS) m/z = 455.2 $[M+H]^+$

Example 162, second eluting diastereomer, 24 mg (27%), ESI(MS) m/z = 455.2 $[M+H]^+$

a) (2-chloro-3-methoxyphenyl)(4-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)methanone

2-(3-chloro-4-fluorophenyl)oxirane (210 mg, 1.22 mmol) and (S)-(2-chloro-3-methoxyphenyl)(3-(hydroxymethyl)piperazin-1-yl)methanone (intermediate 1S, 440 mg, 1.54 mmol) were dissolved in 7 mL MeOH and reacted in the microwave (120 °C, 60 min). It was concentrated in vacuo and purified by silica column chromatography (70 g, MeOH in DCM 0% to 10%). Product was obtained as an yellow oil (206 mg, 37%). ESI(MS) m/z = 457.2 $[M+H]^+$

b) S-(((2S)-4-(2-chloro-3-methoxybenzoyl)-1-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)piperazin-2-yl)methyl) ethanethioate

In a 25 ml glass tube under argon, (2-chloro-3-methoxyphenyl)(4-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)-3-(hydroxymethyl)piperazin-1-yl)methanone (175mg, 383 µmol) was dissolved in THF (3.8 ml) and cooled to 0°C. TEA (46.5 mg, 64 µl, 459 µmol) was added followed by additon of methanesulfonyl chloride (48.2 mg, 32.8 µl, 421 µmol), and DMAP (4.68 mg, 38.3 µmol). The ice bath was removed and stirring was continued for 2hr. The reaction mixture was then concentrated under reduced pressure. The resulting materal was re-dissolved in DMSO 3 ml and treaded with potassium thioacetate (58.1 mg, 509 µmol). The reaction mixture ws stirred at RT under argon overnight. The mixture was diluted with ethyl acetate and washed with water (3 times) and brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 100% heptane to 80% EtOAc/heptane) to give the desired product as a light brown oil (110 mg, 50%). ESI(MS) m/z = 515.3 $[M+H]^+$

c) S-(((2S)-1-(2-chloro-2-(3-chloro-4-fluorophenyl)ethyl)-4-(2-chloro-3-methoxybenzoyl)piperazin-2-yl)methyl) ethanethioate

In a 2 5ml glass tube under argon, to S-(((2S)-4-(2-chloro-3-methoxybenzoyl)-1-(2-(3-chloro-4-fluorophenyl)-2-hydroxyethyl)piperazin-2-yl)methyl) ethanethioate (110mg, 213

µmol) in DCM (2.5 ml) was added thionyl chloride (76.2 mg, 46.7 µl, 640 µmol). The mixture was cooled with an ice bath and pyridine (67.5 mg, 69 µl, 854 µmol) was added in 0.5 ml DCM dropwise. The reacton mixture was stirred at 0-2°C for 20 min, and then allowed to warm to room temperature over a hour and finally stirred over night at room temperature. The reaction mixture was concentrated and the residue was diluted with ethyl acetate, washed with 2x 10 ml water and brine. The organic layer was separated, dried with Na_2SO_4,filtered and concentrated in vacum. Product obtained as a Product obtained as a yellow oil, used directly in the next step (105 mg, crude). ESI(MS) m/z = 535.3 $[M+H]^+$

Example 163

A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

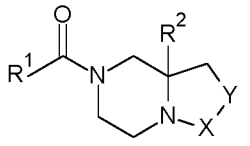
Example 164

A compound of formula (I) can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

CLAIMS

1 A compound of formula (I)

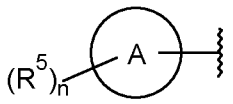


(I)

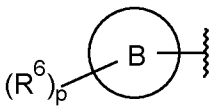
or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

Y is –O–, –S–, –SO–, or $-SO_2-$;

R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are optionally substituted with 1-5 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, cyano, hydroxy, and a group  ;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3 is a group  ;

R^4 is hydrogen, halogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy, amino, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano; wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with 1-2 substituents selected from halogen, cyano, amino, hydroxy, C_1-C_6-alkyl and C_1-C_6-alkoxy;

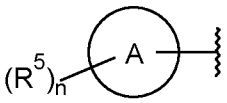
A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl, 3- to 14-membered heterocyclyl or C_3-C_{14}-cycloalkyl; and

n and p are each independently 1, 2, 3, 4 or 5.

2 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2CR^3R^4-$.

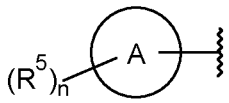
3 The compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Y is –O– or –S–.

4 The compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Y is –O–.

5 The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group 

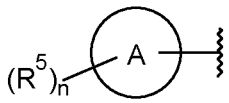
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6 The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_6-C_{14}-aryl substituted with 2-3 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group



.

7 The compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with 2-3 substituents independently selected from chloro, fluoro, methoxy and a group



.

8 The compound of formula (I) according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

9 The compound of formula (I) according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen or hydroxy.

10 The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo.

11 The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, halogen, cyano, hydroxy or oxo.

12 The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, fluoro, cyano, hydroxy or oxo.

13 The compound of formula (I) according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy.

14 The compound of formula (I) according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy.

15 The compound of formula (I) according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy.

16 The compound of formula (I) according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

17 The compound of formula (I) according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein p is 1, 2 or 3.

18 The compound of formula (I) according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein p is 1 or 2.

19 The compound of formula (I) according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein A is 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl.

20 The compound of formula (I) according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl.

21 The compound of formula (I) according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein A is imidazolyl, pyrazolyl, pyrrolyl, or 1,2-dihydropyridinyl.

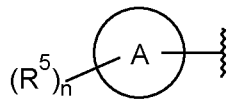
22 The compound of formula (I) according to any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein B is C_6-C_{14}-aryl, 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl.

23 The compound of formula (I) according to any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein B is phenyl, 1,2-dihydropyridinyl or pyridyl.

24 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

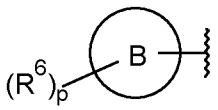
X is $-CH_2CR^3R^4-$ or $-CH=CR^3-$;

Y is –O– or –S–;

R^1 is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl, wherein said C_6-C_{14}-aryl or 5- to 14-membered heteroaryl are substituted with 1-3 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, halogen, cyano and a group 

;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3 is a group 

;

R^4 is hydrogen, halogen or hydroxy;

R^5 is hydrogen, halogen, hydroxy, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkyl, cyano or oxo;

R^6 is hydrogen, halogen, C_6-C_{14}-aryl, 5- to 14-membered heteroaryl, halo-C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-

C_6-alkynyl, C_3-C_{14}-cycloalkyl or cyano, wherein said 5- to 14-membered heteroaryl or C_6-C_{14}-aryl is optionally substituted with a substituent selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy;

A and B are each independently 5- to 14-membered heteroaryl, C_6-C_{14}-aryl or 3- to 14-membered heterocyclyl;

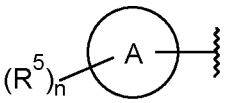
n is 1 or 2; and

p is 1, 2 or 3.

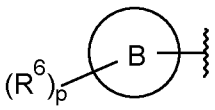
25 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$;

Y is $-O-$;

R^1 is C_6-C_{14}-aryl substituted with 1-2 substituents independently selected from C_1-C_6-alkoxy, halogen, and a group ;

R^2 is hydrogen;

R^3 is a group ;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, halogen, cyano, hydroxy or oxo;

R^6 is halogen, oxo, halo-C_1-C_6-alkyl or halo-C_1-C_6-alkoxy;

A is 5- to 14-membered heteroaryl or 3- to 14-membered heterocyclyl;

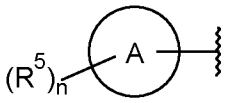
B is C_6-C_{14}-aryl or 5- to 14-membered heteroaryl; and

n and p are each independently 1 or 2.

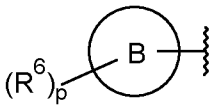
26 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2CR^3R^4-$;

Y is $-O-$;

R^1 is phenyl substituted with 2-3 substituents independently selected from chloro, fluro, methoxy and a group ;

R^2 is hydrogen;

R^3 is a group  ;

R^4 is hydrogen or hydroxy;

R^5 is hydrogen, fluoro, cyano, hydroxy or oxo;

R^6 is chloro, fluoro, oxo, trifluoromethyl or difluoromethoxy;

A is imidazolyl, pyrazolyl, pyrrolyl, or 1,2-dihydropyridinyl;

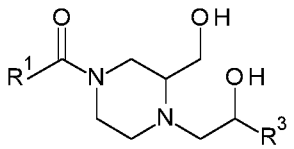
B is phenyl, 1,2-dihydropyridinyl or pyridyl; and

n and p are each independently 1 or 2.

27 The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is selected from the compounds of *Table 1*.

28 A process of manufacturing the compounds of formula (I) according to any one of claims 1 to 27, comprising:

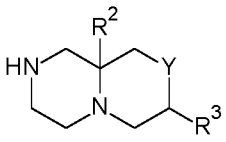
(a) reacting a diol **5**, wherein R^1 and R^3 are as defined herein,



5

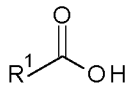
with an etherification reagent, such as (cyanomethylene)tributylphosphorane (CMBP, Tsunoda reagent) to yield said compound of formula (**I**), wherein X is $-CH_2CHR^3-$, Y is –O–, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(b) reacting an amine **8a**, wherein Y, R^2 and R^3 are as defined herein,



8a

with a carboxylic acid **1**, wherein R^1 is as defined herein,



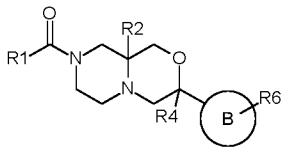
1

in the presence of a base, such as trimethylamine or diisopropylamine, and a coupling reagent, such as HATU, T3P or EDC*HCl, to yield said compound of formula (I), wherein X is $–CH_2CHR^3–$, Y, R^1 and R^3 are as defined herein, and R^2 is hydrogen; or

(c) submitting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy to dehydrating conditions, for example using TES and TFA at elevated temperatures, to yield a compound of formula (I) wherein Y is as defined herein, X is $–CH_2CHR^3–$ and R^1 to R^3 are as defined herein and/or a compound of formula (I) wherein Y is as defined herein, X is $–CH=CR^3–$ and R^1 to R^3 are as defined herein; or

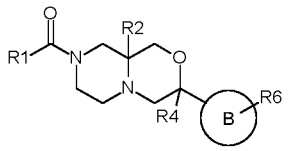
(d) reacting a compound of formula (I), wherein Y is as defined herein, X is $–CH_2CR^3R^4–$, R^1 to R^3 are as defined herein and R^4 is hydroxy, with a nucleophilic fluorinating agent, such as DAST, to yield a compound of formula (I) wherein X is $–CH_2CFR^3–$ and R^1 to R^3 are as defined herein; or

(e) submitting a compound of formula (I),



I

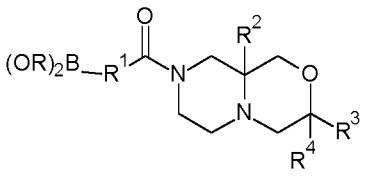
wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is bromo, to a transition metal catalyzed cross-coupling reaction, such as a Suzuki–Miyaura reaction or a Sonogashira reaction, to afford compound of formula (I)



I

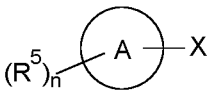
wherein R^1, R^2, R^4, and B are as defined herein, and R^6 is selected from aryl, alkenyl, alkynyl, alkyl, cyano, cycloalkyl, and heteroaryl; or

(f) submitting a compound **12**, wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^4 are as defined herein,



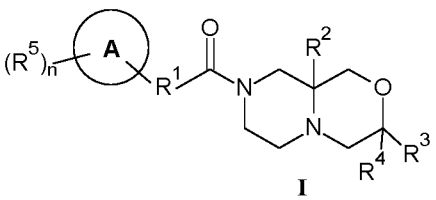
12
$B(OR)_2 = B(OH)_2$ or
boronate pinacol ester

to a Suzuki-Miyaura cross coupling reaction with a compound **13**, wherein A, R^5, and n are as defined herein



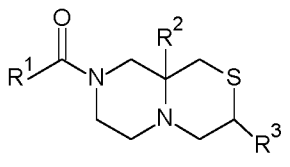
13
X = Cl, Br, I, OTf

in the presence of a transition metal catalyst, e.g. $PdCl_2(dppf)\text{-}CH_2Cl_2$, $Pd_2(dba)_3$ + Xantphos, $(A\text{-}^{ta}Phos)_2PdCl_2$, or cataCXium A Pd G2, and an organic or inorganic base such as sodium carbonate, triethylamine, TMEDA or cesium carbonate; to afford said compound of formula (I), wherein R^1 is aryl or heteroaryl optionally substituted with 1-4 substituents independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen, and cyano; and R^2 to R^5 and n are as defined herein



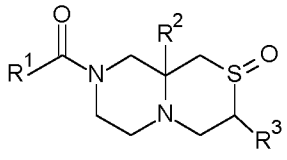
I ; or

(g) reacting a compound of formula (I), wherein Y is sulfur and R^1, R^2, and R^3 are as defined herein,

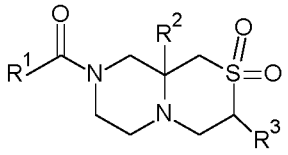


I

with an oxidizing agent, such as mCPBA, hydrogen peroxide or sodium periodate, to afford a compound of formula (I), wherein Y is a sulfoxide or a sulfone and R^1, R^2, and R^3 are as defined herein.


I

+


I

29 A compound of formula (I) according to any one of claims 1 to 27, when manufactured according to the process of claim 28.

30 The compound of formula (I) according to any one of claims 1 to 27 and 29, wherein said compound of formula (I) has an IC_{50} for monoacylglycerol lipase below 10 µM.

31 A compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for use as therapeutically active substance.

32 A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 and a therapeutically inert carrier.

33 The use of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

34 The use of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

35 A compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

36 A compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for use in the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular

carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

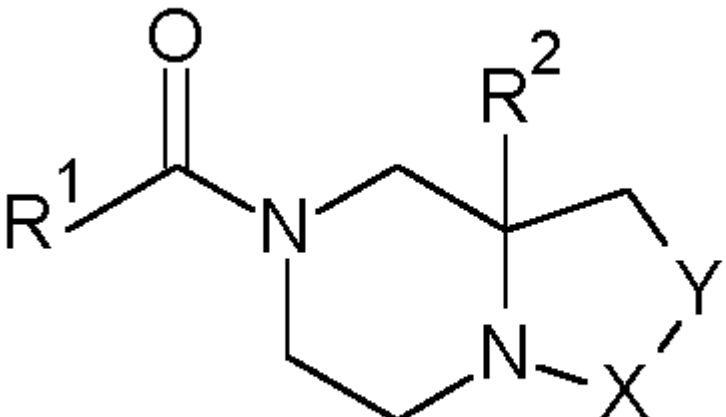
37 The use of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.

38 The use of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 for the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

39 A method for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal, which method comprises administering an effective amount of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 to the mammal.

40 A method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, neurotoxicity, stroke, epilepsy, anxiety, migraine, depression, hepatocellular carcinoma, colon carcinogenesis, ovarian cancer, neuropathic pain, chemotherapy induced neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal, which method comprises administering an effective amount of a compound of formula (I) according to any one of claims 1 to 27, 29 and 30 to the mammal.

41 The invention as described hereinbefore.



(I)