

NEW HETEROCYCLIC COMPOUNDS AS MONOACYLGLYCEROL LIPASE INHIBITORS

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
5 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

10 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 diacylglycerol lipases (DAGL)
15 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
20 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
25 important. These products have been detected at sites of inflammation, e.g. in the cerebrospinal

- 2 -

fluid of patients suffering from neurodegenerative disorders and are believed to contribute to inflammatory response and disease progression. Mice lacking MAGL (Mgl1^{-/-}) 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
5 (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 A₂ (PLA₂) enzymes have been viewed as the principal source of AA, but cPLA₂-deficient mice have unaltered AA levels in their brain, reinforcing the key role of MAGL in the brain for AA
10 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
15 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 Mgl1^{-/-} 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 Mgl1^{-/-} mice.

20 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 multiple sclerosis (Leo A., *Cell Mol Life Sci.* **2007**, 64, 1403.). Importantly, genetic and/or pharmacological disruption of MAGL activity also
25 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
30 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 Mgl1^{-/-} mice phenotype in the brain, including an increase in

- 3 -

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.

- 5 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.*,
10 *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
15 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
20 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.
25 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).

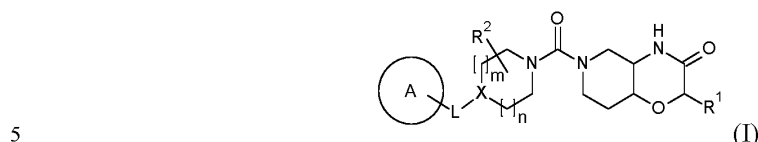
- 30 In conclusion, suppressing the action and/or the activation of MAGL is a promising new therapeutic strategy for the treatment or prevention of neuroinflammation, neurodegenerative diseases, pain, cancer and mental disorders. Furthermore, suppressing the action and/or the

- 4 -

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

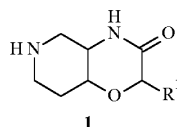
In a first aspect, the present invention provides a compound of formula (I)



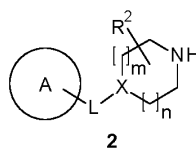
wherein A, L, X, m, n, R¹ and R² are as described herein.

In one aspect, the present invention provides a process of manufacturing the urea compounds of formula (I) described herein, comprising:

10 reacting a first amine of formula **1**, wherein R¹ is as described herein, preferably wherein R¹ is hydrogen,



with a second amine **2**, wherein A, L, m, n, X and R² are as described herein



15 in the presence of a base and a urea forming reagent,
to form said compound of formula (I).

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.

20 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.

- 5 -

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

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

10 In a further aspect, the present invention provides the use of a compound of formula (I) as described herein or of a pharmaceutical composition 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.

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

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

25 In a further aspect, the present invention provides a compound of formula (I) as described herein or a pharmaceutical composition 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.

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

- 6 -

In a further aspect, the present invention provides the use of a compound 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.

- 5 In a further aspect, the present invention provides the use of a compound 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
10 neuropathy, acute pain, chronic pain and/or spasticity associated with pain in a mammal.

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

- 15 In a further 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 or of a pharmaceutical composition described herein to the mammal.

- In a further aspect, the present invention provides a method for the treatment or prophylaxis of
20 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
25 (I) as described herein or of a pharmaceutical composition described herein to the mammal.

In one aspect, the present invention also provides a method for determining the MAGL inhibitory activity of a test compound, e.g. of a compound of formula (I) described herein, comprising measuring the ratio of arachidonic acid / d8-arachidonic acid in a solution.

Detailed Description of the InventionDefinitions

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

The term “alkyl” refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched
15 saturated hydrocarbon group of 1 to 12 carbon atoms. In some preferred embodiments, the alkyl group contains 1 to 6 carbon atoms, e.g., 1, 2, 3, 4, 5, or 6 carbon atoms (“C₁₋₆-alkyl”). In other 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, isobutyl, sec-butyl, tert-butyl, and 2,2-dimethylpropyl. A particularly preferred, yet non-limiting
20 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. Unless otherwise specified, the alkoxy group contains 1 to 12 carbon atoms. In some preferred embodiments, the alkoxy group contains 1 to 6 carbon atoms. In other embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other
25 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 and tert-butoxy. A particularly preferred, yet non-limiting example of alkoxy is methoxy.

The term “alkylsulfonyl” refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an SO₂ moiety. Unless otherwise specified, the alkylsulfonyl group
30 contains 1 to 12 carbon atoms. In some preferred embodiments, the alkylsulfonyl group contains

- 8 -

1 to 6 carbon atoms. In other embodiments, the alkylsulfonyl group contains 1 to 4 carbon atoms. In still other embodiments, the alkylsulfonyl group contains 1 to 3 carbon atoms.

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).

- 5 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 10 ring carbon atoms. In some preferred embodiments, the cycloalkyl group is a saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms.

- 10 "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. Preferably, 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-
15 limiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "heterocycloalkyl" and "heterocyclyl" are used herein interchangeably and refer to a saturated or partly unsaturated mono- or bicyclic, preferably monocyclic ring system of 3 to 10 ring atoms, preferably 3 to 8 ring atoms, wherein 1, 2, or 3 of said ring atoms are heteroatoms

- 20 selected from N, O and S, the remaining ring atoms being carbon. Preferably, 1 to 2 of said ring atoms are selected from N and O, the remaining ring atoms being carbon. "Bicyclic heterocyclyl" refers to heterocyclic moieties consisting of two cycles having two ring 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
25 atom. Some non-limiting examples of monocyclic heterocyclyl groups include azetidin-3-yl, azetidin-2-yl, oxetan-3-yl, oxetan-2-yl, 2-oxopyrrolidin-1-yl, 2-oxopyrrolidin-3-yl, 5-oxopyrrolidin-2-yl, 5-oxopyrrolidin-3-yl, 2-oxo-1-piperidyl, 2-oxo-3-piperidyl, 2-oxo-4-piperidyl, 6-oxo-2-piperidyl, 6-oxo-3-piperidyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, morpholino, morpholin-2-yl and morpholin-3-yl.

- 30 The term "aryl" refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of 6 to 14 ring members, 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. Some non-limiting examples

of aryl include phenyl and 9H-fluorenyl (e.g. 9H-fluoren-9-yl). A particularly preferred, yet non-limiting example of aryl is phenyl.

The term "heteroaryl" refers to a mono- or multivalent, monocyclic or bicyclic, preferably monocyclic ring system having a total of 5 to 14 ring members, 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 2-pyridyl, 3-pyridyl, 4-pyridyl, indol-1-yl, 1H-indol-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indol-7-yl, 1,2-benzoxazol-3-yl, 1,2-benzoxazol-4-yl, 1,2-benzoxazol-5-yl, 1,2-benzoxazol-6-yl, 1,2-benzoxazol-7-yl, 1H-indazol-3-yl, 1H-indazol-4-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1H-indazol-7-yl, pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, imidazol-1-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, oxazol-2-yl, oxazol-4-yl and oxazol-5-yl. A particularly preferred, yet non-limiting example of heteroaryl is pyridyl, in particular 2-pyridyl.

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

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

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 trifluoromethyl and 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. A particularly preferred, yet non-limiting example of haloalkoxy is trifluoromethoxy (-OCF₃).

The term "hydroxyalkyl" refers to an alkyl group, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by a hydroxy group. Preferably, "hydroxyalkyl" refers to an

alkyl group wherein 1, 2 or 3 hydrogen atoms, most preferably 1 hydrogen atom of the alkyl group have been replaced by a hydroxy group. Preferred, yet non-limiting examples of hydroxyalkyl are hydroxymethyl and hydroxyethyl (e.g. 2-hydroxyethyl). A particularly preferred, yet non-limiting example of hydroxyalkyl is hydroxymethyl.

- 5 The term "haloaryl" refers to an aryl group, wherein at least one of the hydrogen atoms of the aryl group has been replaced by a halogen atom. Preferably, "haloaryl" refers to an aryl group wherein 1, 2 or 3 hydrogen atoms, more preferably 1 or 2 hydrogen atoms, most preferably 1 hydrogen atom of the aryl group have been replaced by a halogen atom. A particularly preferred, yet non-limiting example of haloaryl is fluorophenyl, in particular 4-fluorophenyl.
- 10 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
- 25 pharmaceutically acceptable salts of compounds of formula (I) are hydrochloride salts.

The term "pharmaceutically acceptable ester" refers to esters that hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms.

30 Representative examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates. Examples of pharmaceutically acceptable

prodrug types are described in Higuchi and Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

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 term “urea forming reagent” refers to a chemical compound that is able to render a first amine to a reactive species that will react with a second amine, thereby forming an urea derivative. Non-limiting examples of urea forming reagents include bis(trichloromethyl) carbonate, phosgene, trichloromethyl chloroformate, (4-nitrophenyl)carbonate and 1,1'-carbonyldiimidazole. The urea forming reagents described in G. Sartori et al., *Green Chemistry* **2000**, 2, 140 are incorporated herein by reference.

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

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)

- 12 -

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 psychogenic pain. A particular example of pain is neuropathic

- 13 -

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.

- 5 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
- 10 heavy metals, certain foods and food additives, pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances.

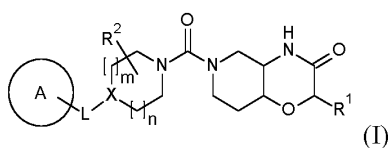
The term "cancer" refers to a disease characterized by the presence of a neoplasm or tumor resulting from abnormal uncontrolled growth of cells (such cells being "cancer cells"). As used herein, the term cancer explicitly includes, but is not limited to, hepatocellular carcinoma, colon

15 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

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



or a pharmaceutically acceptable salt thereof,

wherein:

- 25 X is C-R³; m is 0 or 1; n is selected from 0, 1 and 2; and L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -NR⁵-CH₂-CHR⁴-, -NR⁵-CHR⁴-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-, -C(O)-NR⁸-(CR⁶R⁷)_p-, -(CR⁶R⁷)_p-NR⁸-C(O)-, -NR⁸-C(O)-(CR⁶R⁷)_p-, -(CH₂)_qNR⁹-, -NR⁹-(CH₂)_q-, -S-, -S(O)-, -SO₂-, -SCH₂-, -CH₂S-, -S(O)CH₂-, -CH₂S(O)-, -SO₂CH₂-, and -CH₂SO₂-; or

- 14 -

X is N; m is 1; n is 1 or 2; and L is selected from $-\text{NR}^5-\text{CH}_2-\text{CHR}^4-$, $-\text{NR}^5-\text{CHR}^4-\text{CH}_2-$,
and $-\text{NR}^8-\text{C}(\text{O})-(\text{CR}^6\text{R}^7)_p-$;

p and q are each independently selected from 0, 1 and 2;

A is selected from:

- 5 (i) aryl substituted with R^{10} , R^{11} and R^{12} ;
- (ii) heteroaryl substituted with R^{13} , R^{14} and R^{15} ; and
- (iii) heterocycloalkyl substituted with R^{16} , R^{17} and R^{18} ;

R^1 is hydrogen or C_{1-6} -alkyl;

R^2 is selected from hydrogen, C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl;

10 R^3 is selected from hydrogen, halogen, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkyl and halo- C_{1-6} -alkyl;

R^4 is selected from hydrogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl;

R^5 is selected from hydrogen, C_{1-6} -alkyl and halo- C_{1-5} -alkyl- CH_2- ;

each of R^6 and R^7 is independently hydrogen or C_{1-6} -alkyl; or

15 R^6 and R^7 , taken together with the carbon atom to which they are attached, form a heterocycloalkyl or a C_{3-10} -cycloalkyl;

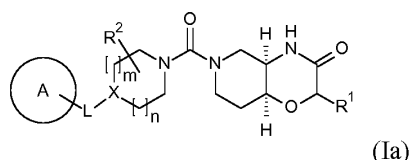
R^8 is selected from hydrogen, C_{1-6} -alkyl, and hydroxy- C_{1-6} -alkyl;

R^9 is selected from hydrogen, C_{1-6} -alkyl, halo- C_{1-5} -alkyl- CH_2- , $(\text{C}_{1-5}\text{-alkyl})(\text{halo-}\text{C}_{1-5}\text{-alkyl})\text{CH-}$ and hydroxy- C_{1-5} -alkyl- CH_2- ;

20 each of R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} is independently selected from hydrogen, halogen, cyano, hydroxy, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, halo- C_{1-5} -alkyl- $\text{CH}(\text{OH})-$, C_{1-6} -alkoxy, halo- C_{1-6} -alkoxy, SF_5 , CH_3SO_2 , C_{3-10} -cycloalkyl, C_{3-10} -cycloalkyl substituted with R^{19} , heterocycloalkyl, heterocycloalkyl substituted with R^{20} , heteroaryl, aryl and haloaryl; and

25 each of R^{19} and R^{20} is independently C_{1-6} -alkyl or hydroxy.

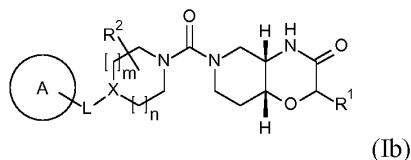
In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (Ia):



30 wherein A, L, X, m, n, R^1 and R^2 are as defined in claim 1.

- 15 -

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 (Ib):



5 wherein A, L, X, m, n, R¹ and R² are as defined in claim 1.

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

X is C-R³;

m and n are each independently 0 or 1; and

10 L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-,
-(CR⁶R⁷)_p-NR⁸-C(O)- and -(CH₂)_qNR⁹-.

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 C-R³;

15 m and n are both 0; or

m and n are both 1; and

L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, and -(CH₂)_qNR⁹-.

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

20 X is C-R³;

m and n are each independently 0 or 1;

L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-,
-(CR⁶R⁷)_p-NR⁸-C(O)- and -(CH₂)_qNR⁹-;

R³ is hydrogen or hydroxy;

25 R⁴ is halo-C₁₋₆-alkyl;

R⁵ is hydrogen;

R⁶ and R⁷ are both hydrogen; or

R⁶ and R⁷, taken together with the carbon atom to which they are attached, form a C₃₋₁₀-cycloalkyl;

- 16 -

R^8 is selected from hydrogen, C_{1-6} -alkyl, and hydroxy- C_{1-6} -alkyl;

R^9 is C_{1-6} -alkyl;

p is 0 or 1; and

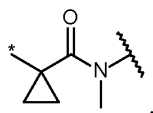
q is 0.

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

X is C-H or C-OH;

m and n are each independently 0 or 1; and

- 10 L is selected from $-C\equiv C-$, $-CH(CF_3)-NH-CH_2-$, $-CH(CF_3)-N(CH_3)-CH_2-$, $-CH_2-NH-CH(CF_3)-$, $-C(O)-NH-$, $-C(O)-N(CH_3)-$, $-CH_2-C(O)-N(CH_3)-$, $-CH_2-NH-C(O)-$, $-CH_2-N(2-hydroxyethyl)-C(O)-$, $-N(CH_3)-$, and



wherein the asterisk indicates the point of attachment to ring A and wherein the wavy line indicates the point of attachment to the central core.

- 15 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 C-H;

m and n are both 0; or

m and n are both 1; and

- 20 L is selected from $-CH(CF_3)-NH-CH_2-$, $-C\equiv C-$, and $-N(CH_3)-$.

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 C-H;

m and n are both 0; and

- 25 L is $-C\equiv C-$.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein p is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein q is 0.

- 17 -

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

- (i) aryl substituted with R¹⁰, R¹¹ and R¹²; and
- (ii) heteroaryl substituted with R¹³, R¹⁴ and R¹⁵.

- 5 In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein A is aryl substituted with R¹⁰, R¹¹ and R¹².

- In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein A is phenyl substituted with R¹⁰, R¹¹ and R¹².
- 10

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

A is selected from:

- (i) aryl substituted with R¹⁰, R¹¹ and R¹²; and
 - 15 (ii) heteroaryl substituted with R¹³, R¹⁴ and R¹⁵;
- R¹⁰ is selected from hydrogen, halo-C₁₋₆-alkyl, and halogen;
R¹¹ is hydrogen or halogen; and
each of R¹², R¹³, R¹⁴, and R¹⁵ is hydrogen.

- In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein:
- 20

A is aryl substituted with R¹⁰, R¹¹ and R¹²;
R¹⁰ is halo-C₁₋₆-alkyl or halogen;
R¹¹ is hydrogen or halogen; and
R¹² is hydrogen.

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

A is phenyl substituted with R¹⁰, R¹¹ and R¹²;
R¹⁰ is CF₃ or chloro;
R¹¹ is hydrogen or fluoro; and
30 R¹² is hydrogen.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein A is selected from phenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 2,4-dichlorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-chloro-4-fluoro-phenyl, 2-chloro-3-(trifluoromethyl)phenyl, 2-chloro-5-(trifluoromethyl)phenyl, 4-chloro-3-pyridyl and 3-chloro-2-pyridyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein A is selected from 4-(trifluoromethyl)phenyl, 2-chlorophenyl, and 2-chloro-4-fluoro-phenyl.

10 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein A is 2-chlorophenyl, or 2-chloro-4-fluoro-phenyl.

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

15 In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R² is hydrogen.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen or hydroxy.

20 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁴ is halo-C₁₋₆-alkyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁴ is CF₃.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁶ and R⁷ are both hydrogen; or

R⁶ and R⁷, together with the carbon atom to which they are attached, form a C₃₋₁₀-cycloalkyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁶ and R⁷ are both hydrogen; or

5 R⁶ and R⁷, together with the carbon atom to which they are attached, form a cyclopropyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁸ is selected from hydrogen, 2-hydroxyethyl, and methyl.

In one embodiment, the present invention provides a compound of formula (I) as described
10 herein, or a pharmaceutically acceptable salt thereof, wherein R⁹ is C₁₋₆-alkyl.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R⁹ is methyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is selected from hydrogen,
15 halo-C₁₋₆-alkyl, and halogen.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is halo-C₁₋₆-alkyl or halogen.

In a particularly preferred embodiment, the present invention provides a compound of formula
20 (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is CF₃ or chloro.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹¹ is hydrogen or halogen.

In a preferred embodiment, the present invention provides a compound of formula (I) as
25 described herein, or a pharmaceutically acceptable salt thereof, wherein R¹¹ is hydrogen or fluoro.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹² is hydrogen.

- 20 -

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^{13} is halogen.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^{14} is hydrogen.

- 5 In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R^{15} is hydrogen.

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

X is $C-R^3$;

- 10 L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-CH_2-NR^5-CHR^4-$, $-(CR^6R^7)_p-C(O)-NR^8-$,
 $-(CR^6R^7)_p-NR^8-C(O)-$ and $-(CH_2)_qNR^9-$;

m, n and p are each independently 0 or 1;

q is 0;

A is selected from:

- 15 (i) aryl substituted with R^{10} , R^{11} and R^{12} ; and
 (ii) heteroaryl substituted with R^{13} , R^{14} and R^{15} ;

R^1 and R^2 are both hydrogen;

R^3 is hydrogen or hydroxy;

R^4 is halo- C_{1-6} -alkyl;

- 20 R^5 is hydrogen or C_{1-6} -alkyl;

R^6 and R^7 are both hydrogen; or

R^6 and R^7 , together with the carbon atom to which they are attached, form a C_{3-10} -cycloalkyl;

R^8 is selected from hydrogen, C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl;

- 25 R^9 is C_{1-6} -alkyl;

R^{10} is selected from hydrogen, halo- C_{1-6} -alkyl, and halogen;

R^{11} is hydrogen or halogen;

R^{12} is hydrogen;

R^{13} is halogen; and

- 30 R^{14} and R^{15} are both hydrogen.

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

- 21 -

X is C-R³;

L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, and $-(\text{CH}_2)_q\text{NR}^9-$;

m and n are both 0; or

m and n are both 1;

5 q is 0;

A is aryl substituted with R¹⁰, R¹¹ and R¹²;

R¹, R² and R³ are all hydrogen;

R⁴ is halo-C₁₋₆-alkyl;

R⁵ is hydrogen;

10 R⁹ is C₁₋₆-alkyl;

R¹⁰ is halo-C₁₋₆-alkyl or halogen;

R¹¹ is hydrogen or halogen; and

R¹² is hydrogen.

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

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

X is C-R³;

L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, and $-(\text{CH}_2)_q\text{NR}^9-$;

m and n are both 0; or

m and n are both 1;

20 q is 0;

A is phenyl substituted with R¹⁰, R¹¹ and R¹²;

R¹, R² and R³ are all hydrogen;

R⁴ is CF₃;

R⁵ is hydrogen;

25 R⁹ is methyl;

R¹⁰ is CF₃ or chloro;

R¹¹ is hydrogen or fluoro; and

R¹² is hydrogen.

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

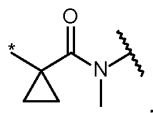
30 herein, or a pharmaceutically acceptable salt thereof, wherein:

X is C-H or C-OH;

m and n are each independently 0 or 1;

- 22 -

L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CH}(\text{CF}_3)-\text{NH}-\text{CH}_2-$, $-\text{CH}(\text{CF}_3)-\text{N}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-\text{CH}(\text{CF}_3)-$, $-\text{C}(\text{O})-\text{NH}-$, $-\text{C}(\text{O})-\text{N}(\text{CH}_3)-$, $-\text{CH}_2-\text{C}(\text{O})-\text{N}(\text{CH}_3)-$, $-\text{CH}_2-\text{NH}-\text{C}(\text{O})-$, $-\text{CH}_2-\text{N}(2\text{-hydroxyethyl})-\text{C}(\text{O})-$, $-\text{N}(\text{CH}_3)-$, and



5 wherein the asterisk indicates the point of attachment to ring A and wherein the wavy line indicates the point of attachment to the central core;

A is selected from phenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 2,4-dichlorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-chloro-4-fluoro-phenyl, 2-chloro-3-(trifluoromethyl)phenyl, 2-chloro-5-(trifluoromethyl)phenyl, 4-chloro-3-pyridyl and 3-chloro-2-pyridyl; and
 10 R^1 and R^2 are both hydrogen.

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 C-H;
 15 m and n are both 0; or
 m and n are both 1;
 L is selected from $-\text{CH}(\text{CF}_3)-\text{NH}-\text{CH}_2-$, $-\text{C}\equiv\text{C}-$, and $-\text{N}(\text{CH}_3)-$;
 A is selected from 4-(trifluoromethyl)phenyl, 2-chlorophenyl, and 2-chloro-4-fluoro-phenyl; and
 20 R^1 and R^2 are both hydrogen.

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

X is $\text{C}-\text{R}^3$; m is 0 or 1; n is selected from 0, 1 and 2; and L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, $-\text{NR}^5-\text{CH}_2-\text{CHR}^4-$, $-\text{NR}^5-\text{CHR}^4-\text{CH}_2-$, $-\text{CH}_2-\text{NR}^5-\text{CHR}^4-$, $-(\text{CR}^6\text{R}^7)_p-\text{C}(\text{O})-\text{NR}^8-$, $-\text{C}(\text{O})-\text{NR}^8-(\text{CR}^6\text{R}^7)_p-$, $-(\text{CR}^6\text{R}^7)_p-\text{NR}^8-\text{C}(\text{O})-$, $-\text{NR}^8-\text{C}(\text{O})-(\text{CR}^6\text{R}^7)_p-$, $-(\text{CH}_2)_q\text{NR}^9-$, $-\text{NR}^9-(\text{CH}_2)_q-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SCH}_2-$, $-\text{CH}_2\text{S}-$, $-\text{S}(\text{O})\text{CH}_2-$, $-\text{CH}_2\text{S}(\text{O})-$, $-\text{SO}_2\text{CH}_2-$, and $-\text{CH}_2\text{SO}_2-$; or
 25 X is N; m is 1; n is 1 or 2; and L is selected from $-\text{NR}^5-\text{CH}_2-\text{CHR}^4-$, $-\text{NR}^5-\text{CHR}^4-\text{CH}_2-$, and $-\text{NR}^8-\text{C}(\text{O})-(\text{CR}^6\text{R}^7)_p-$;
 30 p and q are each independently selected from 0, 1 and 2;
 A is selected from:

- 23 -

- (i) C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;
- (ii) 5- to 14-membered heteroaryl substituted with R¹³, R¹⁴ and R¹⁵; and
- (iii) 3- to 14-membered heterocycloalkyl substituted with R¹⁶, R¹⁷ and R¹⁸;
- (iv) C₃-C₁₀-cycloalkyl substituted with R²², R²³, and R²⁴;

5 R¹ is hydrogen or C₁₋₆-alkyl;

R² is selected from hydrogen, C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;

R³ is selected from hydrogen, halogen, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

R⁴ is selected from hydrogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

10 R⁵ is selected from hydrogen, C₁₋₆-alkyl and halo-C₁₋₆-alkyl-CH₂-;

each of R⁶ and R⁷ is independently hydrogen or C₁₋₆-alkyl; or

R⁶ and R⁷, taken together with the carbon atom to which they are attached, form a 3- to 14-membered heterocycloalkyl or a C₃₋₁₀-cycloalkyl;

R⁸ is selected from hydrogen, C₁₋₆-alkyl, and hydroxy-C₁₋₆-alkyl;

15 R⁹ is selected from hydrogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl-CH₂-, (C₁₋₆-alkyl)(halo-C₁₋₆-alkyl)CH- and hydroxy-C₁₋₆-alkyl-CH₂-;

each of R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ is independently selected from

hydrogen, halogen, cyano, hydroxy, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl,

halo-C₁₋₆-alkyl-CH(OH)-, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, SF₅,

20 C₁₋₆-alkylsulfonyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-cycloalkyl substituted with R¹⁹, 3- to 14-membered heterocycloalkyl, 3- to 14-membered heterocycloalkyl substituted with

R²⁰, 5- to 14-membered heteroaryl, C₆-C₁₄-aryl and halo-C₆-C₁₄-aryl; and

each of R¹⁹ and R²⁰ is independently selected from C₁₋₆-alkyl, cyano, and hydroxy.

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

X is C-R³;

m and n are each independently 0 or 1; and

L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-,
 -(CR⁶R⁷)_p-NR⁸-C(O)-, -(CH₂)_qNR⁹-, -S-, -S(O)-, -SO₂-, -SCH₂-, -CH₂S-, -

30 S(O)CH₂-, -CH₂S(O)-, -SO₂CH₂-, and -CH₂SO₂-.

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 C-R³;

- 24 -

m and n are both 0; or

m and n are both 1; and

L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-(CH_2)_qNR^9-$, $-SCH_2-$, and $-CH_2S-$.

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

- (i) C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;
- (ii) 5- to 14-membered heteroaryl substituted with R¹³, R¹⁴ and R¹⁵; and
- (iii) C₃-C₁₀-cycloalkyl substituted with R²², R²³, and R²⁴.

In a preferred embodiment, the present invention provides a compound of formula (I) as
10 described herein, or a pharmaceutically acceptable salt thereof, wherein A is C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹².

In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein A is phenyl substituted with R¹⁰, R¹¹ and R¹².

15 In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen, hydroxy, or C₁₋₆-alkyl.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkylsulfonyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-cycloalkyl substituted with R¹⁹, cyano, or halogen.
20

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₃₋₁₀-cycloalkyl, or halogen.

25 In a particularly preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is methyl, difluoromethyl, CF₃, OCF₃, cyclopropyl, fluoro, or chloro.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹¹ is hydrogen, C₁₋₆-alkyl, or
30 halogen.

- 25 -

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹¹ is hydrogen, methyl, chloro, or fluoro.

In one embodiment, the present invention provides a compound of formula (I) as described
5 herein, or a pharmaceutically acceptable salt thereof wherein R¹² is hydrogen or halogen.

In a preferred embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R¹² is hydrogen or fluoro.

In one embodiment, the present invention provides a compound of formula (I) as described
10 herein, or a pharmaceutically acceptable salt thereof, wherein R¹⁹ is hydroxy or cyano.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R²² is hydrogen or hydroxy.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R²³ is hydrogen.

15 In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein R²⁴ is hydrogen.

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

X is C-R³;

20 L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-,
-(CR⁶R⁷)_p-NR⁸-C(O)-, -(CH₂)_qNR⁹-, -S-, -S(O)-, -SO₂-, -SCH₂-, -CH₂S-, -
S(O)CH₂-, -CH₂S(O)-, and -SO₂CH₂-;

m, n and p are each independently 0 or 1;

q is 0;

25 A is selected from:

- (i) C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;
- (ii) 5- to 14-heteroaryl substituted with R¹³, R¹⁴ and R¹⁵; and
- (iii) C₃-C₁₀-cycloalkyl substituted with R²², R²³, and R²⁴;

R¹ and R² are both hydrogen;

30 R³ is selected from hydrogen, hydroxy, and C₁₋₆-alkyl;

- 26 -

- R^4 is halo- C_{1-6} -alkyl;
 R^5 is hydrogen or C_{1-6} -alkyl;
 R^6 and R^7 are both hydrogen; or
 R^6 and R^7 , together with the carbon atom to which they are attached, form a C_{3-10} -
 5 cycloalkyl;
 R^8 is selected from hydrogen, C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl;
 R^9 is C_{1-6} -alkyl;
 R^{10} is selected from hydrogen, C_{1-6} -alkyl, C_{1-6} -alkylsulfonyl, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -
 alkyl, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, C_{3-10} -cycloalkyl, C_{3-10} -cycloalkyl substituted
 10 with R^{19} , cyano, and halogen;
 R^{11} is selected from hydrogen, C_{1-6} -alkyl, and halogen;
 R^{12} is hydrogen or halogen;
 R^{13} is halogen;
 R^{14} and R^{15} are both hydrogen;
 15 R^{19} is hydroxy or cyano;
 R^{22} is hydrogen or hydroxy; and
 R^{23} and R^{24} are both hydrogen.

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

- 20 X is $C-R^3$;
 L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-(CH_2)_qNR^9-$, $-SCH_2-$, and $-CH_2S-$;
 m and n are both 0; or
 m and n are both 1;
 q is 0;
 25 A is C_6-C_{14} -aryl substituted with R^{10} , R^{11} and R^{12} ;
 R^1 , R^2 and R^3 are all hydrogen;
 R^4 is halo- C_{1-6} -alkyl;
 R^5 is hydrogen;
 R^9 is C_{1-6} -alkyl;
 30 R^{10} is selected from C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, C_{3-10} -cycloalkyl, and
 halogen;
 R^{11} is selected from hydrogen, C_{1-6} -alkyl, and halogen; and
 R^{12} is hydrogen or halogen.

- 27 -

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 C-R³;
- L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, $-(\text{CH}_2)_q\text{NR}^9-$, $-\text{SCH}_2-$, and $-\text{CH}_2\text{S}-$;
- 5 m and n are both 0; or
- m and n are both 1;
- q is 0;
- A is phenyl substituted with R¹⁰, R¹¹ and R¹²;
- R¹, R² and R³ are all hydrogen;
- 10 R⁴ is CF₃;
- R⁵ is hydrogen;
- R⁹ is methyl;
- R¹⁰ is selected from methyl, difluoromethyl, CF₃, OCF₃, cyclopropyl, chloro, and fluoro;
- R¹¹ is selected from hydrogen, methyl, chloro, and fluoro; and
- 15 R¹² is hydrogen or fluoro.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, wherein X is C-R³ and R³ is selected from hydrogen, hydroxy, and C₁₋₆-alkyl.

- 20 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 C-H.

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

- L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NR}^5-\text{CH}_2-$, $-\text{CH}_2-\text{NR}^5-\text{CHR}^4-$, $-(\text{CR}^6\text{R}^7)_p-\text{C}(\text{O})-\text{NR}^8-$,
 $-(\text{CR}^6\text{R}^7)_p-\text{NR}^8-\text{C}(\text{O})-$, $-(\text{CH}_2)_q\text{NR}^9-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{SCH}_2-$, $-\text{CH}_2\text{S}-$,
 25 $\text{S}(\text{O})\text{CH}_2-$, $-\text{CH}_2\text{S}(\text{O})-$, and $-\text{SO}_2\text{CH}_2-$;
- R⁴ is halo-C₁₋₆-alkyl;
- R⁵ is hydrogen or C₁₋₆-alkyl;
- R⁶ and R⁷ are both hydrogen; or
- R⁶ and R⁷, together with the carbon atom to which they are attached, form a C₃₋₁₀-
 30 cycloalkyl;
- R⁸ is selected from hydrogen, C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;
- R⁹ is C₁₋₆-alkyl;

- 28 -

p is 0 or 1; and

q is 0.

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

- 5 L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NH}-\text{CH}_2-$, $-\text{NR}^9-$, $-\text{SCH}_2-$, and $-\text{CH}_2\text{S}-$;
 R^4 is halo- C_{1-6} -alkyl; and
 R^9 is C_{1-6} -alkyl.

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

- 10 L is selected from $-\text{C}\equiv\text{C}-$, $-\text{CHR}^4-\text{NH}-\text{CH}_2-$, $-\text{NR}^9-$, $-\text{SCH}_2-$, and $-\text{CH}_2\text{S}-$;
 R^4 is CF_3 ; and
 R^9 is methyl.

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

- 15 A is selected from:
 (i) $\text{C}_6\text{-C}_{14}$ -aryl substituted with R^{10} , R^{11} and R^{12} ;
 (ii) 5- to 14-heteroaryl substituted with R^{13} , R^{14} and R^{15} ; and
 (iii) $\text{C}_3\text{-C}_{10}$ -cycloalkyl substituted with R^{22} , R^{23} , and R^{24} ;

- R^{10} is selected from hydrogen, C_{1-6} -alkyl, C_{1-6} -alkylsulfonyl, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl,
20 halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, C_{3-10} -cycloalkyl, C_{3-10} -cycloalkyl substituted with R^{19} ,
 cyano, and halogen;

R^{11} is selected from hydrogen, C_{1-6} -alkyl, and halogen;

R^{12} is hydrogen or halogen;

R^{13} is halogen;

- 25 R^{14} , R^{15} , R^{23} and R^{24} are all hydrogen;

R^{19} is hydroxy or cyano; and

R^{22} is hydrogen or hydroxy.

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

- 30 A is $\text{C}_6\text{-C}_{14}$ -aryl substituted with R^{10} , R^{11} and R^{12} ;
 R^{10} is selected from C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, C_{3-10} -cycloalkyl, and halogen;
 R^{11} is selected from hydrogen, C_{1-6} -alkyl, and halogen; and

R¹² is hydrogen or halogen.

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

A is phenyl substituted with R¹⁰, R¹¹ and R¹²;

5 R¹⁰ is selected from methyl, difluoromethyl, CF₃, OCF₃, cyclopropyl, chloro, and fluoro;

R¹¹ is selected from hydrogen, methyl, chloro, and fluoro; and

R¹² is hydrogen or fluoro.

In one embodiment, the present invention provides a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, selected from the compounds recited in
10 Table 1.

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

- (+)- or (-)-(4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-[4-(trifluoromethyl)phenyl]ethyl]amino]methyl]azetidine-1-carbonyl]hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
15 (4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (+)- or (-)-(4aR,8aS)-6-[4-[2-(2-Chloro-4-fluorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
20 (4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2-Chloro-4-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
25 (4aR,8aS)-6-[4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-(((2-Chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
(4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)thio)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
30 (4aR,8aS)-6-(3-((2,6-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;

- 30 -

- (4aR,8aS)-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-((2-Chloro-6-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 5 (4aR,8aS)-6-(3-((2-Chloro-4-cyclopropylphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-[4-Trifluoromethoxy]phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2,6-Dimethylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 10 (4aR,8aS)-6-[3-[2-[2-(Trifluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-(o-Tolyethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 15 (4aR,8aS)-6-[3-[2-(4-Chloro-2-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Difluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2-Chloro-6-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (4aR,8aS)-6-[3-[2-[2-Chloro-6-fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and
- (4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one.
- 25 In one embodiment, the present invention provides pharmaceutically acceptable salts or esters of the compounds of formula (I) as described herein. In a particular embodiment, the present invention provides pharmaceutically acceptable salts of the compounds according to formula (I) as described herein, especially hydrochloride salts. In a further particular embodiment, the present invention provides pharmaceutically acceptable esters of the compounds according to
- 30 formula (I) as described herein. In yet 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

- 31 -

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, ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Certain isotopically-labeled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e., ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. For example, a compound of formula (I) can be enriched with 1, 2, 5, 10, 25, 50, 75, 90, 95, or 99 percent of a given isotope.

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

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. Wuts, 5th Ed., 2014, John Wiley & Sons, N.Y.) can be introduced before the critical step applying methods well known in the art. Such

- 32 -

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.

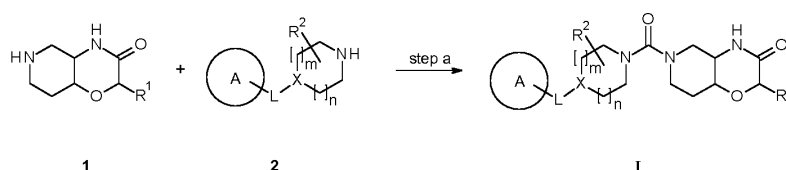
The following abbreviations are used in the present text:

AcOH = acetic acid, ACN = acetonitrile, Bn = benzyl, Boc = tert-butyloxycarbonyl, CAS RN = chemical abstracts registration number, Cbz = benzyloxycarbonyl, Cs₂CO₃ = 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, H₂O = water, H₂SO₄ = 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'-tetramethyl-uronium-hexafluorophosphate, HCl = hydrogen chloride, HOBT = 1-hydroxy-1H-benzotriazole; HPLC = high performance liquid chromatography, iPrMgCl = isopropylmagnesium chloride, I₂ = iodine, IPA = 2-propanol, ISP = ion spray positive (mode), ISN = ion spray negative (mode), K₂CO₃ = potassium carbonate, KHCO₃ = potassium bicarbonate, KI = potassium iodide, KOH = potassium hydroxide, K₃PO₄ = potassium phosphate tribasic, LiAlH₄ or LAH = lithium aluminium hydride, LiHMDS = lithium bis(trimethylsilyl)amide, LiOH = lithium hydroxide, mCPBA = meta-chloroperoxybenzoic acid, MgSO₄ = magnesium sulfate, min = minute(s), mL = milliliter, MPLC = medium pressure liquid chromatography, MS = mass spectrum, nBuLi = n-butyllithium, NaBH₃CN = sodium cyanoborohydride, NaH = sodium hydride, NaHCO₃ = sodium hydrogen carbonate, NaNO₂ = sodium nitrite, NaBH(OAc)₃ = sodium

- 34 -

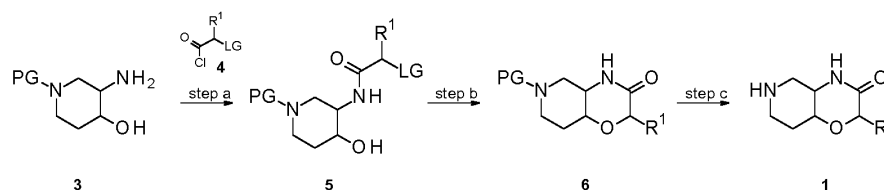
triacetoxyborohydride, NaOH = sodium hydroxide, Na₂CO₃ = sodium carbonate, Na₂SO₄ = sodium sulfate, Na₂S₂O₃ = sodium thiosulfate, NBS = N-bromosuccinimide, nBuLi = n-butyllithium, NEt₃ = triethylamine (TEA), NH₄Cl = ammonium chloride, NMP = N-methyl-2-pyrrolidone, OAc = Acetoxy, T₃P = propylphosphonic anhydride, PE = petroleum ether, PG = protective group, Pd-C = palladium on activated carbon, PdCl₂(dppf)-CH₂Cl₂ = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0), Pd(OAc)₂ = palladium(II) acetate, Pd(OH)₂ = palladium hydroxide, Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium(0), PTSA = p-toluenesulfonic acid, R = any group, RT = room temperature, SFC = Supercritical Fluid Chromatography, S-PHOS = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TBAI = tetra butyl ammonium iodine, TEA = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMEDA = N,N,N',N'-tetramethylethylenediamine, ZnCl₂ = zinc chloride, Hal = halogen.

Compounds of formula **I** wherein A, L, X, m, n, R¹ and R² are as described herein can be synthesized in analogy to literature procedures and/or as depicted for example in Scheme 1.

Scheme 1

Accordingly, 4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-ones **1** are reacted with intermediates **2** in the presence of a urea forming reagent such as bis(trichloromethyl) carbonate using a suitable base and solvent such as, e.g. sodium bicarbonate in DCM, to give compounds of formula **I** (step a). Further urea forming reagents include but are not limited to phosgene, trichloromethyl chloroformate, (4-nitrophenyl)carbonate or 1,1'-carbonyldiimidazole. Reactions of this type and the use of these reagents are widely described in literature (e.g. G. Sartori et al., *Green Chemistry* **2000**, 2, 140). A person skilled in the art will acknowledge that the order of the addition of the reagents can be important in this type of reactions due to the reactivity and stability of the intermediary formed carbamoyl chlorides, as well as for avoiding formation of undesired symmetrical urea by-products.

Intermediates **1** may be synthesized as depicted for example in Scheme 2 and/or in analogy to methods described in literature.



Scheme 2

- Thus, 3-aminopiperidin-4-ol derivatives **3** in which “PG” signifies a suitable protective group such as a Cbz or Boc protective group can be acylated for example with acyl chlorides **4** in which R¹ is as defined herein and “LG” signifies a suitable leaving group (e.g., Cl or Br), using a suitable base such as sodium or potassium carbonate, sodium hydroxide or sodium acetate in an appropriate solvent such as THF, water, acetone or mixtures thereof, to provide intermediates **5** (step a). Intermediates **4** are either commercially available or can be prepared according to literature methods in achiral (R¹ = H) racemic (R¹ not H) or enantiomerically pure form (R¹ not H).

- Intermediates **5** can be cyclized to intermediates **6** using methods well known in the art, for example by treatment of **5** with sodium hydride in THF or potassium tert-butoxide in IPA and water (step b). Reactions of that type are described in literature (e.g. Z. Rafinski et al., *J. Org. Chem.* **2015**, *80*, 7468; S. Dugar et al., *Synthesis* **2015**, *47*(5), 712; WO2005/066187).

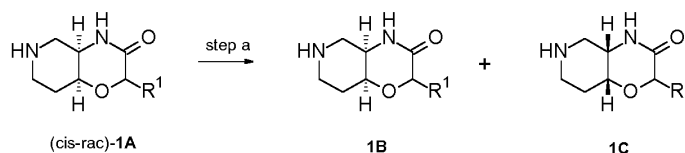
- Removal of the protective group in intermediates **6**, applying methods known in the art (e.g., a Boc group using TFA in DCM at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y.), furnishes intermediates **1** (step c).

- Intermediates **1** can be obtained as mixtures of diastereomers and enantiomers, respectively, or as single stereoisomers depending on whether racemic mixtures or enantiomerically pure forms of cis- or trans-3-aminopiperidin-4-ol derivatives **3** are employed in their syntheses.

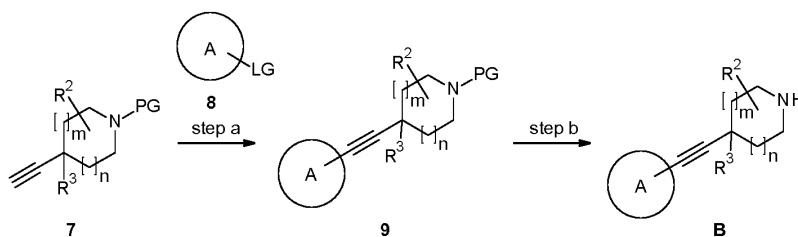
Intermediates **3** are commercially available and their synthesis has also been described in literature (e.g. WO2005/066187; WO2011/0059118; WO2016/185279). Optically pure cis-

- 36 -

configured intermediates **1B** and **1C** can be obtained for example according to Scheme 3 by chiral separation of commercially available rac-(4aR,8aS)-4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one (**1A**) (optionally in form of a salt such as, e.g. a hydrochloride salt) using methods known in the art, e.g. by diastereomeric salt crystallization or by chiral chromatography (step a).

Scheme 3

In some embodiments, intermediates **2** are intermediates of type **B**. Intermediates of type **B** in which m, n, R² and R³ are as described herein and A is aryl or heteroaryl as described herein, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 4.

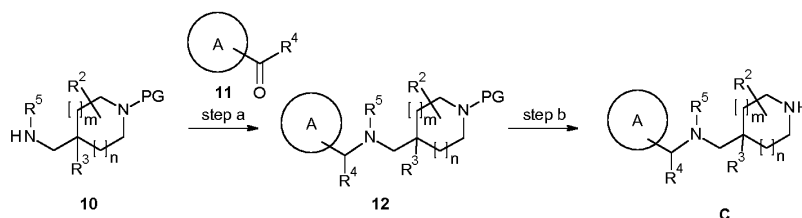
Scheme 4

Alkynes **7**, either commercially available or prepared by methods known in the art and in which PG signifies a suitable protecting group such as, e.g. a Boc, Cbz or Bn protecting group, can be subjected to a Sonogashira reaction (e.g. *Chem. Soc. Rev.* **2011**, *40*, 5084) with aryl or heteroaryl halides **8**, wherein LG is preferably Br, I or OTf and using a suitable catalyst, such as, Pd(OAc)₂/PPh₃, Pd(PPh₃)₄, preferably PdCl₂(PPh₃)₄ in presence of CuI and an appropriate base such as, e.g. K₂CO₃, Cs₂CO₃, DIPEA or preferably TEA and suitable solvent such as, e.g. THF, DMSO, DMF, NMP, CH₃CN or dioxane, preferably THF and in a temperature range between room temperature and 100°C, preferably around 65°C to give intermediates **9** (step a).

- 37 -

Removal of the optional protective group from intermediates **9**, applying methods known in the art, e.g., a Boc group using TFA in DCM or 4M HCl in dioxane at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y.), furnishes intermediates **B** (step b).

In some embodiments, intermediates **2** are intermediates of type **C**. Intermediates of type **C** in which A, m, n, R², R³, R⁴ and R⁵ are as described herein, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in Scheme 5.



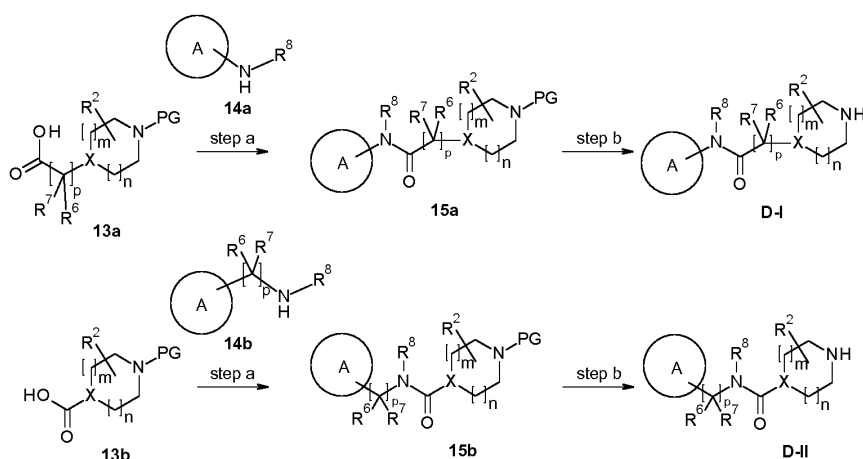
Scheme 5

Amines **10**, either commercially available or prepared by methods known in the art, in which R⁵ is for example selected from hydrogen, C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl or halo-C₁₋₆-alkyl, preferably methyl, and in which PG signifies a suitable protecting group such as, e.g. a Boc, Cbz or Bn protecting group, can be subjected to a reductive amination (e.g. *Tetrahedron Letters* **1990**, 31, p. 5547) with aryl or heteroaryl aldehydes or ketones **11**, and using a suitable acid such as TiCl₄, acetic acid, and an appropriate reducing agent such as e.g. sodium cyanoborohydride and suitable solvent system such as, e.g. DCE, MeOH, NMP and mixtures thereof, or preferably DCM and in a temperature range between 0°C and room temperature, to give intermediates **12** (step a).

Removal of the protective group from intermediates **12** by applying methods known in the art or as described under Scheme 4, step b, furnishes intermediates **C** (step b).

In some embodiment, intermediates **2** are intermediates of type **D-I** or **D-II**. Intermediates of type **D-I** or **D-II** in which A, m, n, p, R², R⁶ and R⁷ are as described herein, and X is N or CR³,

wherein R^3 is as defined herein, can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in [Scheme 6](#).



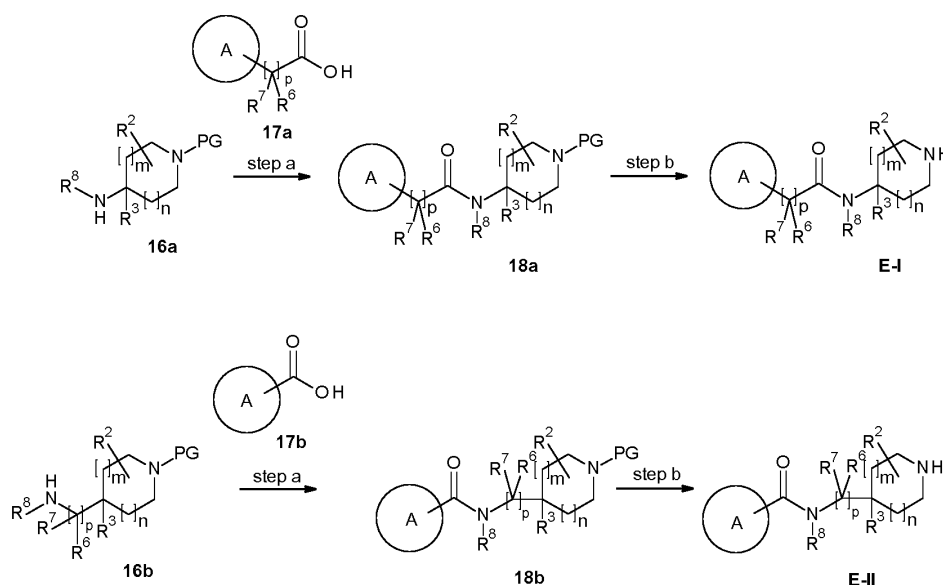
[Scheme 6](#)

- 5 Carboxylates **13a/13b**, either commercially available or prepared by methods known in the art, and in which PG signifies a suitable protecting group such as, e.g. a Boc, Cbz or Bn protecting group, can be subjected to an amide coupling with amines **14a/14b**, in which R^8 is for example selected from hydrogen, C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl or halo- C_{1-6} -alkyl, preferably hydroxy- C_{1-6} -alkyl, and using a suitable coupling reagent, such as HATU, HBTU, DCC, EDC, preferably
- 10 HATU and an appropriate base such as, e.g., DIPEA and suitable solvent system such as, e.g. DMF, NMP, CH_3CN or DCM, preferably DMF and in a temperature range between room temperature and $100^\circ C$, preferably around room temperature to give intermediates **15a/15b** ([step a](#)).

- Removal of the protective group from intermediates **15a/15b** applying methods known in the art
- 15 or as described under Scheme 4, step b, furnishes intermediates **D-I** and **D-II**, respectively ([step b](#)).

In some embodiment, intermediates **2** are intermediates of type **E**. Intermediates of type **E** in which A, m, n, p, R^2 , R^3 , R^6 , R^7 and R^8 are as described herein, can be prepared by methods well known in the art and as exemplified by the general synthetic procedures outlined in [Scheme 7](#).

- 39 -



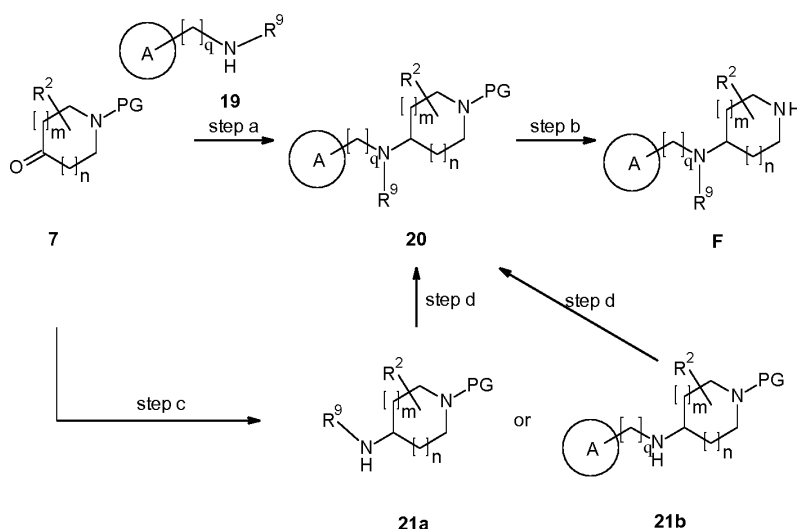
Scheme 7

Amines **16a/16b**, either commercially available or prepared by methods known in the art, in which R^8 is for example selected from hydrogen, C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl or halo- C_{1-6} -alkyl, preferably hydroxy- C_{1-6} -alkyl and in which PG signifies a suitable protecting group such as, e.g. a Boc, Cbz or Bn protecting group, can be subjected to an amide coupling with carboxylates **17a/17b**, using a suitable coupling reagent, such as HATU, HBTU, DCC, EDC, preferably HATU and an appropriate base such as, e.g., DIPEA and suitable solvent system such as, e.g. DMF, NMP, CH_3CN , DCM or preferably DMF and in a temperature range between room temperature and $100^\circ C$, preferably around room temperature to give intermediates **18a/18b**, respectively (step a).

Removal of the protective group from intermediates **18a/18b** applying methods known in the art or as described under Scheme 4, step b, furnishes intermediates **E-I/E-II**, respectively (step b).

In some embodiments, intermediates **2** are intermediates of type **F**. Intermediates of type **F** in which m , n , q , R^2 , R^9 and A are as described herein can be prepared by methods well known in the art and as exemplified by the general synthetic procedure outlined in Scheme 8.

- 40 -



Scheme 8

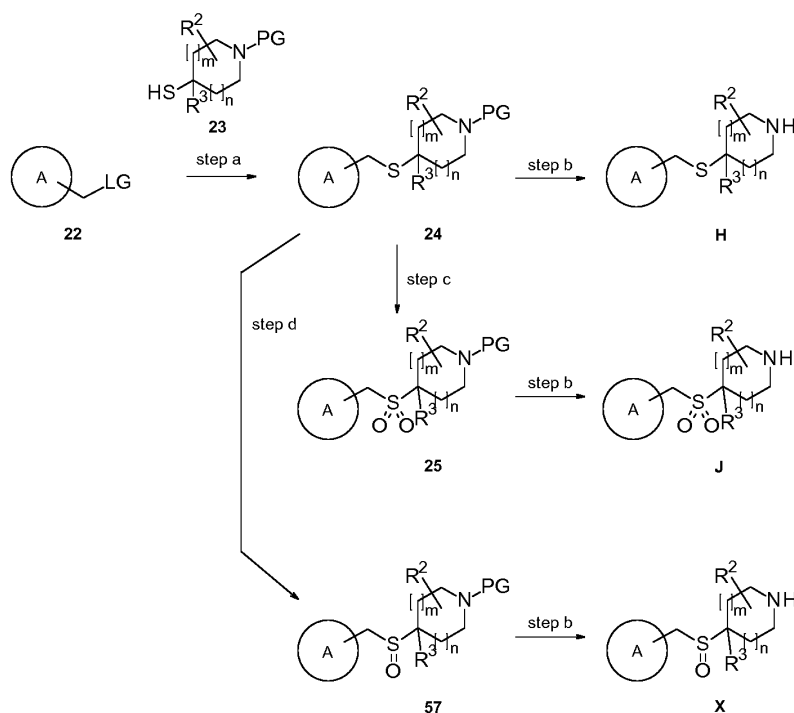
- Ketones of type **7**, either commercially available or prepared by methods known in the art, can be subjected to a reductive amination reaction (e.g. *Tetrahedron Letters* **1990**, 31, 5547; *Bioorg. Med. Chem. Lett.* **2008**, 16(14), 7021) with primary or secondary amines **19** using a suitable acid such as acetic acid, an appropriate reducing agent such as NaBH₃CN, NaBH(OAc)₃ or borane-THF complex and a suitable solvent system such as DCM, DCE, MeOH, NMP or mixtures thereof, preferably DCM, in a temperature range between 0°C and room temperature, to give intermediates **20** (step a).
- Removal of the protective group in intermediates **20**, applying methods known in the art (e.g., a Boc group using TFA in DCM at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y.), furnishes intermediates **F** (step b).

Alternatively, intermediates **F** can be prepared starting from ketones **7** and primary amines of type R⁹NH₂ applying the same method as described under step a above to give intermediates **21a** (step c). Likewise, intermediates **21b** are obtained if primary amines of type A-(CH₂)_q-NH₂ are employed.

Further reacting intermediates **21a** using the reagents and conditions outlined under step a, and using aldehydes A-CHO, affords intermediates **20**, wherein q is 1 (step e). Likewise, further reacting intermediates **21b** with aldehydes R⁹-CHO affords intermediates **20**. In case A signifies an optionally substituted aryl or heteroaryl ring and q is 0, intermediates **21a** can alternatively be
 5 reacted with aryl or heteroaryl bromide or iodides (A-Br or A-I) using a suitable catalyst, base and solvent system such as Pd(OAc)₂, BINAP and potassium tert-butyrate in toluene to afford intermediates **20** (step e). These type of reactions are well known in the art (e.g. *J. Med. Chem.* **2004**, 47(8), 1939; *Bioorg. Med. Chem. Lett.* **2008**, 18, 2000).

In some embodiment, intermediates **2** are intermediates of type **H** and **J**, respectively.

10 Intermediates of type **H** and **J** in which A, m, n and R² are as described herein, can be prepared by methods well known in the art and as exemplified by the general synthetic procedures outlined in Scheme 9.



Scheme 9

15 Intermediates **24** may be prepared from thiols **23** in which PG is a suitable protective group such as a Cbz, Boc or Bn, that can be alkylated with compounds **22** in which LG is a suitable leaving

- 42 -

group such as chlorine, bromine, iodine, OSO₂alkyl (e.g. methanesulfonate), OSO₂fluoroalkyl (e.g. trifluoromethanesulfonate) or OSO₂aryl (e.g. p-toluenesulfonate) using a suitable base, such as sodium hydride, potassium tert-butoxide, in an appropriate solvent (e.g. in DMF or THF) at temperatures between 0°C and the boiling temperature of the solvent (step a).

- 5 Removal of the protective group from intermediates **24** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **H** (step b).

Intermediates **24** can be oxidized to intermediates **25**, using a suitable oxidizing reagent, such as mCPBA, in an appropriate solvent (e.g. in DCM) at temperatures between 0°C and the boiling temperature of the solvent (step c).

- 10 Removal of the protective group from intermediates **25** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **J** (step b).

Intermediates **24** can also be oxidized to intermediates **57**, using a suitable oxidizing reagent such as mCPBA in a suitable stoichiometry and in an appropriate solvent (e.g. in DCM) at temperatures between 0°C and the boiling temperature of the solvent (step d).

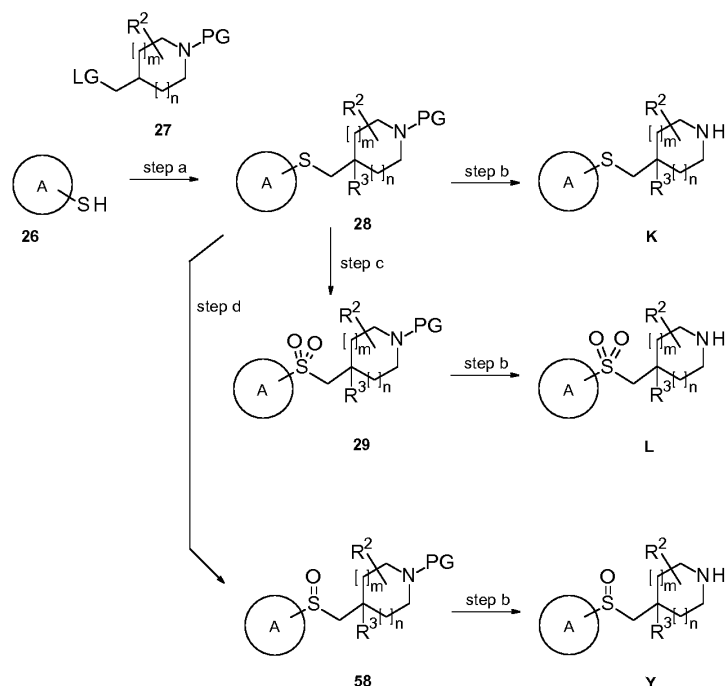
- 15 Removal of the protective group from intermediates **57** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **X** (step b).

In some embodiment, intermediates **2** are intermediates of type **K** and **L**, respectively.

Intermediates of type **K** and **L** in which A, m, n and R² are as described herein, can be prepared by methods well known in the art and as exemplified by the general synthetic procedures

- 20 outlined in Scheme 10.

- 43 -



Scheme 10

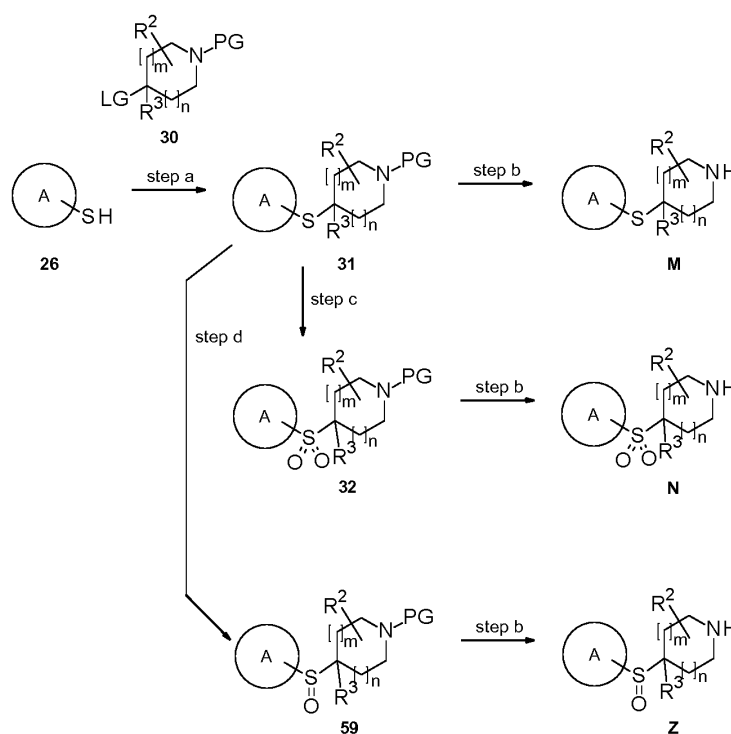
- Intermediates **28** may be prepared from thiols **26**, that can be alkylated with compounds **27** in which LG is a suitable leaving group such as chlorine, bromine, iodine, OSO₂alkyl (e.g. methanesulfonate), OSO₂fluoroalkyl (e.g. trifluoromethanesulfonate) or OSO₂aryl (e.g. p-toluenesulfonate), and in which PG is a suitable protective group such as a Cbz, Boc or Bn, using a suitable base, such as sodium hydride, potassium tert-butoxide, in an appropriate solvent (e.g. in DMF or THF) at temperatures between 0°C and the boiling temperature of the solvent (step a).
- 10 Removal of the protective group from intermediates **28** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **K** (step b).
- Intermediates **28** can be oxidized to intermediates **29**, using a suitable oxidizing reagent, such as mCPBA, in an appropriate solvent (e.g. in DCM) at temperatures between 0°C and the boiling temperature of the solvent (step c).
- 15 Removal of the protective group from intermediates **29** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **L** (step b).

- 44 -

Intermediates **28** can be also oxidized to intermediates **58**, using a suitable oxidizing reagent, such as mCPBA using an appropriate stoichiometry, in a suitable solvent (e.g. in DCM) at temperatures between 0°C and the boiling temperature of the solvent (step c).

Removal of the protective group from intermediates **58** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **Y** (step b).

In some embodiments, intermediates **2** are intermediates of type **M** and **N**, respectively. Intermediates of type **M** and **N** in which A, m, n and R² are as described herein, can be prepared by methods well known in the art and as exemplified by the general synthetic procedures outlined in Scheme 11.



10

Scheme 11

Intermediates **31** may be prepared from thiols **26**, that can be alkylated with compounds **30** in which LG is a suitable leaving group such as chlorine, bromine, iodine, OSO₂alkyl (e.g. methanesulfonate), OSO₂fluoroalkyl (e.g. trifluoromethanesulfonate) or OSO₂aryl (e.g. p-toluenesulfonate), and in which PG is a suitable protective group such as a Cbz, Boc or Bn, using a suitable base, such as sodium hydride, potassium tert-butoxide, in an appropriate solvent

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- 45 -

(e.g. in DMF or THF) at temperatures between 0°C and the boiling temperature of the solvent (step a).

Removal of the protective group from intermediates **31** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **M** (step b).

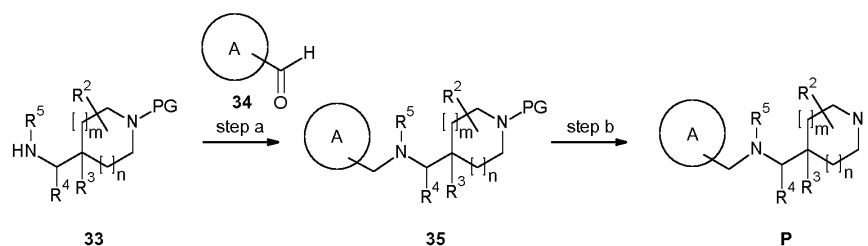
- 5 Intermediates **31** can be oxidized to intermediates **32**, using a suitable oxidizing reagent, such as mCPBA, in an appropriate solvent (e.g. in DCM) at temperatures between 0°C and the boiling temperature of the solvent (step c).

Removal of the protective group from intermediates **32** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **N** (step b).

- 10 Intermediates **31** can also be oxidized to intermediates **59**, using a suitable oxidizing reagent, such as mCPBA using an appropriate stoichiometry, in a suitable solvent such as DCM at temperatures between 0°C and the boiling temperature of the solvent (step c).

Removal of the protective group from intermediates **59** applying literature methods and as described for example under Scheme 4, step b, furnishes intermediates **Z** (step b).

- 15 In some embodiments, intermediates **2** are intermediates of type **P**. Intermediates of type **P** in which A, m, n, R², R³, R⁴, and R⁵ are as described herein can be prepared by methods well known by a person skilled in the art and as exemplified by the general synthetic procedure outlined in [Scheme 12](#).



20 [Scheme 12](#)

Amines **33**, either commercially available or prepared by methods known in the art, in which R⁵ is for example selected from hydrogen, C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl or halo-C₁₋₆-alkyl, preferably methyl, and in which PG signifies a suitable protecting group such as, e.g. a Boc, Cbz or Bn protecting group, can be subjected to a reductive amination (e.g. *Tetrahedron Letters*

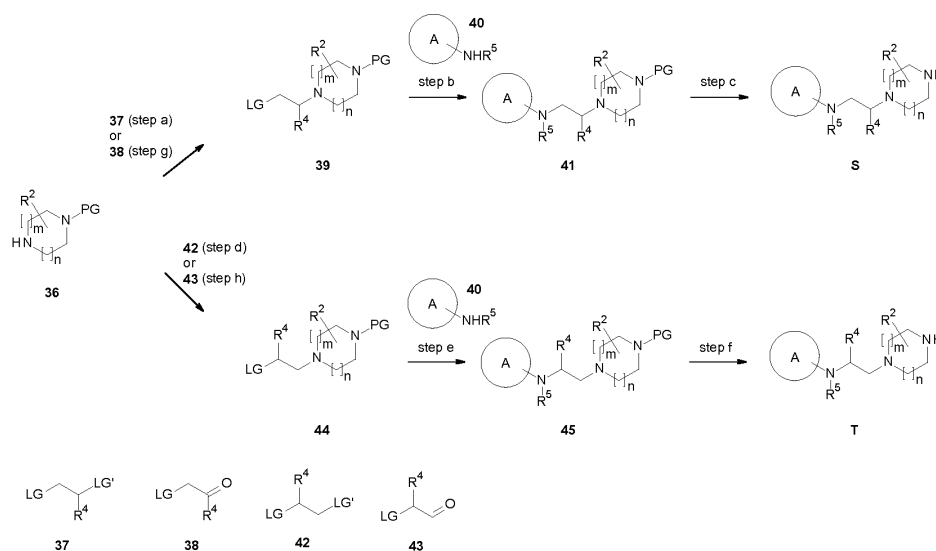
- 46 -

1990, 31, p. 5547) with aryl or heteroaryl aldehydes **34**, and using a suitable acid such as TiCl_4 or acetic acid, and an appropriate reducing agent such as e.g. sodium cyanoborohydride or sodium triacetoxyborohydride, and suitable solvent system such as, e.g. DCE, MeOH, NMP or mixtures thereof, preferably DCE and in a temperature range between 0°C and room temperature, to give intermediates **35** (step a).

Removal of the protective group from intermediates **35** by applying methods known in the art or as described under Scheme 4, step b, furnishes intermediates **P** (step b).

In some embodiments, intermediates **2** are intermediates of type **S** and **T**, respectively.

Intermediates of type **S** and **T** in which R^2 , R^4 and R^5 are as described herein and $(m+n)=2$ or 3 can be prepared by methods well known in the art and as exemplified by the general synthetic procedure outlined in Scheme 13.



Scheme 13

Alkylation of mono-protected piperazine or 1,4-diazepane derivatives **36** (commercially available or synthesized in analogy to literature methods) with alkylating reagents of type **37** in which LG and LG' signify a suitable leaving group such as chlorine or bromine, commercially available or prepared by methods known in the art, using a suitable base and solvent systems such as, e.g. Cs_2CO_3 in ACN or K_2CO_3 in acetone, gives intermediates **39** (step a). Reactions of that type are known in the art and described in literature, e.g. *RSC Advances* **2015**, 5(125), 103172; *Bioorg. Chem.* **2018**, 77, 125).

- 47 -

Intermediates **39** can be further alkylated with amines **40** (commercially available or synthesized in analogy to literature methods) using an appropriate suitable base and solvent systems such as NaH in THF or DMF, to yield intermediates **41** (step b).

Removal of the protective group from intermediates **41** applying methods known in the art (e.g.,
5 a Boc group using TFA in DCM or 4M HCl in dioxane at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y.), furnishes intermediates **S** (step c).

10 Alkylation of mono-protected piperazine or 1,4-diazepane derivatives **36** (commercially available or synthesized in analogy to literature methods) with alkylating reagents of type **42** in which LG and LG' signify a suitable leaving group such as chlorine or bromine, commercially available or prepared by methods known in the art, applying the conditions under step a, yields intermediates **43** (step a).

15 Alkylation of intermediates **44** with amines **40** (commercially available or synthesized in analogy to literature methods) using for example the conditions described under step b, an appropriate suitable base and solvent systems such as NaH in THF or DMF, gives intermediates **45** (step b).

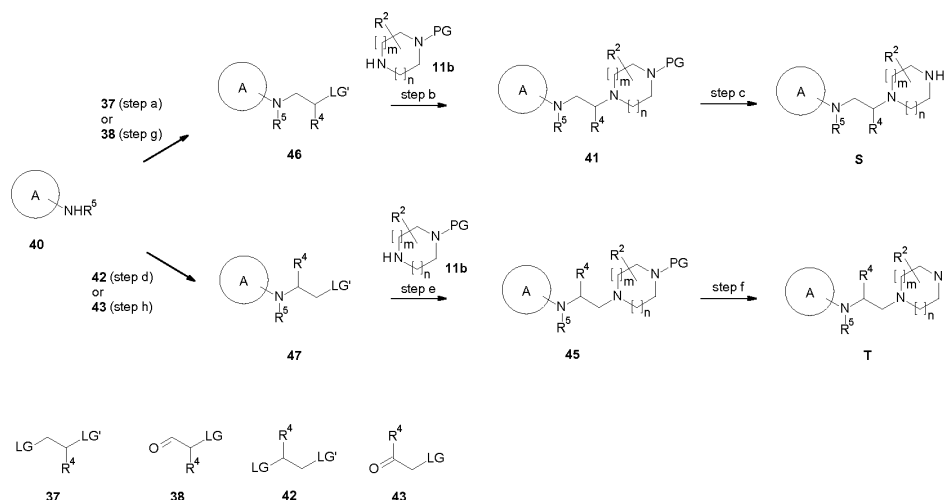
Removal of the protective group from intermediates **45** using the methods described under step
20 c, furnishes intermediates **T** (step f).

Alternatively, intermediates **39** may be prepared from compounds **36** and **38** (commercially available or synthesized by methods known in the art) by reductive amination (e.g. *Tetrahedron Letters* **1990**, 31, 5547; *Bioorg. Med. Chem. Lett.* **2008**, 16(14), 7021) using a suitable acid such as acetic acid, an appropriate reducing agent such as NaBH₃CN, NaBH(OAc)₃ or borane-THF
25 complex and a suitable solvent system such as DCM, DCE, MeOH, NMP or mixtures thereof, preferably DCM, in a temperature range between 0°C and room temperature (step g).

Intermediates **44** may alternatively be synthesized from compounds **36** and aldehydes **43** (commercially available or synthesized by methods known in the art) applying a reductive amination reaction using the conditions described under step g above (step h).

- 48 -

Intermediates **S** and **T** may alternatively be prepared according to the general synthetic procedures depicted in Scheme 14 using methods well known in the art.



Scheme 14

- 5 Amines **40** (commercially available or synthesized in analogy to literature methods) can be alkylated with compounds of type **37**, in which LG and LG' signify a suitable leaving group such as chlorine or bromine (commercially available or prepared by methods known in the art), using a suitable base and solvent systems such as, e.g. NaH in DMF, Cs₂CO₃ in ACN or K₂CO₃ in acetone, to give compounds **46** (step a).
- 10 Alkylation of compounds **46** with compounds **36** using for example the methods described under step a, yields intermediates **41** (step b).
- Removal of the protective group from intermediates **41** applying literature methods (e.g., a Boc group using TFA in DCM or 4M HCl in dioxane at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or
- 15 Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in "Protective Groups in Organic Chemistry" by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y) furnishes intermediates **S** (step c).
- Alkylation of amines **40** with reagents of type **42** in which LG and LG' signify a suitable leaving group such as chlorine or bromine, commercially available or prepared by methods known in the
- 20 art, and applying for example the methods as outlined under step a, gives compounds **47** (step d).

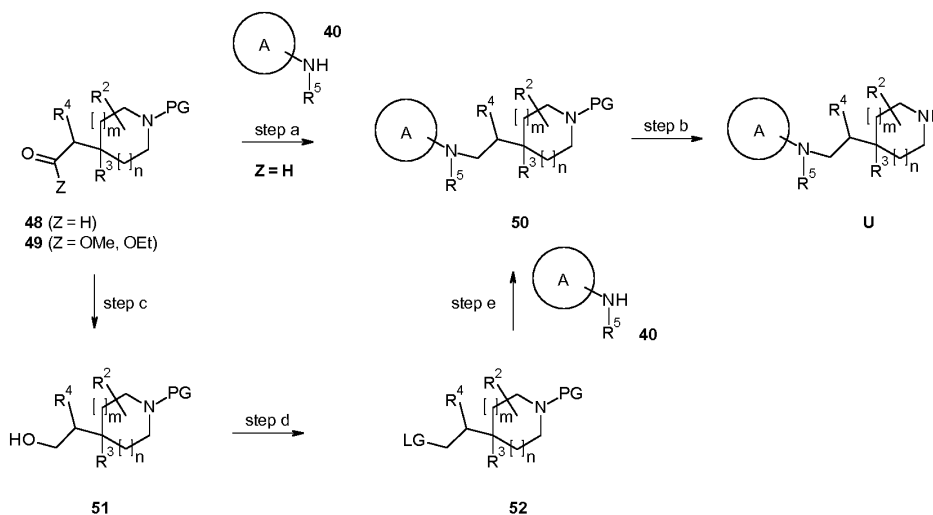
- 49 -

Alkylation of compounds **47** with compounds **36** applying for example the conditions described under step a, yields intermediates **45** (step e).

Removal of the protective group from intermediates **45** using for example the methods described under step c, furnishes intermediates **T** (step f).

- 5 Intermediates **46** may alternatively be prepared from amines **40** and aldehydes **38** via a reductive amination reaction using a suitable acid such as acetic acid, an appropriate reducing agent such as NaBH_3CN , $\text{NaBH}(\text{OAc})_3$ or borane-THF complex and a suitable solvent system such as DCM, DCE, MeOH, NMP or mixtures thereof, preferably DCM, in a temperature range between 0°C and room temperature (step g).
- 10 Intermediates **47** may alternatively be prepared for example from amines **40** and ketones **43** by reductive amination and using, e.g. the reagents and conditions described under step g (step h).

In some embodiments, intermediates **2** are intermediates of type **U**. Intermediates of type **U** in which R^2 , R^3 , R^4 , and R^5 m, n are as described herein can be prepared by methods well known in the art and as exemplified by the general synthetic procedure outlined in Scheme 15.



15

Scheme 15

- Aldehydes **48**, either commercially available or synthesized by methods known by a person skilled in the art and in which PG is a suitable protecting group and Z signifies hydrogen, can be subjected to a reductive amination reaction with primary or secondary amines **40** using a suitable acid such as acetic acid, an appropriate reducing agent such as NaBH_4 , NaBH_3CN , $\text{NaBH}(\text{OAc})_3$ or borane-THF complex and a suitable solvent system such as DCM, DCE, MeOH, NMP or
- 20

- 50 -

mixtures thereof, preferably DCM, in a temperature range between 0°C and room temperature, to give intermediates **50** (step a).

Removal of the protective group from intermediates **50** applying methods described in literature (e.g., a Boc group using TFA in DCM or 4M HCl in dioxane at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y) furnishes intermediates **U** (step b).

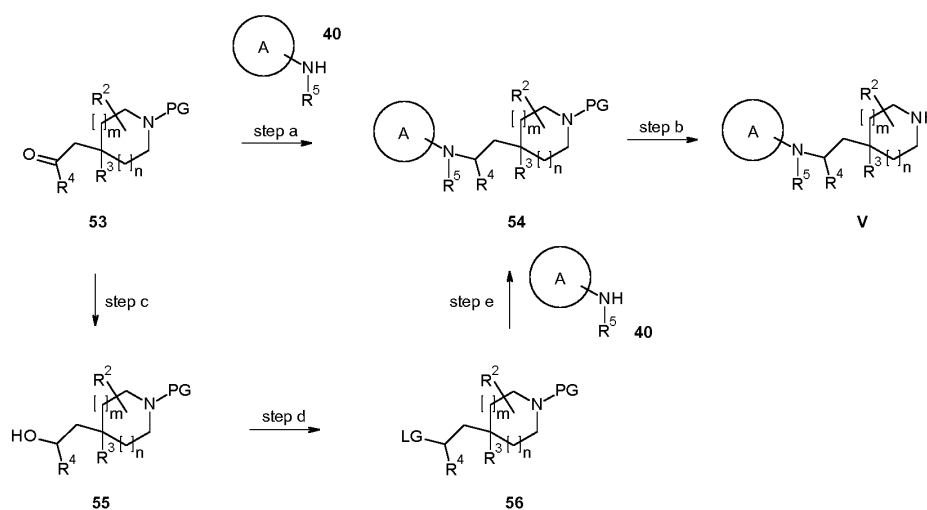
Alternatively, the ester function in intermediates **49**, either commercially available or synthesized by methods known by a person skilled in the art and in which PG is a suitable protecting group and Z signifies a methoxy or ethoxy group, can be reduced according to literature procedures using, e.g. LiAlH₄, DIBAL-H, BH₃-SMe₂ complex, preferably in ethereal solvents such as THF, or NaBH₄ in MeOH or EtOH, to give intermediates **51** (step c).

The alcohol function in intermediates **51** can be converted into a suitable leaving group such as Cl, Br, mesylate, tosylate or triflate by methods broadly described in literature to yield intermediates **52** which can be isolated or used in situ for the next step (step d).

Alkylation of compounds **40** with intermediates **52** using an appropriate base and solvent system such as NaH in DMF furnishes intermediates **50** (step e).

In some embodiment, intermediates **2** are intermediates of type **V**. Intermediates of type **V** in which R², R³, R⁴, R⁵, m and n are as described herein can be prepared by methods well known in the art and as exemplified by the general synthetic procedure outlined in Scheme 16.

- 51 -



Scheme 16

- Compounds **53**, either commercially available or synthesized by methods known by a person skilled in the art, and in which PG is a suitable protecting group can be subjected to a reductive amination reaction with primary or secondary amines **40** using a suitable acid such as acetic acid, an appropriate reducing agent such as NaBH₄, NaBH₃CN, NaBH(OAc)₃ or borane-THF complex and a suitable solvent system such as DCM, DCE, MeOH, NMP or mixtures thereof, preferably DCM, in a temperature range between 0°C and room temperature, to give intermediates **54** (step a).
- Removal of the protective group from intermediates **54** applying literature methods (e.g., a Boc group using TFA in DCM or 4M HCl in dioxane at temperatures between 0°C and room temperature, a Cbz group using hydrogen in the presence of a suitable catalyst such as Pd or Pd(OH)₂ on charcoal in a suitable solvent such as MeOH, EtOH, EtOAc or mixtures thereof and as described for example in “Protective Groups in Organic Chemistry” by T.W. Greene and P.G.M. Wuts, 4th Ed., 2006, Wiley N.Y) furnishes intermediates **V** (step b).

Compounds **53** can be reduced by using an appropriate reducing system such as NaBH₄ in MeOH or hydrogen in the presence of a suitable catalyst such as platinum in toluene at elevated pressure and temperatures ranging from room temperature to the boiling point of the solvent to give intermediates **55** (step c).

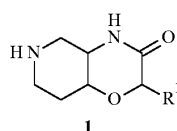
- 52 -

The alcohol function in intermediates **55** can be converted into a suitable leaving group such as Cl, Br, mesylate, tosylate or triflate by methods broadly described in literature to yield intermediates **56** which can be isolated or used in situ for the next step (step d).

Alkylation of compounds **40** with intermediates **56** using an appropriate base and solvent system
 5 such as NaH in DMF furnishes intermediates **V** (step e).

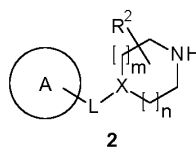
In one aspect, the present invention provides a process of manufacturing the urea compounds of formula (I) described herein, comprising:

reacting a first amine of formula **1**, wherein R^1 is as described herein, preferably wherein R^1 is hydrogen,



10

with a second amine **2**, wherein A, L, m, n, X and R^2 are as described herein



in the presence of a base and a urea forming reagent,
 to form said compound of formula (I).

15 In one embodiment, there is provided a process according to the invention, wherein said base is sodium bicarbonate.

In one embodiment, there is provided a process according to the invention, wherein said urea forming reagent is selected from bis(trichloromethyl) carbonate, phosgene, trichloromethyl chloroformate, (4-nitrophenyl)carbonate and 1,1'-carbonyldiimidazole, preferably wherein said
 20 urea forming reagent is bis(trichloromethyl) carbonate.

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.

- 5 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,
10 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 measuring the enzymatic activity of MAGL by following the hydrolysis of 4-nitrophenylacetate resulting in 4-nitrophenol, which absorbs at 405-412 nm (G.G. Muccioli, G. Labar, D.M. Lambert, *Chem. Bio. Chem.* **2008**, 9,
15 2704-2710). This assay is hereinafter abbreviated “4-NPA assay”.

- The 4-NPA assay was carried out in 384 well assay plates (black with clear bottom, non-binding surface treated, Corning Ref. 3655) in a total volume of 40 μ L. 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 25 μ M to 1.7 nM. 1 μ L compound dilutions
20 (100% DMSO) were added to 19 μ L MAGL (recombinant wild-type) in assay buffer (50 mM TRIS (GIBCO, 15567-027), 1 mM EDTA (Fluka, 03690-100mL)). The plate was shaken for 1 min at 2000 rpm (Variomag Teleshake) and then incubated for 15 min at RT. To start the reaction, 20 μ L 4-Nitrophenylacetate (Sigma N-8130) in assay buffer with 6% EtOH was added. The final concentrations in the assay were 1 nM MAGL and 300 μ M 4-Nitrophenylacetate.
25 After shaking (1 min, 2000 rpm) and 5 min incubation at RT, the absorbance at 405 nm was measured for a first time (Molecular Devices, SpectraMax Paradigm). A second measurement was then done after incubation for 80 min at RT. From the two measurements, the slope was calculated by subtracting the first from the second measurement.

- Alternatively, compounds were profiled for MAGL inhibitory activity by determining the
30 enzymatic activity by following the hydrolysis of the natural substrate, 2-arachidonoylglycerol,

- 54 -

resulting in arachidonic acid, which can be followed by mass spectrometry. This assay is hereinafter abbreviated "2-AG assay".

Detection by mass spectrometry in the present 2-AG assay has the advantage over known optical assays that the natural enzyme substrate, 2-arachidonoylglycerol, can be used instead of
5 structurally unrelated compounds needed for optical readouts (such as 4-NPA). It thereby delivers more relevant data for activity determination, reduces false positives and generally adds to data quality. In addition, this assay reduces the analysis time from about 10 minutes per sample with standard methods to under 10 seconds per sample. This allows for using the present 2-AG assay in a method for high throughput screening of compounds for their MAGL inhibitory
10 activity.

The term "analysis time" as used herein refers to the total time needed per sample for sample generation (i.e., incubation of enzyme together with test substance and substrate, and stopping the reaction), sample preparation (i.e., purifying the reaction mixture) and determining the ratio of intensities [arachidonic acid / d8-arachidonic acid] by mass spectrometry.

15 This low analysis time is achieved by running the sample generation in parallel for up to thousands of samples, followed by a very fast serial sample preparation and serial determination of intensity ratios by mass spectrometry.

The 2-AG assay was carried out in 384 well assay plates (PP, Greiner Cat# 784201) in a total volume of 20 μ L. Compound dilutions were made in 100% DMSO (VWR Chemicals
20 23500.297) in a polypropylene plate in 3-fold dilution steps to give a final concentration range in the assay from 12.5 μ M to 0.8 pM. 0.25 μ L compound dilutions (100% DMSO) were added to 9 μ L MAGL in assay buffer (50 mM TRIS (GIBCO, 15567-027), 1 mM EDTA (Fluka, 03690-100mL), 0.01% (v/v) Tween. After shaking, the plate was incubated for 15 min at RT. To start the reaction, 10 μ L 2-arachidonoylglycerol in assay buffer was added. The final concentrations
25 in the assay was 50 pM MAGL and 8 μ M 2-arachidonoylglycerol. After shaking and 30 min incubation at RT, the reaction was quenched by the addition of 40 μ L of acetonitrile containing 4 μ M 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 acetonitrile/water liquid setup. The mass
30 spectrometer was operated in negative electrospray mode following the mass transitions 303.1 $\rightarrow$ 259.1 for arachidonic acid and 311.1 $\rightarrow$ 267.0 for d8-arachidonic acid. The activity of the

- 55 -

compounds was calculated based on the ratio of intensities [arachidonic acid / d8-arachidonic acid].

In one aspect, the present invention also provides a method for determining the MAGL inhibitory activity of a test compound, e.g. of a compound of formula (I) described herein,
5 comprising measuring the ratio of arachidonic acid / d8-arachidonic acid in a solution.

In one embodiment, said measuring is measuring by mass spectrometry.

In one embodiment, said method is a method for high throughput screening (HTS).

In one embodiment, said method is a method for high throughput screening and takes less than 1 minute, for example less than 50 seconds, less than 40 seconds, less than 30 seconds, less than
10 20 seconds, less than 10 seconds or less than 5 seconds. In a preferred embodiment, said method takes between about 1 second and about 10 seconds, for example about 1 second, about 2 seconds, about 3 seconds, about 4 seconds, about 5 seconds, about 6 seconds, about 7 seconds, about 8 seconds, about 9 seconds or about 10 seconds.

In a preferred embodiment, the method for determining the MAGL inhibitory activity of a test
15 compound according to the invention, comprises:

- (i) providing a solution of a test compound;
- (ii) adding the solution of step (i) to a solution of MAGL;
- (iii) shaking the mixture obtained from step (ii);
- (iv) incubating the mixture obtained from step (iii);
- 20 (v) adding a solution of 2-arachidonoylglycerol;
- (vi) incubating the mixture obtained from step (v);
- (vii) adding a solution of d8-arachidonic acid; and
- (viii) determining the ratio of intensities arachidonic acid / d8-arachidonic acid using a mass spectrometer.

25 In a further preferred embodiment, the method of the invention is a method for HTS of test compounds for their MAGL inhibitory activity, comprising:

- (i) providing solutions of test compounds;
- (ii) adding the solutions of step (i) to solutions of MAGL;
- (iii) shaking the mixtures obtained from step (ii);
- 30 (iv) incubating the mixtures obtained from step (iii);
- (v) adding a solution of 2-arachidonoylglycerol to each mixture obtained from step (iv);

- 56 -

- (vi) incubating the mixtures obtained from step (v);
- (vii) adding a solution of d8-arachidonic acid to each mixture obtained from step (vi); and
- (viii) determining the ratios of intensities arachidonic acid / d8-arachidonic acid using a mass spectrometer;
- 5 wherein steps (i)-(vii) are run in parallel for all test compounds and step (viii) is run in series for one test compounds after the other.

Table 1

Example	IC ₅₀ MAGL [μM]
41	0.024 ^[a]
63	4.4 ^[b]
65	2.9 ^[b]
68	0.018 ^[a]
69	0.008 ^[a]
70	0.012 ^[a]
71	0.105 ^[a]
78	4.6 ^[a]
80	0.004 ^[a]
82	0.349 ^[a]
83	0.608 ^[a]
84	1.138 ^[a]
85	1.994 ^[b]
86	0.519 ^[b]
106	0.264 ^[a]

Example	IC ₅₀ MAGL [μM]
107	0.055 ^[a]
125	0.03 ^[a]
126	0.306 ^[a]
127	0.308 ^[a]
128	0.023 ^[a]
129	0.103 ^[a]
130	0.082 ^[a]
131	0.022 ^[a]
132	0.889 ^[a]
133	0.009 ^[a]
134	0.005 ^[a]
135	0.013 ^[a]
136	0.022 ^[a]
137	1.1 ^[a]
143	0.105 ^[a]

- 57 -

Example	IC ₅₀ MAGL [μM]
144	2.64 ^[a]
145	5.62 ^[a]
146	2.72 ^[a]
147	12.5 ^[a]
148	0.002 ^[a]
149	11.4 ^[a]
150	12.5 ^[a]
151	4.28 ^[a]
152	0.655 ^[a]
153	0.318 ^[a]
154	0.307 ^[a]
155	1.98 ^[a]
156	0.007 ^[a]
157	0.005 ^[a]
158	0.005 ^[a]
159	0.034 ^[a]
160	0.001 ^[a]
161	0.005 ^[a]
162	0.001 ^[a]
163	0.049 ^[a]
164	0.003 ^[a]

Example	IC ₅₀ MAGL [μM]
165	0.008 ^[a]
166	0.009 ^[a]
167	0.010 ^[a]
168	0.006 ^[a]
169	0.004 ^[a]
170	0.004 ^[a]
171	0.007 ^[a]
172	0.016 ^[a]
173	0.010 ^[a]
174	0.012 ^[a]
175	0.033 ^[a]
176	0.050 ^[a]
177	0.022 ^[a]
178	0.056 ^[a]
179	0.006 ^[a]
180	0.038 ^[a]
181	0.013 ^[a]
182	0.014 ^[a]
183	0.011 ^[a]
184	0.006 ^[a]
185	0.036 ^[a]

- 58 -

Example	IC ₅₀ MAGL [μM]
186	0.753 ^[a]
187	0.018 ^[a]
188	0.013 ^[a]
189	0.001 ^[a]
190	0.535 ^[a]
191	0.081 ^[a]
192	0.018 ^[a]
193	0.086 ^[a]

Example	IC ₅₀ MAGL [μM]
194	0.031 ^[a]
195	0.025 ^[a]
196	0.092 ^[a]
197	0.230 ^[a]
198	0.507 ^[a]
199	0.107 ^[a]
200	0.002 ^[a]
295	0.023 ^[a]

[a]: measured in 2-AG assay; [b]: measured in 4-NPA assay; n/a: not available.

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 IC₅₀'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 IC₅₀ (MAGL inhibition) values between 0.000001 μM and 25 μM, particular compounds have IC₅₀ values between 0.000005 μM and 10 μM, further particular compounds have IC₅₀ values between 0.00005 μM and 5 μM, as measured in the MAGL assay described herein.

In one embodiment, 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 an IC₅₀ for MAGL below 25 μM, preferably below 10 μM, more preferably below 5 μM as measured in an assay comprising the steps of:

- 59 -

- a) providing a solution of a compound formula (I), or a pharmaceutically acceptable salt or ester thereof, in DMSO;
- b) providing a solution of MAGL (recombinant wild-type) in assay buffer (50 mM tris(hydroxymethyl)aminomethane; 1 mM ethylenediaminetetraacetic acid);
- 5 c) adding 1 μ L of compound solution from step a) to 19 μ L of MAGL solution from step b);
- d) shaking the mixture for 1 min at 2000 rpm;
- e) incubating for 15 min at RT;
- f) adding 20 μ L of a solution of 4-nitrophenylacetate in assay buffer (50 mM tris(hydroxymethyl)aminomethane; 1 mM ethylenediaminetetraacetic acid, 6% EtOH);
- 10 g) shaking the mixture for 1 min at 2000 rpm;
- h) incubating for 5 min at RT;
- i) measuring the absorbance of the mixture at 405 nm a first time;
- 15 j) incubating a further 80 min at RT;
- k) measuring the absorbance of the mixture at 405 nm a second time;
- l) subtracting the absorbance measured under i) from the absorbance measured under k) and calculating the slope of absorbance;
- wherein:
- 20 i) the concentration of the compound of formula (I), or the pharmaceutically acceptable salt or ester thereof in the assay after step f) is in the range of 25 μ M to 1.7 nM;
- ii) the concentration of MAGL in the assay after step f) is 1 nM;
- iii) the concentration of 4-nitrophenylacetate in the assay after step f) is 300 μ M; and
- 25 iv) steps a) to l) are repeated for at least 3 times, each time with a different concentration of the compound of formula (I), or the pharmaceutically acceptable salt or ester thereof.

Using the Compounds of the Invention

In one aspect, the present invention provides compounds of formula (I) as described herein for

30 use as therapeutically active substance.

- 60 -

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
5 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
10 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,
15 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.

20 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,
25 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.

- 61 -

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.

- 5 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
10 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)
15 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.

- 20 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
25 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.

- 62 -

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.

10 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.

25 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,

- 63 -

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
5 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.

10 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
15 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
20 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,
25 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.

- 64 -

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.

- 5 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
10 limit given herein can be exceeded when this is shown to be indicated.

In accordance with the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of type 2 diabetes related microvascular complications (such as, but not limited to diabetic retinopathy, diabetic neuropathy and diabetic nephropathy), coronary artery disease, obesity and underlying
15 inflammatory diseases, chronic inflammatory and autoimmune/inflammatory diseases.

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
20 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.

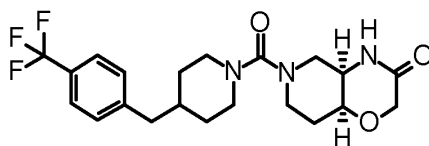
Method A1

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Example 11

**rac-(4aR,8aS)-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-
4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one**

- 65 -

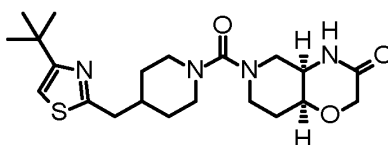


To a solution of 4-nitrophenyl 4-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (100 mg, 245 μmol , BB2) in DMF (1.5 mL), *rac*-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one dihydrochloride (45.9 mg, 294 μmol , ChemBridge Corporation, BB1) and TEA (49.6 mg, 68.3 μL , 490 μmol) were added. The resultant reaction mixture was heated at 80 °C for 18 h. The reaction mixture was diluted with EtOAc and washed three times with H₂O and NaHCO₃. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, eluting with a gradient of MeOH/EtOAc 0-10%) to afford the title compound as an off-white oil (0.045 g; 43.2%). MS (ESI): m/z = 426.4 [M+H]⁺.

Method A2

Example 3

***rac*-(4aR,8aS)-6-[4-[(4-*tert*-Butylthiazol-2-yl)methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one**



15

To an ice-cold suspension of bis(trichloromethyl) carbonate (45.3 mg, 153 μmol , CAS RN 32315-10-9) and NaHCO₃ (73.3 mg, 873 μmol) in DCM (2 mL) was added in one portion 4-*tert*-butyl-2-(4-piperidylmethyl)thiazole hydrochloride (60 mg, 218 μmol , Enamine Ltd) and the mixture was stirred at RT overnight. The suspension was filtered and the filtrate was evaporated. The residue was diluted in DCM (1 mL) and added dropwise to an ice-cold solution of *rac*-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one dihydrochloride (50 mg, 218 μmol , ChemBridge Corporation, BB1) and DIPEA (152 μL , 870 μmol) in DCM (1 mL). The suspension was stirred at RT for 19 h to become a solution. The reaction mixture was poured on H₂O and DCM and the layers were separated. The aqueous layer was extracted three times with DCM. The organic layers were washed twice with water, dried over MgSO₄, filtered, treated

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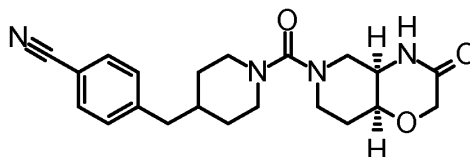
- 66 -

with silica gel and evaporated. The compound was purified by silica gel chromatography on a 4 g column using an MPLC system eluting with a gradient of DCM : MeOH (100 : 0 to 90 : 10) to provide the desired compound as a colorless foam (0.039 g; 42.5%). MS (ESI): $m/z = 421.2$ $[M+H]^+$.

5

Method A3**Example 34**

(+)- or (-)-4-[[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]-4-piperidyl)methyl]benzonitrile

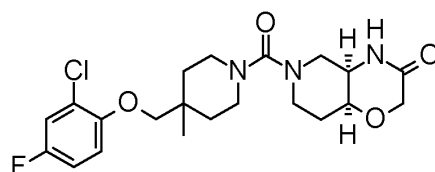


- 10 To an ice-cold solution of bis(trichloromethyl) carbonate (39.9 mg, 134 μ mol, CAS RN 32315-10-9) in DCM were added NaHCO_3 (64.5 mg, 768 μ mol) and (+)-cis-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (30 mg, 192 μ mol, BB1a) and the mixture was stirred at RT overnight. To the suspension was added 4-(piperidin-4-ylmethyl)benzonitrile (38.5 mg, 192 μ mol, CAS RN 333987-57-8) and DIPEA (99.3 mg, 134 μ L, 768 μ mol). The suspension was stirred at RT for
- 15 4.5 h. The reaction mixture was poured on H_2O and DCM and the layers were separated. The aqueous layer was extracted three times with DCM. The organic layers were washed twice with H_2O , dried over MgSO_4 , filtered, treated with silica gel and evaporated. The compound was purified by silica gel chromatography on a 4 g column using an MPLC system eluting with a gradient of DCM : MeOH (100 : 0 to 90 : 10) to furnish the desired compound as a colorless
- 20 gum (0.023 g; 31.3%). MS (ESI): $m/z = 383.2$ $[M+H]^+$.

Method A4**Example 79**

(4aR,8aS)-6-(4-((2-chloro-4-fluorophenoxy)methyl)-4-methylpiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

- 67 -

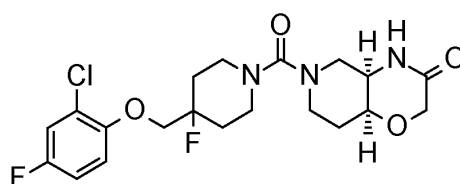


To a solution of 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (25 mg, 77.8 μ mol, BB7a) in NMP (1 mL) was added DIPEA (25.1 mg, 34 μ L, 195 μ mol) and 4-((2-chloro-4-fluorophenoxy)methyl)-4-methylpiperidine; hydrochloride salt (19.5 mg, 66.1 μ mol, BB12). The reaction vial was stirred at 140 $^{\circ}$ C for 45 min. The crude material was purified by reversed-phase HPLC to yield 23.2 mg of the desired product. MS (ESI): m/z = 440.2 $[M+H]^+$.

Method A5

Example 64

10 **(4aR,8aS)-6-(4-((2-Chloro-4-fluorophenoxy)methyl)-4-fluoropiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one**



A microwave vial was heat gun-dried and charged with bis(trichloromethyl) carbonate (26.6 mg, 89.6 μ mol) and sodium bicarbonate (32.3 mg, 384 μ mol). The flask was placed under argon and DCM (1 mL) was added to give a suspension. The suspension was cooled by an ice-bath and 4-((2-chloro-4-fluorophenoxy)methyl)-4-fluoropiperidine; hydrochloride salt (36.1 mg, 121 μ mol, BB15) was added. The mixture was stirred at 0 $^{\circ}$ C for 15 min and at RT overnight. The reaction mixture was cooled down in an-ice bath and DCM (500 μ L) and DIPEA (49.7 mg, 67.1 μ L, 384 μ mol) followed by (4aR,8aS)-6-(4-((2-chloro-4-fluorophenoxy)methyl)-4-fluoropiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (21.1 mg, 47.5 μ mol, BB1a) were added. The resulting off-white suspension was stirred at room temperature for 7 h. The reaction mixture was poured on water, DCM was added and the layers were separated. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to afford a yellow oil (58 mg). The crude product was

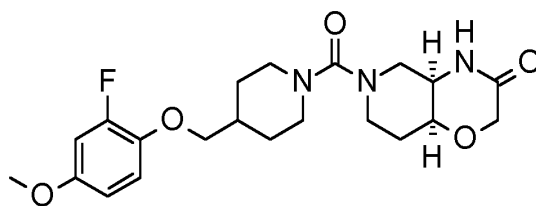
- 68 -

purified by reverse-phase HPLC and lyophilized to provide the title compound as a white solid (21.1 mg, 37.1% yield). MS (ESI): $m/z = 444.2 [M+H]^+$.

Method A6

Example 39

- 5 **(4aR,8aS)-6-[4-[(2-Fluoro-4-methoxyphenoxy)methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one**



- To a solution of 2-fluoro-4-methoxyphenol (16.5 mg, 13 μ L, 116 μ mol), (4aR,8aS)-6-[4-(hydroxymethyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one
 10 (34.5 mg, 116 μ mol, BB16) and triphenylphosphine (33.5 mg, 128 μ mol) in DCM (580 μ L) was added DIAD (25.8 mg, 24.8 μ L, 128 μ mol) dropwise and the reaction was stirred at room temperature for 22 h. The reaction mixture was diluted with DCM and washed with 1M aq. NaOH. The phases were separated and the aq. phase was extracted with DCM twice. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness to
 15 give a red oil (99 mg). The crude product was purified by reverse-phase HPLC and lyophilized to afford the desired compound (20 mg, 40.9 % yield) as a white solid. MS (ESI): $m/z = 422.3[M+H]^+$.

Method A7

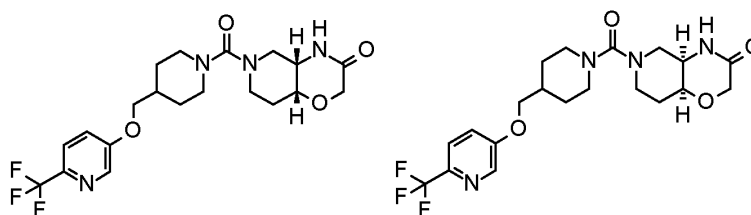
Example 42 and 43

- 20 **(4aS,8aR)-6-(4-(((6-(Trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (Example 42)**

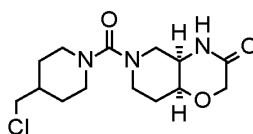
and

(4aR,8aS)-6-(4-(((6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (Example 43)

- 69 -

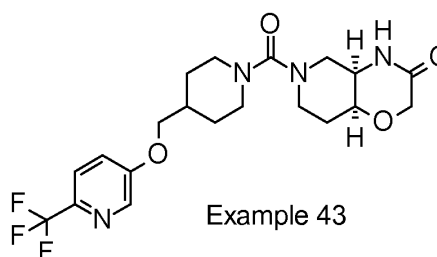
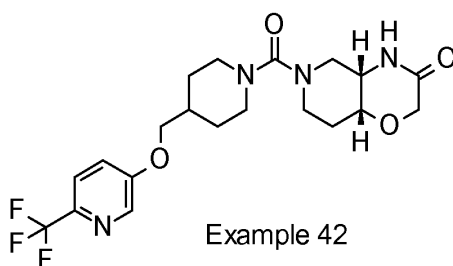


Step a) *rac*-(4*aR*,8*aS*)-6-(4-(Chloromethyl)piperidine-1-carbonyl)hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one



- 5 To a solution of *rac*-(4*aR*,8*aS*)-6-(4-(hydroxymethyl)piperidine-1-carbonyl)hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one (80 mg, 269 μ mol, BB16) in dry DMF (2 mL) was added DIPEA (52.2 mg, 70.5 μ L, 404 μ mol), DMAP (1.64 mg, 13.5 μ mol) and methanesulfonyl chloride (46.2 mg, 404 μ mol) and the reaction mixture was stirred at room temperature for 2 h. Addition of 4,4-difluoropiperidine; hydrochloride salt (84.8 mg, 538 μ mol), DIPEA (139 mg, 188 μ L, 1.08 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction was then stirred at 70 $^{\circ}$ C for 14 h. The crude reaction was submitted for reversed-phase HPLC purification to yield the title compound as a side product (35 mg). MS (ESI): m/z = 315.1 [M+H]⁺.

- Step b) (4*aS*,8*aR*)-6-(4-(((6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carbonyl)hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one (Example 42) and (4*aR*,8*aS*)-6-(4-(((6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carbonyl)hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one (Example 43)

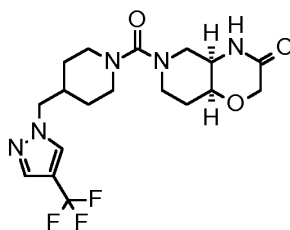


- 70 -

To a solution of rac-(4aR,8aS)-6-(4-(chloromethyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (70 mg, 222 μ mol) in dry DMF (1 mL) was added 6-(trifluoromethyl)pyridin-3-ol (54.2 mg, 332 μ mol) and Cs₂CO₃ (108 mg, 332 μ mol). The reaction mixture was stirred at 95 °C for 18 h. Insolubles were removed by filtration over Celite, the filtrate was concentrated down to dryness and the crude residue was purified and the enantiomers separated by chiral SFC to yield Example 42 (33.8mg) and Example 43 (32.5 mg). MS (ESI): m/z = 443.2 [M+H]⁺ for both examples.

Method A8**Example 26**

10 **(4aS,8aR)-6-(4-((4-(Trifluoromethyl)-1H-pyrazol-1-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one**

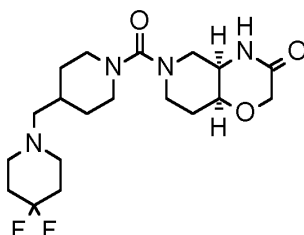


To a solution of rac-(4aR,8aS)-6-(4-(hydroxymethyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (75 mg, 252 μ mol, BB16) in dry DMF (2 mL) was added DIPEA (39.1 mg, 52.9 μ L, 303 μ mol), DMAP (3.08 mg, 25.2 μ mol) and methanesulfonyl chloride (30.3 mg, 265 μ mol) and the reaction mixture was stirred at room temperature for 2 h. 4-(Trifluoromethyl)-1H-pyrazole (68.6 mg, 504 μ mol) and K₂CO₃ (87.1 mg, 631 μ mol) were added and the reaction mixture was stirred at 90 °C for 18 h. Insolubles were removed by filtration over celite, the filtrate was concentrated to dryness in vacuo and the crude residue was directly purified by flash chromatography with an eluent mixture of DCM and MeOH (0% to 10%), to yield 90 mg of the desired product as a racemate. This was submitted for SFC chiral separation to yield Example 26 (25 mg) as a colorless oil and the enantiomer (31 mg) as a colorless oil. MS (ESI): m/z = 416.2 [M+H]⁺.

- 71 -

Method A9**Example 37**

(4aR,8aS)-6-(4-((4,4-Difluoropiperidin-1-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



5

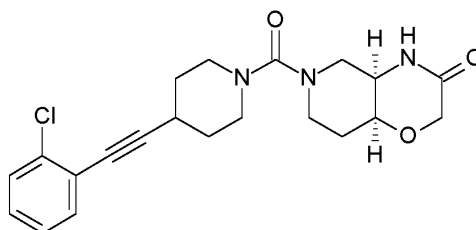
To a solution of (4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (40 mg, 256 μ mol, BB1a) in dry DMF (2 mL) cooled down to 0 °C was added DIPEA (39.7 mg, 53.7 μ L, 307 μ mol) and 4-nitrophenyl carbonochloridate (61.9 mg, 307 μ mol). The reaction mixture was stirred at 0 °C for 20 min. LCMS control showed formation of the intermediate carbamate.

- 10 DIPEA (116 mg, 157 μ L, 896 μ mol) and 4,4-difluoro-1-(piperidin-4-ylmethyl)piperidine; dihydrochloride salt (89.5 mg, 307 μ mol, BB17) were added and the reaction mixture was then stirred at room temperature for 30 min, then stirred at 100 °C for 14 h. Volatiles were removed in vacuo and the crude residue was directly submitted for SFC purification to yield the desired compound (9.5 mg) as a light orange oil. MS (ESI): m/z = 401.3 $[M+H]^+$.

15

Method A10**Example 125**

(+)-(4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



- 20 In a sealed tube, 4-[2-(2-chlorophenyl)ethynyl]piperidine (BB18, 0.02 g, 0.078 mmol) and 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate

- 72 -

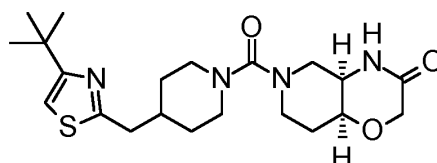
(BB7a, 0.025 g, 0.078 mmol) were mixed in ACN (0.6 mL). Then, Huenig's base (0.041 mL, 0.234 mmol) was added, followed by DMAP (0.005 g, 0.039 mmol) and the reaction mixture was heated to 90 °C overnight. The mixture was evaporated to dryness and the crude residue purified by reverse phase HPLC to give the title compound (0.013 g, 41%) as a colorless solid.

5 MS (ESI): $m/z = 402.2$ $[M+H]^+$.

Method B1

Example 1

(+)-(4aR,8aS)-6-(4-((4-(tert-Butyl)thiazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



10

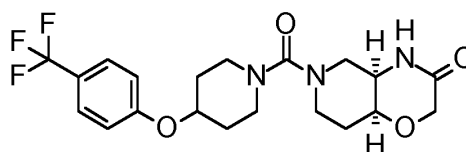
The enantiomers of example 3 were separated by preparative chiral HPLC (Chiralcel OD column) using an isocratic mixture of EtOH (containing 0.05% of NH_4OAc) : n-heptane (20 : 80). The fractions were evaporated to provide the desired compound as a colorless solid (0.012 g; 34.3%). MS (ESI): $m/z = 421.2$ $[M+H]^+$.

15

Method B2

Example 12

(+)- or (-)-(4aR,8aS)-6-(4-(4-(Trifluoromethyl)phenoxy)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

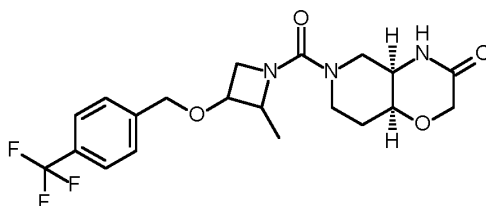


20 The enantiomers of example 13 were separated using preparative chiral HPLC (Chiralpak AD column) using an isocratic mixture of EtOH (containing 0.05% of NH_4OAc): n-heptane (40 : 60). The fractions were evaporated to yield the desired compound as a light brown oil (0.013 g; 28.4%). MS (ESI): $m/z = 428.2$ $[M+H]^+$.

- 73 -

Method B3**Examples 103, 104 and 105**

(4aR,8aS)-6-[2-Methyl-3-[[4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (Isomer A+B, Isomer C, Isomer D)



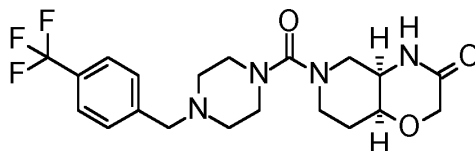
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The stereoisomers of example 117 were separated by preparative chiral HPLC (Reprosil Chiral NR column) using an isocratic mixture of EtOH (containing 0.05% of NH₄OAc) : n-heptane (40 : 60) to provide examples 103 and 104 as single isomers and example 105 as mixture of two stereoisomers. The fractions were evaporated to provide the desired compounds as colorless solids.

10

Method C**Example 21**

rac-(4aR,8aS)-6-(4-(4-(Trifluoromethyl)benzyl)piperazine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

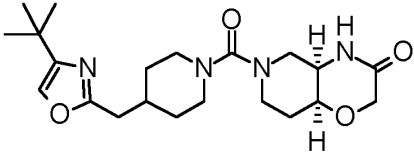
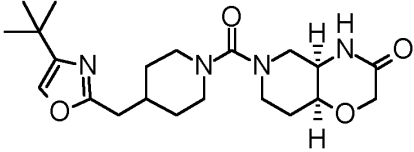
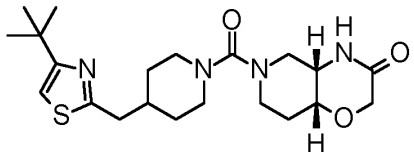


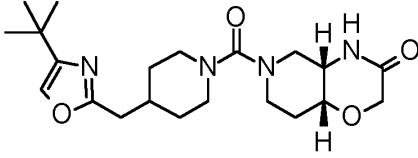
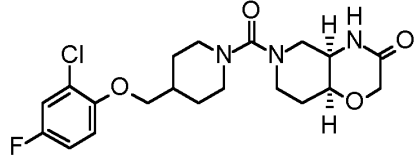
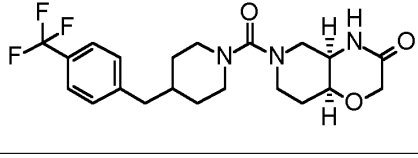
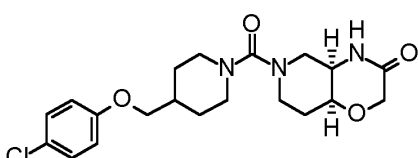
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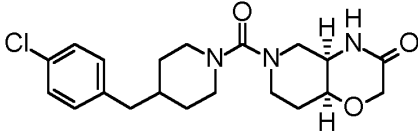
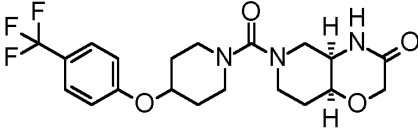
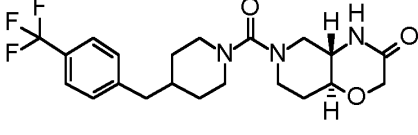
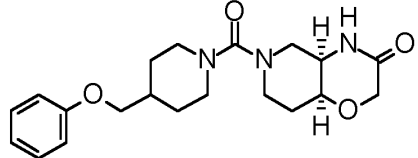
A mixture of rac-cis-6-(piperazine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (35 mg, 130 μmol, BB3), 4-(trifluoromethyl)benzaldehyde (22.7 mg, 17.4 μL, 130 μmol) and sodium triacetoxyborohydride (27.6 mg, 130 μmol) in DCM (1 mL) was stirred at RT for 15 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC to give the desired compound as a white solid (8 mg, 14.4%). MS (ESI): m/z = 427.4 [M+H]⁺.

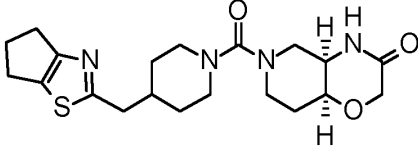
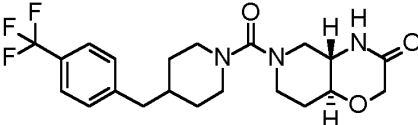
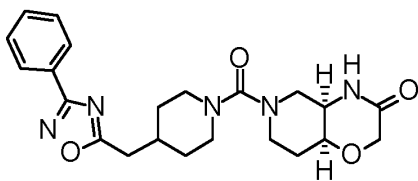
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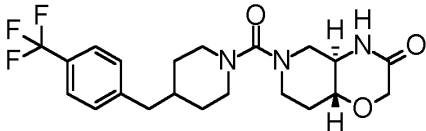
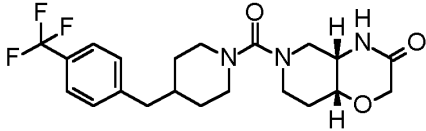
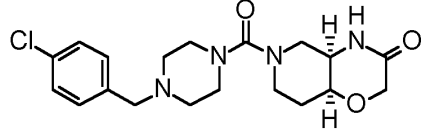
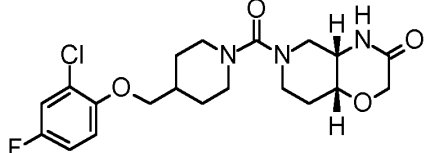
If not indicated otherwise the following examples were synthesized from rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one dihydrochloride (ChemBridge Corporation) and the suitable building blocks in analogy to the reaction methods described herein.

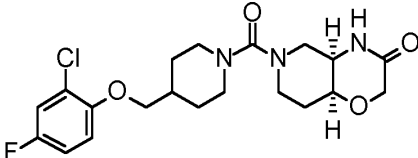
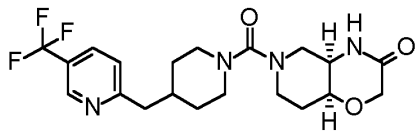
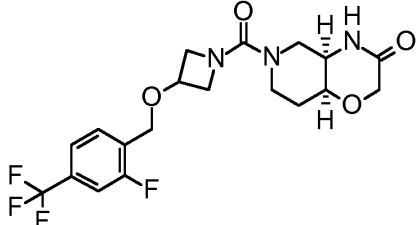
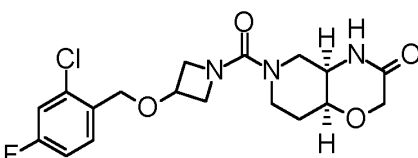
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
2	(+)-(4aR,8aS)-6-(4-((4-(tert-Butyl)oxazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 4	405.3 [M+H] ⁺	B1
4	rac-(4aR,8aS)-6-(4-((4-(tert-Butyl)oxazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Supplier of building block: BCH Research (UK) and BB1	405.4 [M+H] ⁺	A2
5	(-)-(4aS,8aR)-6-(4-((4-(tert-Butyl)thiazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 3	421.2 [M+H] ⁺	B1

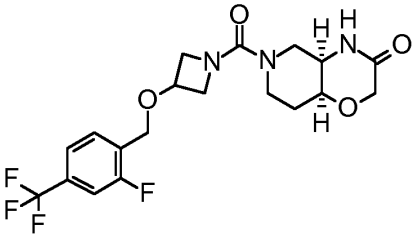
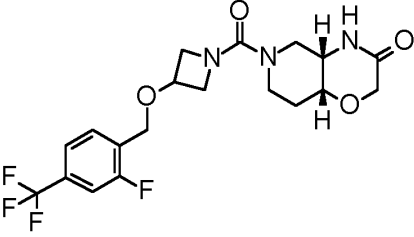
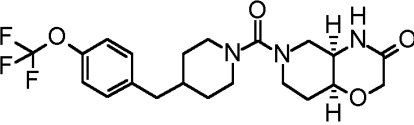
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
6	(-)-(4aS,8aR)-6-(4-((4-(tert-Butyl)oxazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 4	405.3 [M+H] ⁺	B1
7	rac-(4aR,8aS)-6-(4-((2-Chloro-4-fluorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Supplier of building block: UkrOrgSyntez Ltd. and BB1	426.2 [M+H] ⁺	A2
8	(+)-(4aR,8aS)-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 11	426.4 [M+H] ⁺	B1
9	rac-(4aR,8aS)-6-(4-((4-Chlorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-[(4-Chlorophenoxy)methyl]piperidine (CAS RN 63608-33-3) and BB1	408.3 [M+H] ⁺	A2

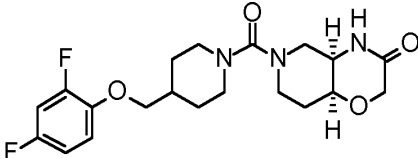
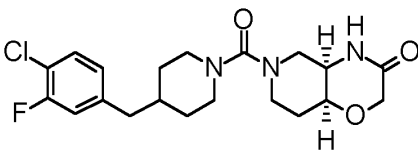
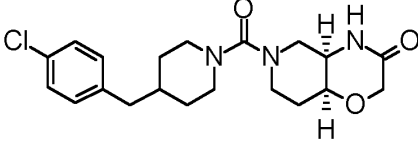
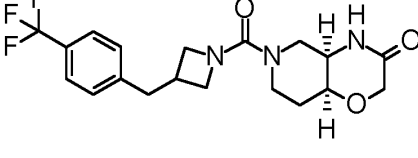
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
10	rac-(4aR,8aS)-6-(4-(4-Chlorobenzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-(4-Chloro-benzyl)-piperidine hydrochloride (CAS RN 36938-76-8) and BB1	392.2 [M+H]⁺	A2
13	rac-(4aR,8aS)-6-(4-(4-(Trifluoromethyl)phenoxy)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-(4-Trifluoromethylphenoxy)piperidine hydrochloride (CAS RN 28033-37-6) and BB1	428.2 [M+H]⁺	A2
14	(+)-(4aS,8aS)-6-(4-(4-(Trifluoromethyl)benzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 17	426.3 [M+H]⁺	B1
15	rac-(4aR,8aS)-6-[4-(Phenoxymethyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB4 and BB1	374.4 [M+H]⁺	A1

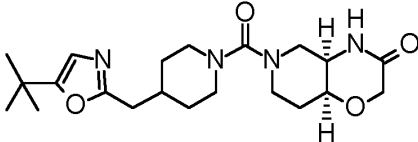
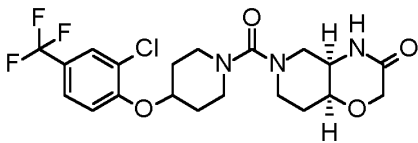
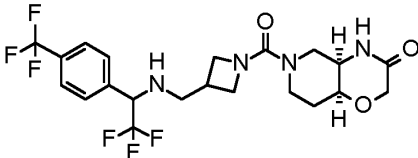
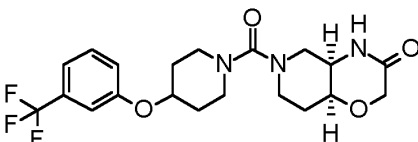
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
16	rac-(4aR,8aS)-6-(4-((5,6-Dihydro-4H-cyclopenta[d]thiazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	FCH Group and BB1	405.2 [M+H] ⁺	A2
17	rac-(4aS,8aS)-6-(4-(4-(Trifluoromethyl)benzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-(4-Trifluoromethyl benzyl) piperidine HCl (CAS RN 192990-03-7) and BB6	426.3 [M+H] ⁺	A2
18	rac-(4aR,8aS)-6-(4-((3-Phenyl-1,2,4-oxadiazol-5-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	3-Phenyl-5-(piperidin-4-ylmethyl)-1,2,4-oxadiazole (CAS RN 1239730-22-3) and BB1	426.3 [M+H] ⁺	A2

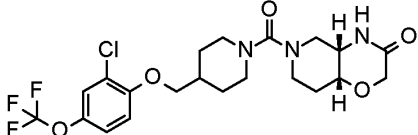
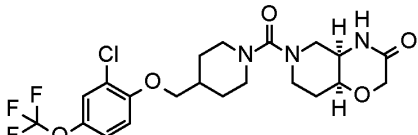
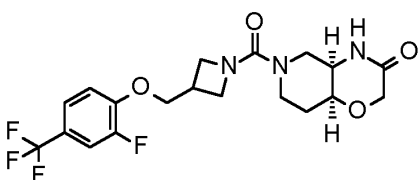
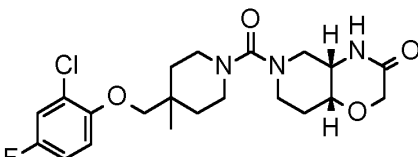
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
19	(-)-(4aR,8aR)-6-(4-(4-(Trifluoromethyl)benzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 17	426.4 [M+H] ⁺	B1
20	(-)-(4aS,8aR)-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 11	426.4 [M+H] ⁺	B1
22	rac-(4aR,8aS)-6-(4-(4-Chlorobenzyl)piperazine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	1-(4-Chlorobenzyl)-piperazine (CAS RN 23145-88-2) and BB1	393.2 [M+H] ⁺	A2
23	(-)-(4aS,8aR)-6-(4-((2-Chloro-4-fluorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 7	426.2 [M+H] ⁺	B1

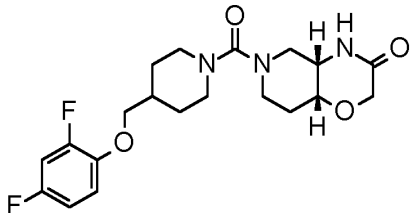
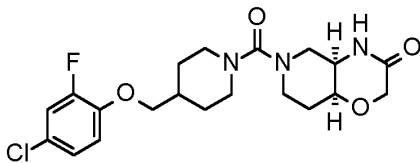
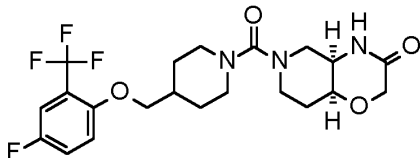
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
24	(+)-(4aR,8aS)-6-(4-((2-Chloro-4-fluorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 7	426.2 [M+H] ⁺	B1
25	rac-(4aR,8aS)-6-[4-[[5-(Trifluoromethyl)-2-pyridyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB5 and BB1	427.2 [M+H] ⁺	A2
27	rac-(4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Supplier of building block: HDH Pharma, Inc. and BB1	432.2 [M+H] ⁺	A2
28	(+)- or (-)-(4aR,8aS)-6-(3-((2-Chloro-4-fluorobenzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Supplier of building block: ZereneX Molecular Limited and BB1a	398.1 [M+H] ⁺	A2

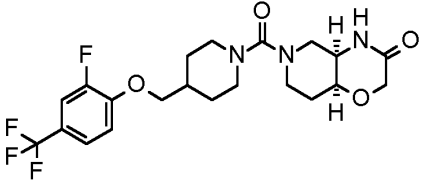
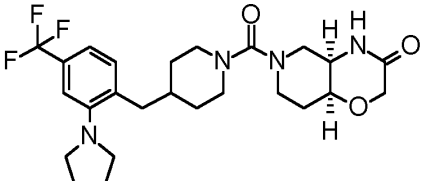
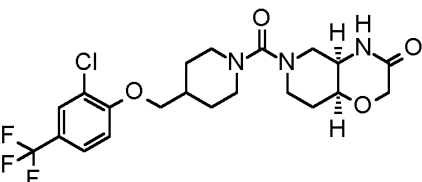
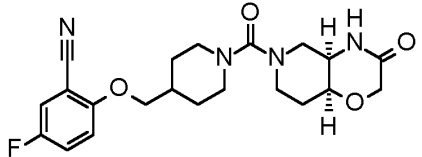
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
29	(+)- or (-)-(4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 27	432.2 [M+H] ⁺	B1
30	(+)- or (-)-(4aS,8aR)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 27	432.2 [M+H] ⁺	B1
31	(+)- or (-)-(4aR,8aS)-6-(4-(4-(Trifluoromethoxy)benzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-[4-(Trifluoromethoxy)benzyl]piperidine (CAS RN 681482-50-8) and BB1a	442.2 [M+H] ⁺	A2

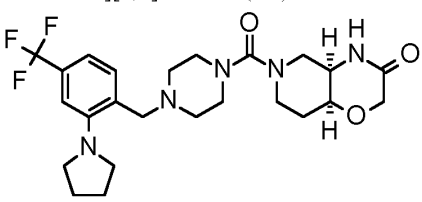
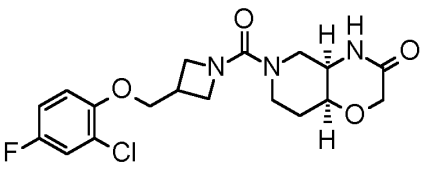
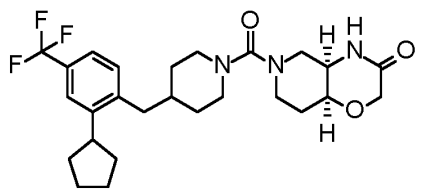
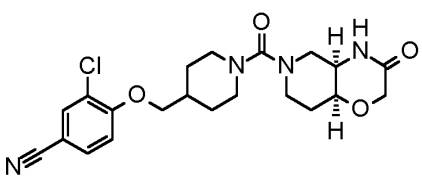
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
32	(+)- or (-)-(4aR,8aS)-6-(4-((2,4-Difluorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-((2,4-Difluorophenoxy)methyl)piperidine HCl CAS RN 614731-39-4 and BB 1a	410.2 [M+H] ⁺	A5
33	(+)- or (-)-(4aR,8aS)-6-(4-(4-Chloro-3-fluorobenzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Building block prepared as described in WO2013/179024 and BB 1a	410.2 [M+H] ⁺	A2
35	(+)- or (-)-(4aR,8aS)-6-(4-(4-Chlorobenzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-(4-Chloro-benzyl)-piperidine hydrochloride (CAS RN 36938-76-8) and BB 1a	392.2 [M+H] ⁺	A2
36	(+)- or (-)-(4aR,8aS)-6-[3-[[4-(Trifluoromethyl)phenyl]methyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	3-[[4-(Trifluoromethyl)phenyl]methyl]azetidine (CAS RN 937614-88-5) and BB 1a	398.3 [M+H] ⁺	A1

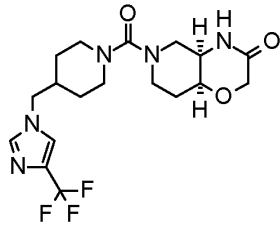
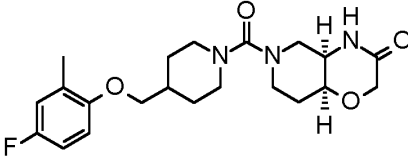
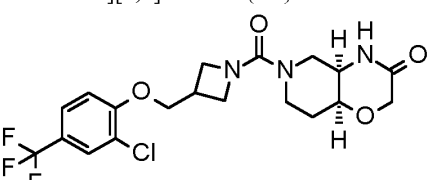
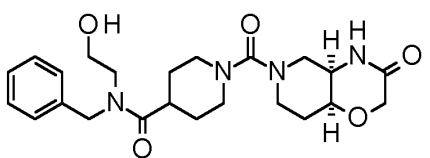
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
38	(+)- or (-)-(4aR,8aS)-6-(4-((5-(tert-Butyl)oxazol-2-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB8 and BB1a	405.3 [M+H] ⁺	A2
40	(+)- or (-)-(4aR,8aS)-6-(4-(2-Chloro-4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB9 and BB1a	462.1 [M+H] ⁺	A2
41	(4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-[4-(trifluoromethyl)phenyl]ethyl]amino]methyl]azetidine-1-carbonyl]hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB19 and BB1a	495.18 [M+H] ⁺	A3
44	(+)- or (-)-(4aR,8aS)-6-(4-(3-(Trifluoromethyl)phenoxy)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-(3-(Trifluoromethyl)phenoxy)piperidine (CAS RN 337912-66-0) and BB1a	428.2 [M+H] ⁺	A3

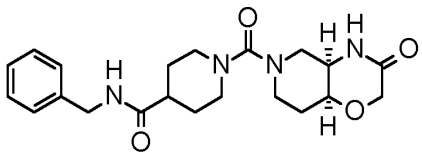
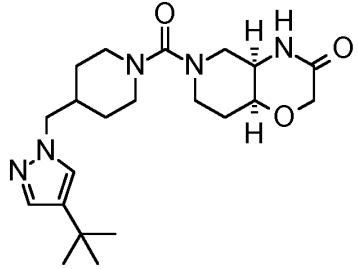
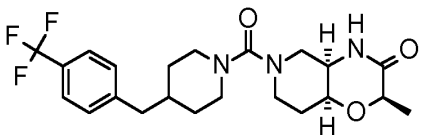
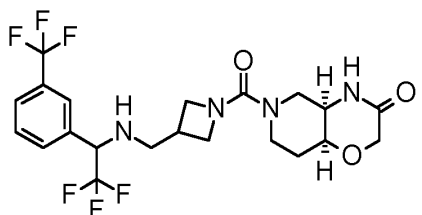
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
45	(4aS,8aR)-6-[4-[[2-Chloro-4-(trifluoromethoxy)phenoxy]methyl]piperidin-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	2-Chloro-4-(trifluoromethoxy)phenol (CAS: 35852-58-5) and BB1b	492.2 [M+H] ⁺	A6
46	(4aR,8aS)-6-[4-[[2-Chloro-4-(trifluoromethoxy)phenoxy]methyl]piperidin-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	2-Chloro-4-(trifluoromethoxy)phenol (CAS RN: 35852-58-5) and BB1a	492.2 [M+H] ⁺	A6
47	(4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)phenoxy)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB20 and BB1a	432.2 [M+H] ⁺	A5
48	(4aS,8aR)-6-[4-[(2-Chloro-4-fluorophenoxy)methyl]-4-methylpiperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB12 and BB7b	440.2 [M+H] ⁺	A4 (1:1 ACN: iPrOH)

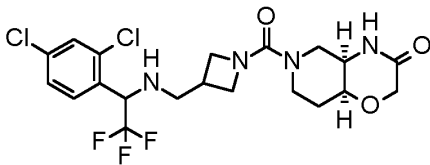
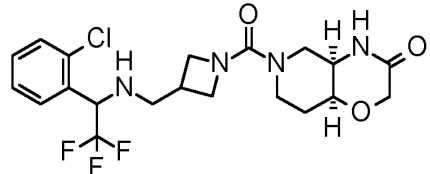
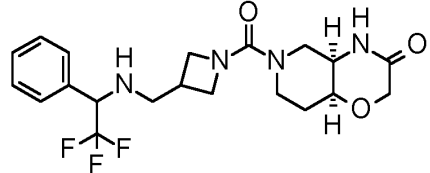
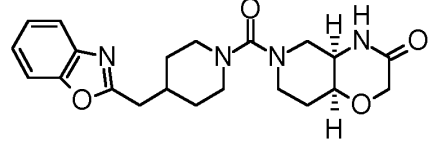
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
49	(4aS,8aR)-6-(4-((2,4-Difluorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-[(2,4-Difluorophenoxy)methyl]piperidine hydrochloride (CAS RN: 614731-39-4) and BB7b	410.2 [M+H]⁺	A4
50	(4aR,8aS)-6-(4-((4-Chloro-2-fluorophenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	4-Chloro-2-fluorophenyl 4-piperidinylmethyl ether; hydrochloride salt (CAS: 946680-87-1) and BB7A	426.2 [M+H]⁺	A4 (microwave heating)
51	(4aR,8aS)-6-(4-((4-Fluoro-2-(trifluoromethyl)phenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB21 and BB7a	460.2 [M+H]⁺	A4

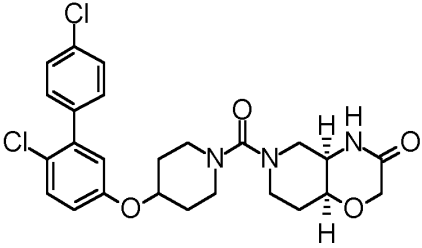
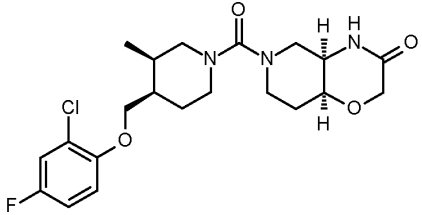
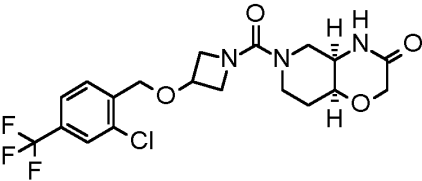
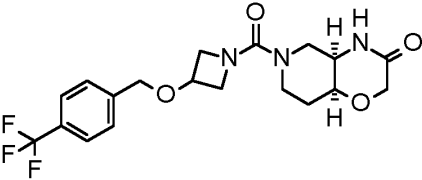
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
52	(4aR,8aS)-6-(4-((2-Fluoro-4-(trifluoromethyl)phenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB22 and BB7a	460.2 [M+H] ⁺	A4
53	(+)- or (-)-(4aR,8aS)-6-(4-(2-(Pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB91 and BB1a	495.3 [M+H] ⁺	A3
54	(4aR,8aS)-6-(4-((2-Chloro-4-(trifluoromethyl)phenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB23 and BB1a	476.3 [M+H] ⁺	A5
55	5-Fluoro-2-((1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperidin-4-yl)methoxy)benzonitrile 	BB24 and BB1a	417.2 [M+H] ⁺	A5

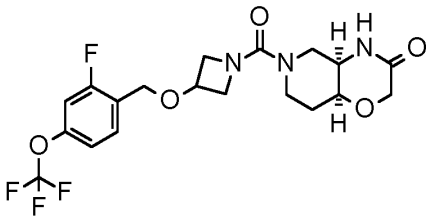
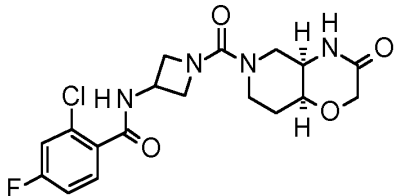
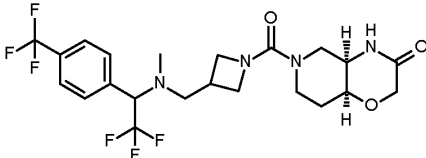
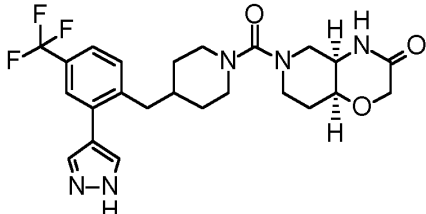
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
56	(4aR,8aS)-6-(4-(2-(Pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	1-[[2-(Pyrrolidin-1-yl)-4-(trifluoromethyl)phenyl]methyl]piperazine (synthesized according to WO2015/179559) and BB1a	496.26 [M+H]⁺	A3
57	(4aR,8aS)-6-(3-((2-Chloro-4-fluorophenoxy)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB25 and BB1a	398.2 [M+H]⁺	A5
58	(+)- or (-)-(4aR,8aS)-6-[4-[[2-Cyclopentyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB10 and BB1a	494.3 [M+H]⁺	A3
59	(4aR,8aS)-3-Chloro-4-((1-(3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperidin-4-yl)methoxy)benzonitrile 	BB26 and BB1a	433.2 [M+H]⁺	A5

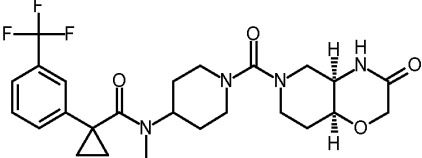
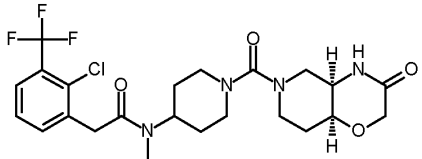
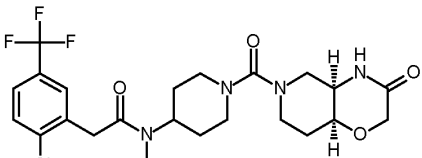
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
60	(4aR,8aS)-6-(4-((4-(Trifluoromethyl)-1H-imidazol-1-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB27 and BB1a	416.3 [M+H] ⁺	A9
61	(4aR,8aS)-6-(4-((4-Fluoro-2-methylphenoxy)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB28 and BB1a	406.3 [M+H] ⁺	A5
62	(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenoxy)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB29 and BB1a	448.2 [M+H] ⁺	A5
63	N-Benzyl-N-(2-hydroxyethyl)-1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperidine-4-carboxamide 	BB30 andBB1a	445.24 [M+H] ⁺	A3

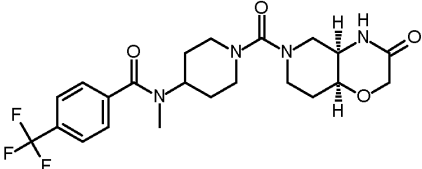
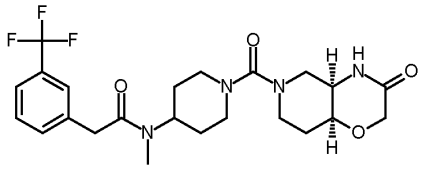
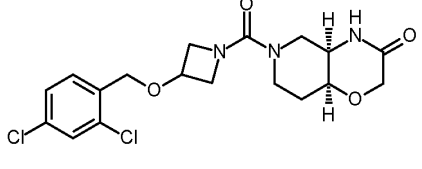
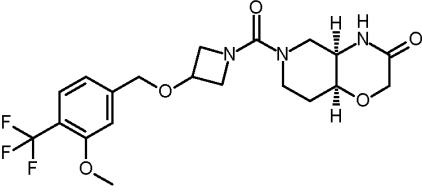
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
65	N-Benzyl-1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperidine-4-carboxamide 	BB31 and BB1a	401.22 [M+H] ⁺	A3
66	(4aR,8aS)-6-(4-((4-(tert-Butyl)-1H-pyrazol-1-yl)methyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB32 and BB1a	404.3 [M+H] ⁺	A9 (purified by RP- HPLC)
67	(2R,4aR,8aS)-2-Methyl-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	4-(4-Trifluoromethyl benzyl)piperidine HCl (CAS RN 192990-03-7) and BB33	440.3 [M+H] ⁺	A3
68	(4aR,8aS)-6-(3-(((2,2,2-Trifluoro-1-(3-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB34 and BB1a	495.18 [M+H] ⁺	A3

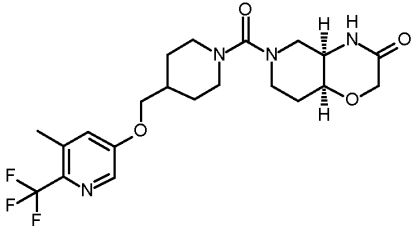
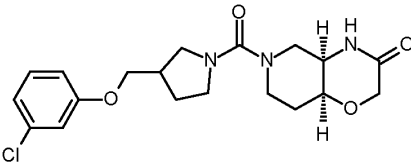
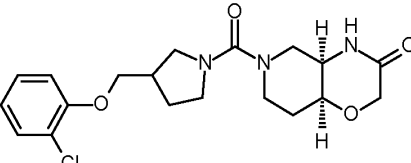
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
69	(4aR,8aS)-6-(3-(((1-(2,4-Dichlorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB35 and BB1a	495.11 [M+H] ⁺	A3 followed by RP- HPLC
70	(4aR,8aS)-6-(3-(((1-(2-Chlorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB35 and BB1a	461.16 [M+H] ⁺	A3 followed by RP- HPLC
71	(4aR,8aS)-6-(3-(((2,2,2-Trifluoro-1-phenylethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB35 and BB1a	427.2 [M+H] ⁺	A3 followed by RP- HPLC
72	(+)- or (-)-(4aR,8aS)-6-(4-(Benzo[d]oxazol-2-ylmethyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB11 and BB7a	399.2 [M+H] ⁺	A1

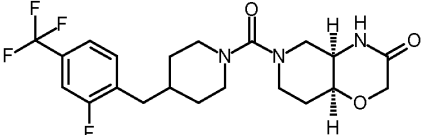
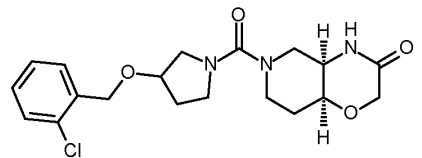
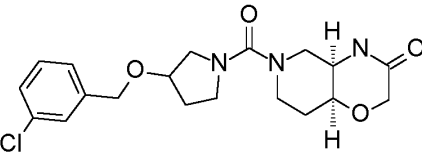
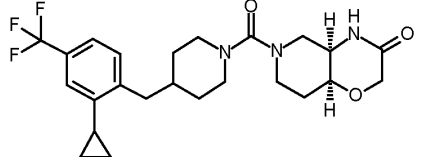
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
73	(+)- or (-)-(4aR,8aS)-6-(4-((4',6-Dichloro-[1,1'-biphenyl]-3-yl)oxy)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB13 and BB7a	504.1 [M+H] ⁺	A1
74	(4aR,8aS)-6-<i>cis</i>-4-((2-Chloro-4-fluorophenoxy)methyl)-3-methylpiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB36 and BB 1a	440.1 [M+H] ⁺	A3
75	(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB37	448.2 [M+H] ⁺	A4 (solvent ACN instead of NMP)
76	(4aR,8aS)-6-(3-((4-(Trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB38	414.2 [M+H] ⁺	A4 (solvent ACN instead of NMP)

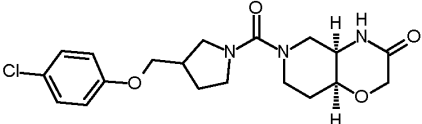
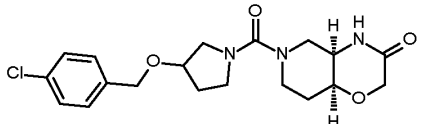
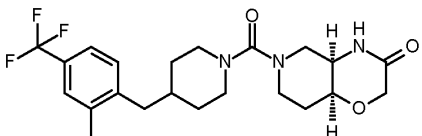
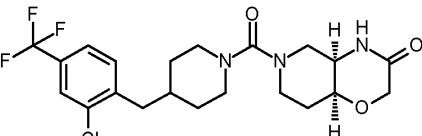
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
77	(4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethoxy)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB39	448.2 [M+H] ⁺	A4 (solvent ACN instead of NMP)
78	2-chloro-4-fluoro-N-(1-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)azetidin-3-yl)benzamide 	BB7a and BB40	411.2 [M+H] ⁺	A4 (solvent ACN not NMP)
80	(4aR,8aS)-6-(3-((Methyl(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB41 and BB 1a	509.2 [M+H] ⁺	A3
81	(+)- or (-)-(4aR,8aS)-6-(4-(2-(1H-Pyrazol-4-yl)-4-(trifluoromethyl)benzyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB14 and BB7a	492.2 [M+H] ⁺	A1

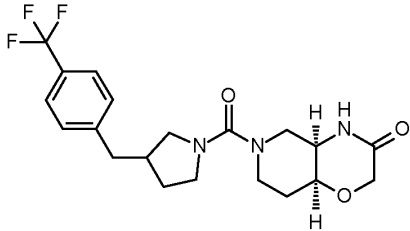
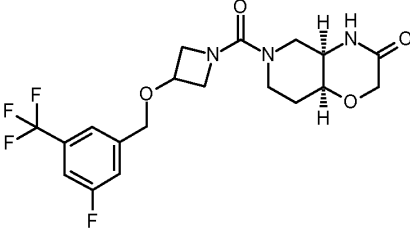
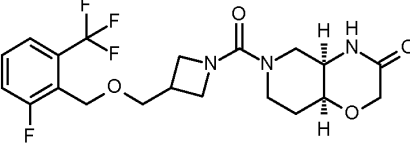
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
82	N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-N-methyl-1-[3-(trifluoromethyl)phenyl]cyclopropane-1-carboxamide 	BB42 and BB1a	509.2 [M+H] ⁺	A3
83	N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-2-[2-chloro-3-(trifluoromethyl)phenyl]-N-methylacetamide 	BB43 and BB1a	517.18 [M+H] ⁺	A3
84	N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-2-[2-chloro-5-(trifluoromethyl)phenyl]-N-methylacetamide 	BB44 and BB1a	517.18 [M+H] ⁺	A3

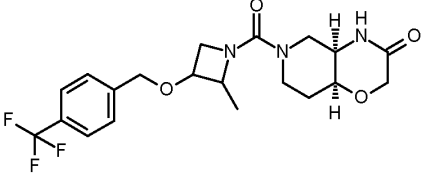
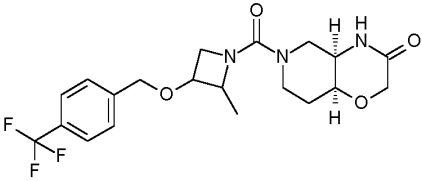
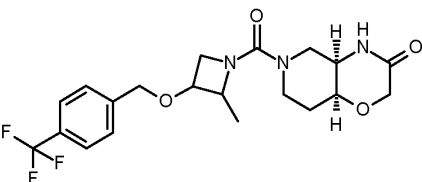
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
85	N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-N-methyl-4-(trifluoromethyl)benzamide 	N-methyl-N-(piperidin-4-yl)-4-(trifluoromethyl)benzamide hydrochloride (CAS RN 1580795-67-0) and BB1a	469.20 [M+H] ⁺	A3
86	N-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]-N-methyl-2-[3-(trifluoromethyl)phenyl]acetamide 	BB94 and BB1a	483.22 [M+H] ⁺	A3
87	(4aR,8aS)-6-[3-[(2,4-Dichlorophenyl)methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB88 and BB1a	414.3 [M+H] ⁺	A5
88	(4aR,8aS)-6-[3-[[3-Methoxy-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB45 and BB1a	444.3 [M+H] ⁺	A4 (ACN as solvent)

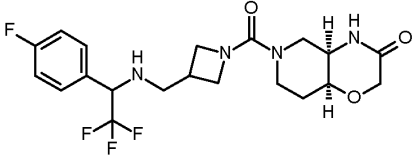
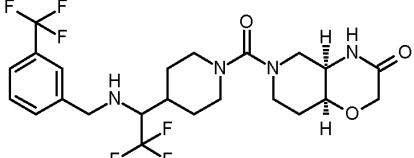
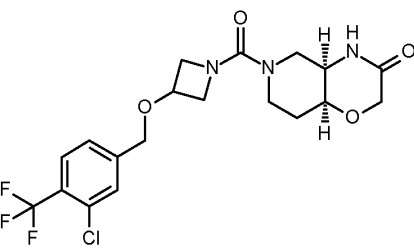
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
89	(4aR,8aS)-6-[4-[[5-Methyl-6-(trifluoromethyl)pyridin-3-yl]oxymethyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB46 and BB1a	457.2 [M+H] ⁺	A3
90	(4aR,8aS)-6-[3-[(3-Chlorophenoxy)methyl]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	3-[(3-Chlorophenoxy)methyl]pyrrolidine (CAS RN 914299-54-0) and BB 1a	394.15 [M+H] ⁺	A4 (ACN as solvent)
91	(4aR,8aS)-6-[3-[(2-Chlorophenoxy)methyl]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB47 and BB1a	394.15 [M+H] ⁺	A4 (ACN as solvent)

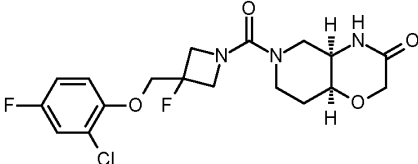
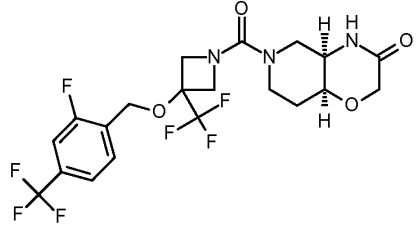
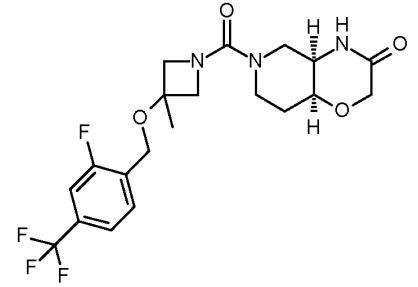
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
92	(4aR,8aS)-6-[4-[[2-Fluoro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB48 and BB1a	444.2 [M+H] ⁺	A4 (ACN as solvent)
93	(4aR,8aS)-6-[3-[(2-Chlorophenyl)methoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB49 and BB1a	394.15 [M+H] ⁺	A4 (ACN as solvent)
94	(4aR,8aS)-6-[3-[(3-Chlorophenyl)methoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB50 and BB1a	394.15 [M+H] ⁺	A4 (ACN as solvent)
95	(4aR,8aS)-6-[4-[[2-Cyclopropyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB51 and BB1a	466.23 [M+H] ⁺	A4 (ACN as solvent)

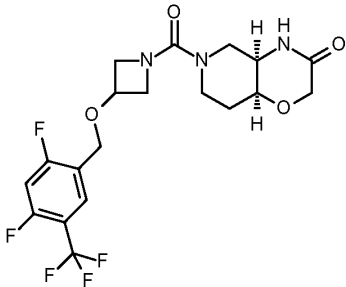
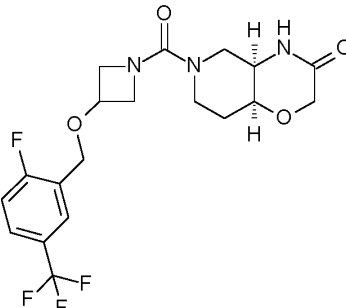
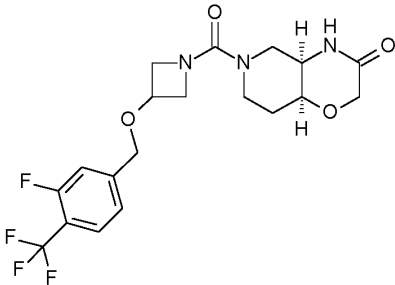
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
96	(4aR,8aS)-6-[3-[(4-Chlorophenoxy)methyl]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB52 and BB 1a	394.15 [M+H] ⁺	A4 (ACN as solvent)
97	(4aR,8aS)-6-[3-[(4-Chlorophenyl)methoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB53 and BB 1a	394.15 [M+H] ⁺	A4 (ACN as solvent)
98	(4aR,8aS)-6-[4-[[2-Methyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB54 and BB 1a	440.4 [M+H] ⁺	A3
99	(4aR,8aS)-6-[4-[[2-Chloro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB55 and BB 1a	460.16 [M+H] ⁺	A3

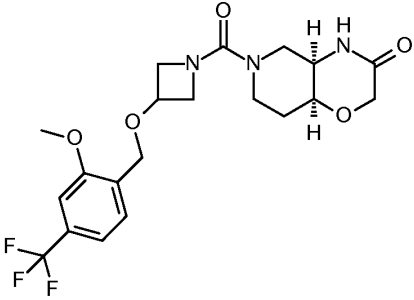
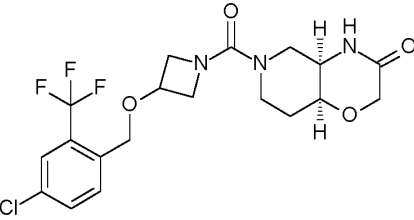
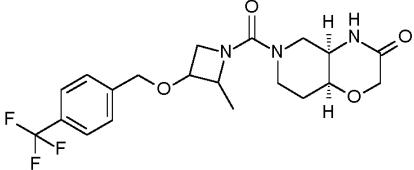
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
100	(4aR,8aS)-6-[3-[[4-(Trifluoromethyl)phenyl]methyl]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	3-(4-Trifluoromethylbenzyl)pyrrolidine hydrochloride salt (CAS RN: 957988-84-4) and BB 1a	412.19 [M+H]⁺	A3
101	(4aR,8aS)-6-[3-[[3-Fluoro-5-(Trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB56 and BB 1a	432.2 [M+H]⁺	A4 (ACN as solvent)
102	(4aR,8aS)-6-[3-[[2-Fluoro-6-(trifluoromethyl)phenyl]methoxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB 1a and BB57	446.3 [M+H]⁺	A4 (ACN as solvent)

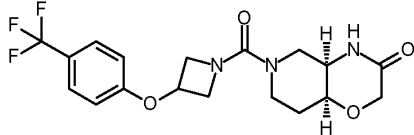
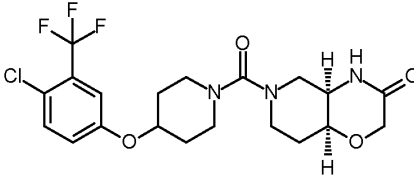
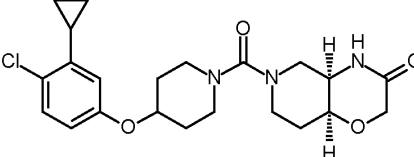
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
103	(4aR,8aS)-6-[2-Methyl-3-[[4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (Isomer D) 	Example 117	428.19 [M+H] ⁺	B3
104	(4aR,8aS)-6-[2-Methyl-3-[[4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (Isomer C) 	Example 117	428.19 [M+H] ⁺	B3
105	(4aR,8aS)-6-[2-Methyl-3-[[4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (Isomers A and D) 	Example 117	428.19 [M+H] ⁺	B3

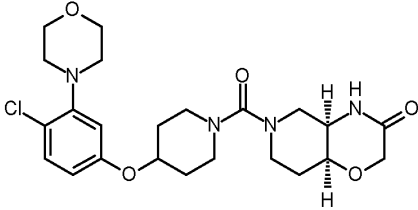
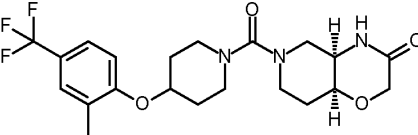
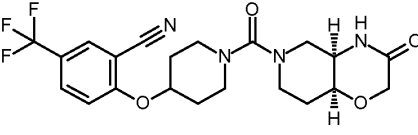
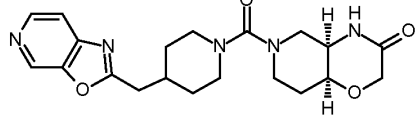
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
106	(4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-(4-fluorophenyl)ethyl]amino]methyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB58 and BB1a	445.19 [M+H] ⁺	A3
107	(4aR,8aS)-6-[4-[2,2,2-Trifluoro-1-[[3-(trifluoromethyl)phenyl]methylamino]ethyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB59 and BB1a	523.22 [M+H] ⁺	A3
108	(4aR,8aS)-6-[3-[[3-Chloro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB60 and BB1a	448.2 [M+H] ⁺	A4 (1:1 iPrOH: ACN as solvent)

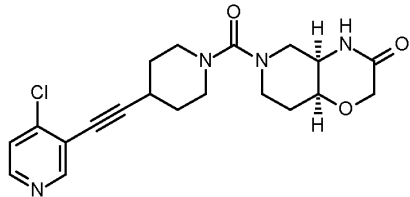
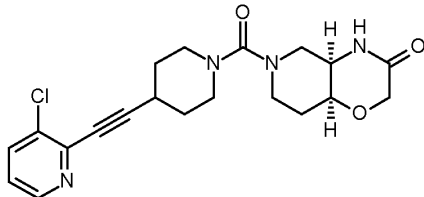
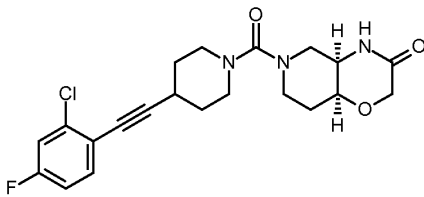
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
109	(4aR,8aS)-6-[3-[(2-Chloro-4-fluorophenoxy)methyl]-3-fluoroazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB61 and BB1a	416.2 [M+H] ⁺	A4 (1:1 iPrOH: ACN as solvent)
110	(4aR,8aS)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]-3-(trifluoromethyl)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB62 and BB1a	500.2 [M+H] ⁺	A4 (ACN as solvent)
111	(4aR,8aS)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methoxy]-3-methylazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB63 and BB1a	446.2 [M+H] ⁺	A4 (ACN as solvent)

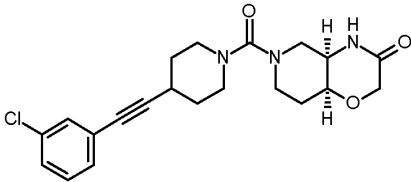
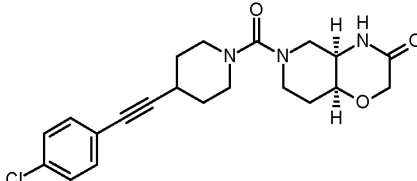
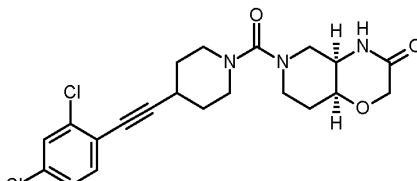
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
112	(4aR,8aS)-6-[3-[[2,4-Difluoro-5-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB64 and BB1a	450.2 [M+H] ⁺	A4 (ACN as solvent)
113	(4aR,8aS)-6-[3-[[2-Fluoro-5-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB65 and BB1a	432.2 [M+H] ⁺	A4 (ACN as solvent)
114	(4aR,8aS)-6-[3-[[3-Fluoro-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB66 and BB1a	432.2 [M+H] ⁺	A4 (ACN as solvent)

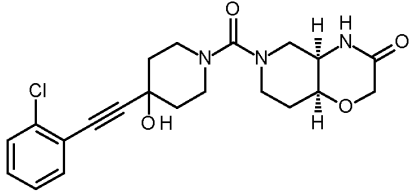
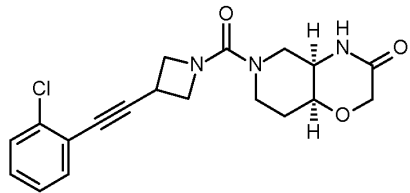
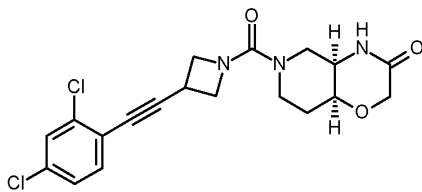
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
115	(4aR,8aS)-6-[3-[[2-Methoxy-4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB67 and BB1a	444.3 [M+H] ⁺	A4 (ACN as solvent)
116	(4aR,8aS)-6-[3-[[4-Chloro-2-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB68 and BB1a	448.2 [M+H] ⁺	A4 (1:1 iPrOH: ACN as solvent)
117	(4aR,8aS)-6-[2-Methyl-3-[[4-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB69 and BB1a	428.18 [M+H] ⁺	A3

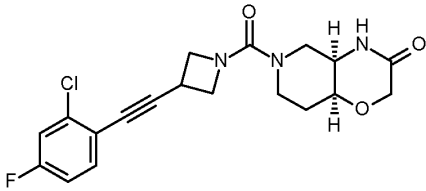
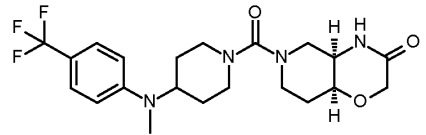
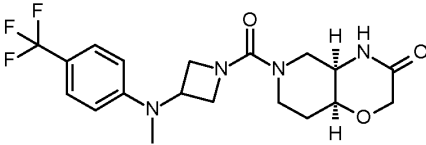
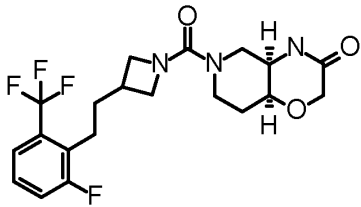
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
118	(4aR,8aS)-6-[3-[4-(Trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB70 and BB1a	400.2 [M+H] ⁺	A4 (ACN as solvent)
119	(4aR,8aS)-6-[4-[4-Chloro-3-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB71 and BB1a	462.2 [M+H] ⁺	A4 (ACN as solvent)
120	(4aR,8aS)-6-[4-(4-Chloro-3-cyclopropylphenoxy)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB72 and BB1a	434.1 [M+H] ⁺	A4 (ACN as solvent)

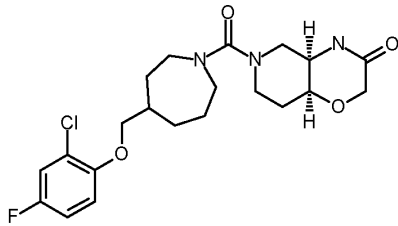
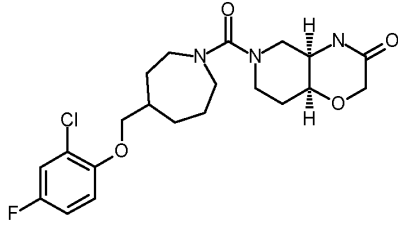
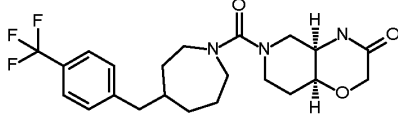
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
121	(4aR,8aS)-6-[4-(4-Chloro-3-morpholin-4-ylphenoxy)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB73 and BB1a	479.2 [M+H] ⁺	A4 (ACN as solvent)
122	(4aR,8aS)-6-[4-[2-Methyl-4-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB74 and BB1a	442.1 [M+H] ⁺ Hans	A4 (ACN as solvent)
123	2-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]piperidin-4-yl]oxy-5-(trifluoromethyl)benzonitrile 	BB75 and BB1a	453.0 [M+H] ⁺ Hans	A4 (ACN as solvent)
124	(4aR,8aS)-6-[4-(Oxazolo[5,4-c]pyridin-2-ylmethyl)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB76 and BB1a	400.2 [M+H] ⁺	A4 (ACN as solvent)

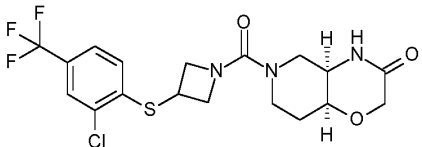
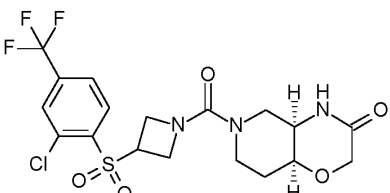
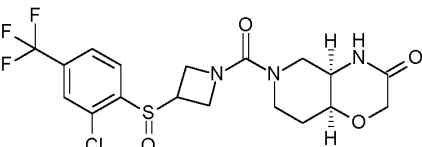
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
126	(+)-(4aR,8aS)-6-[4-[2-(4-Chloropyridin-3-yl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB77	403.3 [M+H] ⁺	A10
127	(+)-(4aR,8aS)-6-[4-[2-(3-Chloropyridin-2-yl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB78	403.2 [M+H] ⁺	A10
128	(+)-(4aR,8aS)-6-[4-[2-(2-Chloro-4-fluorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB79	420.3 [M+H] ⁺	A10

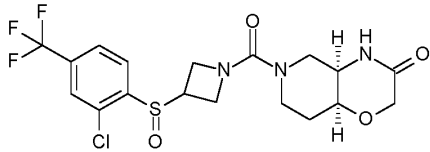
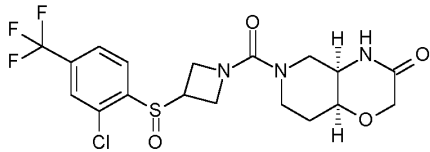
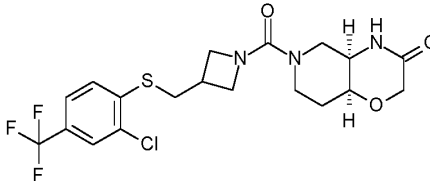
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
129	(+)-(4aR,8aS)-6-[4-[2-(3-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB80	402.3 [M+H] ⁺	A10
130	(+)-(4aR,8aS)-6-[4-[2-(4-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB81	402.3 [M+H] ⁺	A10
131	(+)-(4aR,8aS)-6-[4-[2-(2,4-Dichlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB82	436.3 [M+H] ⁺	A10

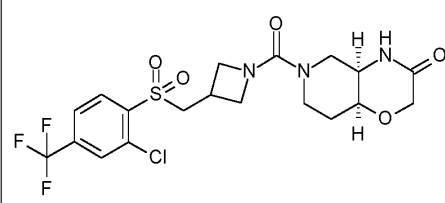
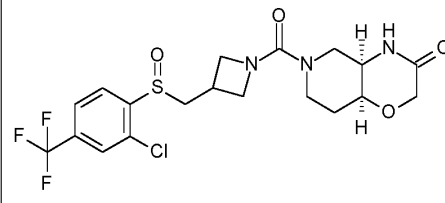
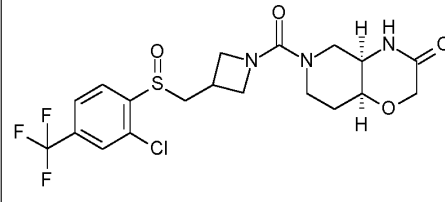
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
132	(+)-(4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]-4-hydroxypiperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB83	418.4 [M+H] ⁺	A10
133	(+)-(4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB84	374.2 [M+H] ⁺	A10
134	(+)-(4aR,8aS)-6-(3-((2,4-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB85	408.3 [M+H] ⁺	A10

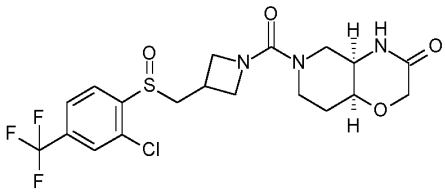
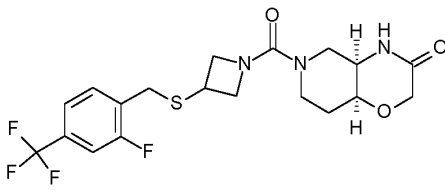
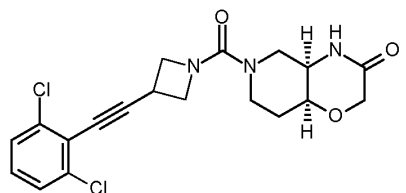
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
135	(+)-(4aR,8aS)-6-[3-[2-(2-Chloro-4-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB86	392.2 [M+H] ⁺	A10
136	rac-(4aR,8aS)-6-[4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB92	413.2 [M+H] ⁺	A1 (ACN as solvent DIPEA as base)
137	rac-(4aR,8aS)-6-[3-[N-methyl-4-(trifluoromethyl)anilino]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB93	441.2 [M+H] ⁺	A1 (ACN as solvent DIPEA as base)
139	(4aR,8aS)-6-[3-[2-[2-Fluoro-6-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB95	430.4 [M+H] ⁺	A1 (ACN as solvent DIPEA as base)

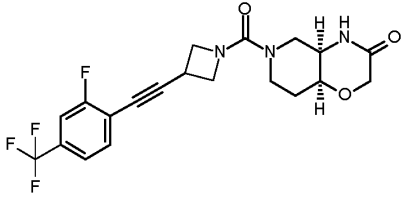
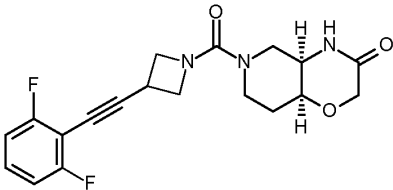
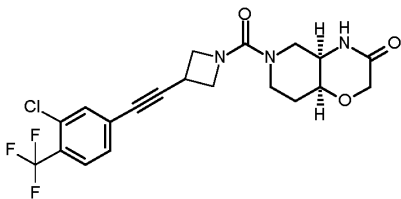
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
140	(4aR,8aS)-6-[4-[(2-Chloro-4-fluorophenoxy)methyl]azepane-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one [Epimer A] 	BB96	440.18 [M+H] ⁺	A3 followed by chiral SFC
141	(4aR,8aS)-6-[4-[(2-Chloro-4-fluorophenoxy)methyl]azepane-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one [Epimer B] 	BB96	440.18 [M+H] ⁺	A3 followed by chiral SFC
142	(4aR,8aS)-6-[4-[[4-(Trifluoromethyl)phenyl]methyl]azepane-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB97	440.2 [M+H] ⁺	A3

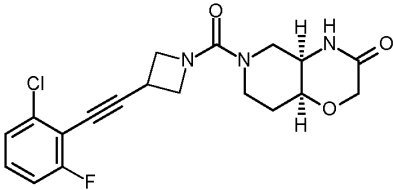
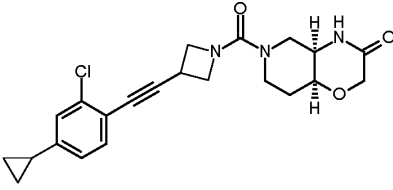
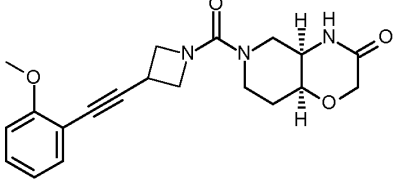
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
143	(4aR,8aS)-6-[3-[2-Chloro-4-(trifluoromethyl)phenyl]sulfanylazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB98 and BB1a	450.1 [M+H] ⁺	A3
144	(4aR,8aS)-6-[3-[2-Chloro-4-(trifluoromethyl)phenyl]sulfonylazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB99 and BB1a	482.2 [M+H] ⁺	A3
145	(4aR,8aS)-6-[3-[2-Chloro-4-(trifluoromethyl)phenyl]sulfinylazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (mixture of sulfoxide isomers) 	BB100 and BB1a	466.2 [M+H] ⁺	A3

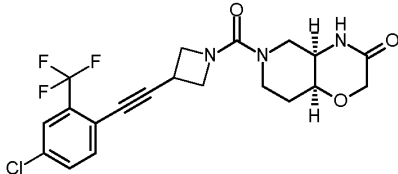
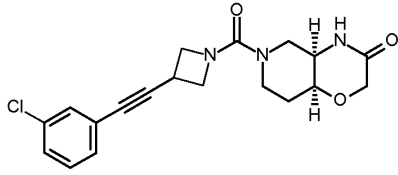
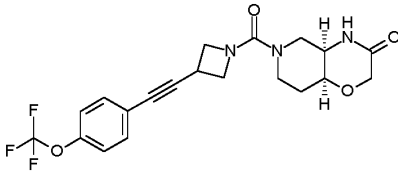
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
146	(4aR,8aS)-6-[3-[2-Chloro-4-(trifluoromethyl)phenyl]sulfinylazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (sulfoxide isomer A) 	Example 145	466.2 [M+H] ⁺	SFC, Chiral-pak AD, 40% MeOH
147	(4aR,8aS)-6-[3-[2-Chloro-4-(trifluoromethyl)phenyl]sulfinylazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (sulfoxide isomer B) 	Example 145	466.2 [M+H] ⁺	SFC, Chiral-pak AD, 40% MeOH
148	(4aR,8aS)-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]sulfanylmethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB101 and BB1a	464.1 [M+H] ⁺	A3

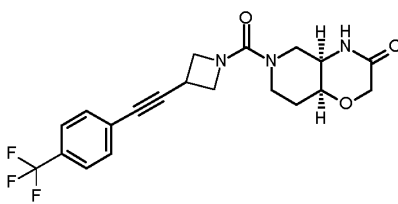
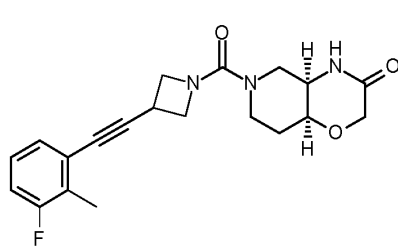
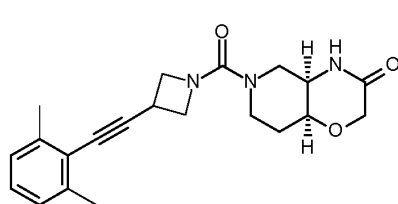
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
152	(4aR,8aS)-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]sulfonylmethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB104 and BB1a	496.1 [M+H] ⁺	A3
153	(4aR,8aS)-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]sulfinylmethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (mixture of sulfoxide isomers) 	BB105 and BB1a	480.1 [M+H] ⁺	A3
154	(4aR,8aS)-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]sulfinylmethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (sulfoxide isomer A) 	Example 153	480.1 [M+H] ⁺	A3, then HPLC Reprosil Chiral NR, 60% heptane, 40% EtOH + NH ₄ Ac

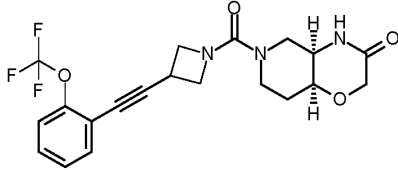
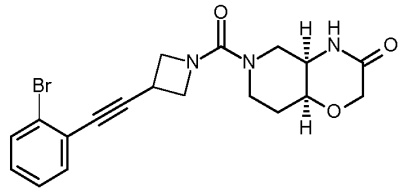
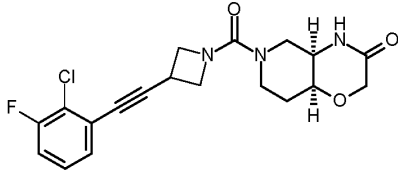
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
155	(4aR,8aS)-6-[3-[[2-Chloro-4-(trifluoromethyl)phenyl]sulfinylmethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (sulfoxide isomer B) 	Example 153	480.1 [M+H] ⁺	A3, then HPLC Reprosil Chiral NR, 60% heptane, 40% EtOH + NH ₄ Ac
156	(4aR,8aS)-6-[3-[[2-Fluoro-4-(trifluoromethyl)phenyl]methylsulfanyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB106 and BB1a	448.1 [M+H] ⁺	A3
157	(+)-(4aR,8aS)-6-(3-((2,6-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB107	408.2 [M+H] ⁺	A10

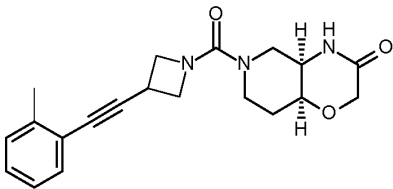
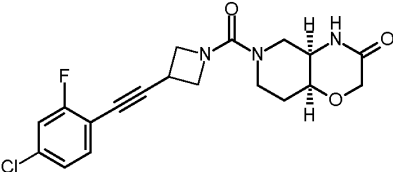
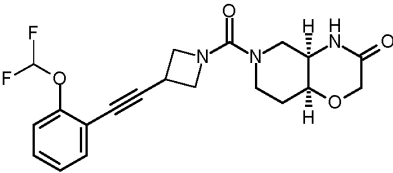
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
158	(4aR,8aS)-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB108	426.3 [M+H] ⁺	A10
159	(4aR,8aS)-6-(3-((2,6-Difluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB109	376.3 [M+H] ⁺	A10
160	(4aR,8aS)-6-(3-((3-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB110	442.3 [M+H] ⁺	A10

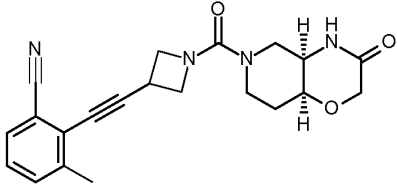
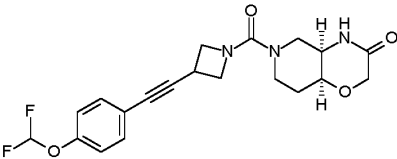
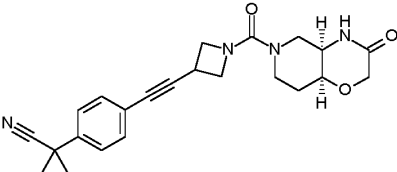
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
161	(4aR,8aS)-6-(3-((2-Chloro-6-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB111	392.3 [M+H] ⁺	A10
162	(4aR,8aS)-6-(3-((2-Chloro-4-cyclopropylphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB112	414.4 [M+H] ⁺	A10
163	(4aR,8aS)-6-(3-((2-Methoxyphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB113	370.4 [M+H] ⁺	A10

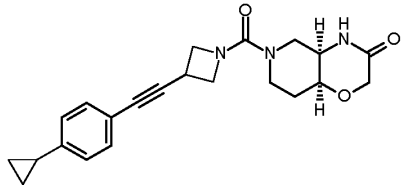
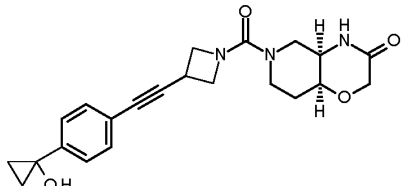
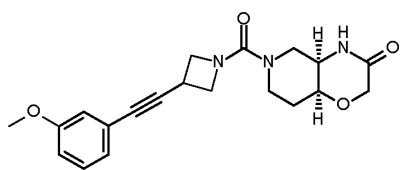
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
164	(4aR,8aS)-6-[3-[2-[4-Chloro-2-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB114	442.3 [M+H] ⁺	A10
165	(4aR,8aS)-6-[3-[2-(3-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB115	374.3 [M+H] ⁺	A10
166	(4aR,8aS)-6-[3-[2-[4-(Trifluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB116	424.3 [M+H] ⁺	A10

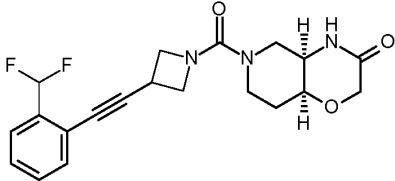
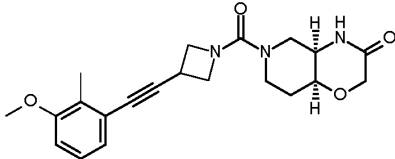
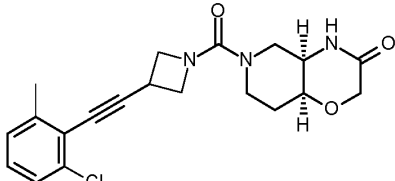
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
167	(4aR,8aS)-6-[3-[2-[4-(Trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB117	408.4 [M+H] ⁺	A10
168	(4aR,8aS)-6-[3-[2-(3-Fluoro-2-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB118	372.2 [M+H] ⁺	A10
169	(4aR,8aS)-6-[3-[2-(2,6-Dimethylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB119	368.4 [M+H] ⁺	A10

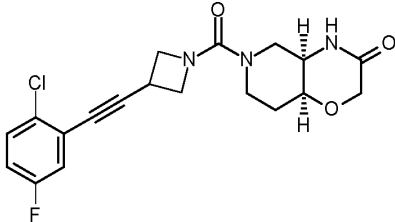
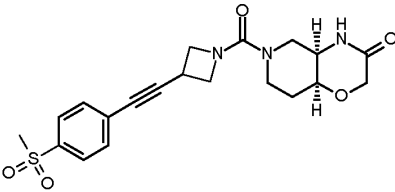
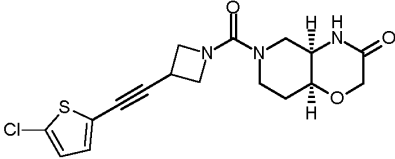
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
170	(4aR,8aS)-6-[3-[2-(2-(Trifluoromethoxy)phenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB120	424.3 [M+H] ⁺	A10
171	(4aR,8aS)-6-[3-[2-(2-Bromophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB121	420.3 [M+H] ⁺	A10
172	(4aR,8aS)-6-(3-((2-Chloro-3-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB122	392.3 [M+H] ⁺	A10

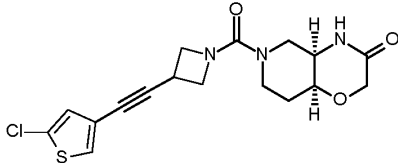
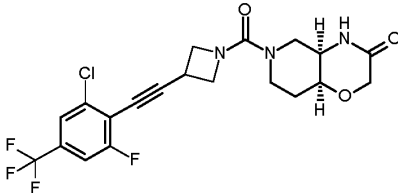
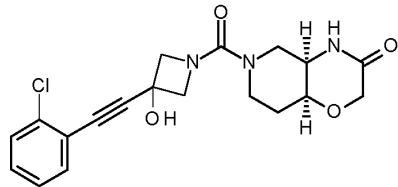
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
173	(4aR,8aS)-6-(3-(o-Tolyethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB123	354.3 [M+H] ⁺	A10
174	(4aR,8aS)-6-[3-[2-(4-Chloro-2-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB124	392.3 [M+H] ⁺	A10
175	(4aR,8aS)-6-[3-[2-(2-(Difluoromethoxy)phenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB125	406.3 [M+H] ⁺	A10

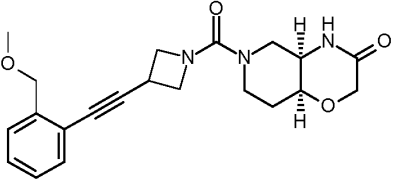
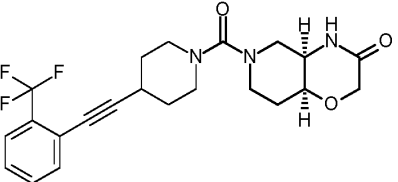
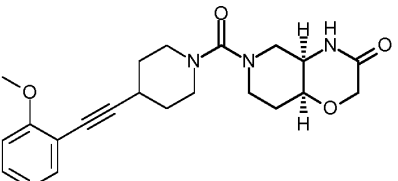
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
176	2-[2-[1-[(4aR,8aS)-3-oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]ethynyl]-3-chlorobenzonitrile 	BB126	399.3 [M+H] ⁺	A10
177	(4aR,8aS)-6-[3-[2-[4-(Difluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB127	406.3 [M+H] ⁺	A10
178	1-[4-[2-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]ethynyl]phenyl]cyclopropane-1-carbonitrile 	BB128	405.4 [M+H] ⁺	A10

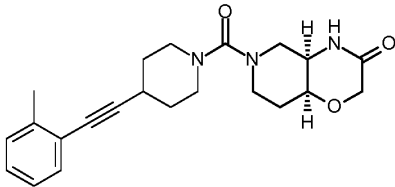
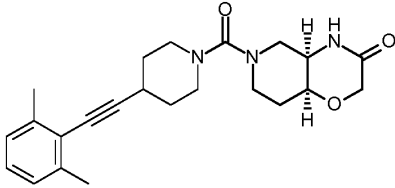
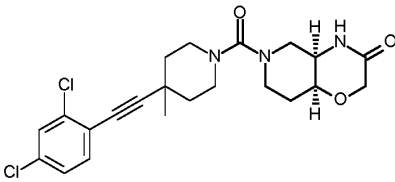
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
179	(4aR,8aS)-6-[3-[2-(4-Cyclopropylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB129	380.4 [M+H] ⁺	A10
180	(4aR,8aS)-6-[3-[2-(4-(1-Hydroxycyclopropyl)phenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB130	396.4 [M+H] ⁺	A10
181	(4aR,8aS)-6-[3-[2-(3-Methoxyphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB131	370.3 [M+H] ⁺	A10

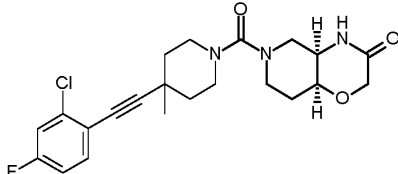
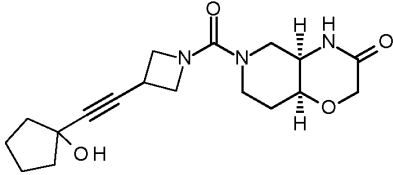
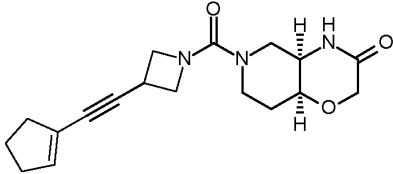
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
182	(4aR,8aS)-6-[3-[2-(2-(Difluoromethyl)phenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB132	390.3 [M+H] ⁺	A10
183	(4aR,8aS)-6-[3-[2-(3-Methoxy-2-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB133	384.3 [M+H] ⁺	A10
184	(4aR,8aS)-6-[3-[2-(2-Chloro-6-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB134	388.3 [M+H] ⁺	A10

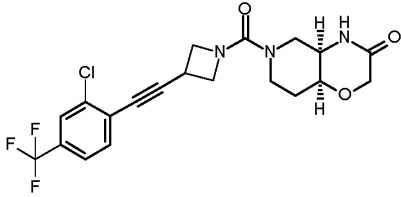
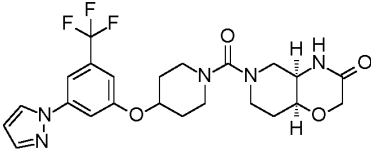
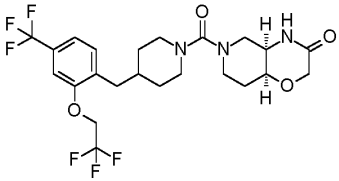
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
185	(4aR,8aS)-6-[3-[2-(2-Chloro-5-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB135	392.2 [M+H] ⁺	A10
186	(4aR,8aS)-6-[3-[2-(4-Methylsulfonylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB136	418.3 [M+H] ⁺	A10
187	(4aR,8aS)-6-[3-[2-(5-Chlorothiophen-2-yl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB137	380.2 [M+H] ⁺	A10

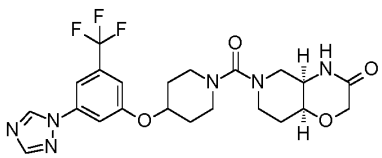
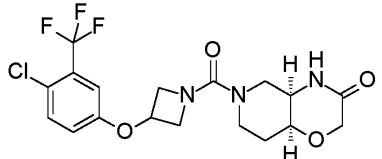
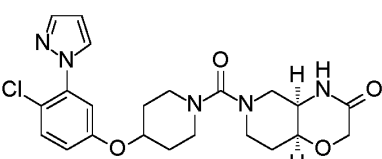
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
188	(4aR,8aS)-6-[3-[2-(5-Chlorothiophen-3-yl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB138	380.2 [M+H] ⁺	A10
189	(4aR,8aS)-6-[3-[2-[2-Chloro-6-fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB139	460.3 [M+H] ⁺	A10
190	(4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]-3-hydroxyazetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB140	390.3 [M+H] ⁺	A10

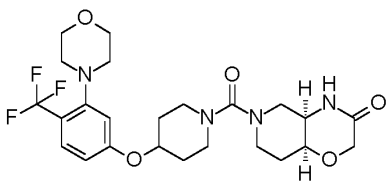
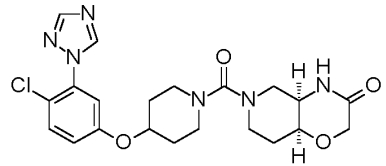
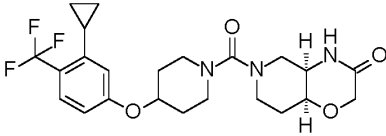
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
191	(4aR,8aS)-6-[3-[2-(2-(Methoxymethyl)phenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB141	384.3 [M+H] ⁺	A10
192	(4aR,8aS)-6-(4-((2-(Trifluoromethyl)phenyl)ethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB143	436.4 [M+H] ⁺	A10
193	(4aR,8aS)-6-(4-((2-Methoxyphenyl)ethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB144	398.4 [M+H] ⁺	A10

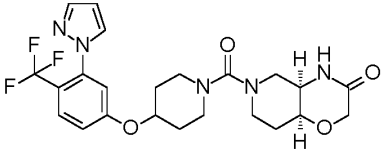
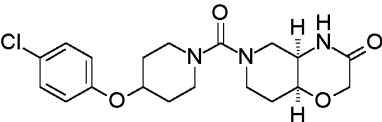
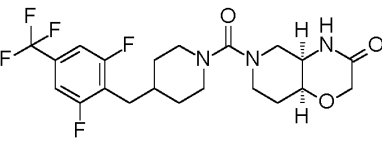
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
194	(4aR,8aS)-6-(4-(o-Tolylethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB145	382.4 [M+H] ⁺	A10
195	(4aR,8aS)-6-(4-((2,6-Dimethylphenyl)ethynyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB146	396.4 [M+H] ⁺	A10
196	(4aR,8aS)-6-(4-((2,4-Dichlorophenyl)ethynyl)-4-methylpiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB147	450.3 [M+H] ⁺	A10

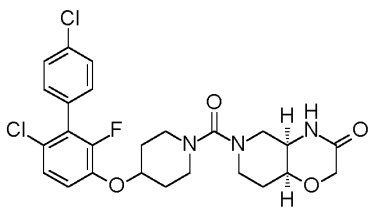
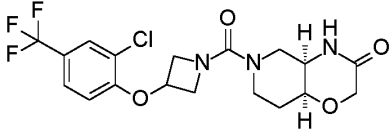
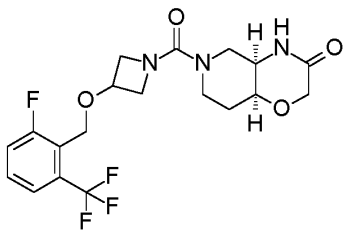
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
197	(4aR,8aS)-6-(4-((2-Chloro-4-fluorophenyl)ethynyl)-4-methylpiperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB148	434.4 [M+H] ⁺	A10
198	(4aR,8aS)-6-[3-[2-(1-Hydroxycyclopentyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB149	330.3 [M-H ₂ O+H] ⁺	A10
199	(4aR,8aS)-6-[3-[2-(Cyclopenten-1-yl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB149 (Elimination product isolated during synthesis of example 198)	330.3 [M+H] ⁺	A10

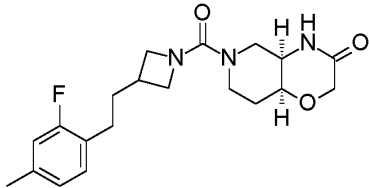
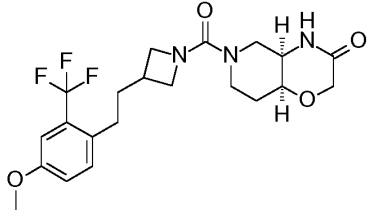
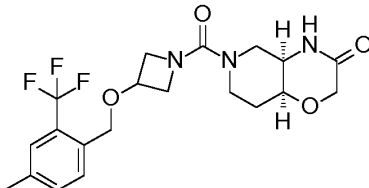
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
200	(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB142	442.3 [M+H] ⁺	A10
201	(4aR,8aS)-6-[4-[3-Pyrazol-1-yl-5-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB98	494.2 [M+H] ⁺	A4
202	(4aR,8aS)-6-[4-[[2-(2,2,2-Trifluoroethoxy)-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB99	524.2 [M+H] ⁺	A4

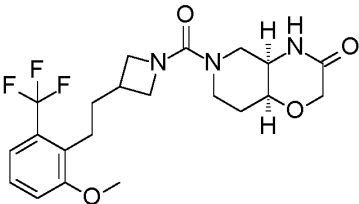
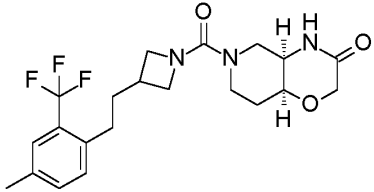
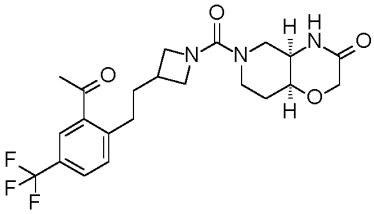
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
203	(4aR,8aS)-6-[4-[3-(1,2,4-Triazol-1-yl)-5-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB100	495.2 [M+H] ⁺	A4
204	(4aR,8aS)-6-[3-[4-Chloro-3-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB101	434.1 [M+H] ⁺	A4
205	(4aR,8aS)-6-[4-(4-Chloro-3-pyrazol-1-yl-phenoxy)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB102	460.2 [M+H] ⁺	A4

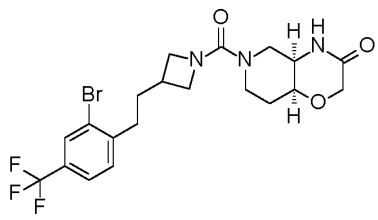
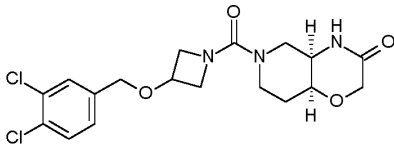
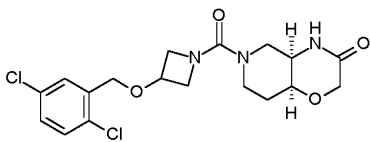
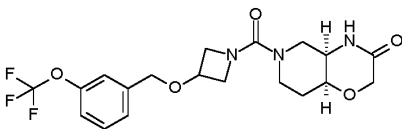
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
206	(4aR,8aS)-6-(4-(3-Morpholino-4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB103	513.3 [M+H] ⁺	A4
207	(4aR,8aS)-6-[4-[4-Chloro-3-(1,2,4-triazol-1-yl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB104	461.2 [M+H] ⁺	A4
208	(4aR,8aS)-6-[4-[3-Cyclopropyl-4-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB105	468.2 [M+H] ⁺	A4

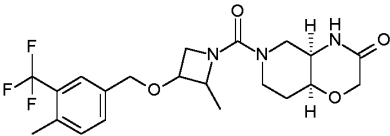
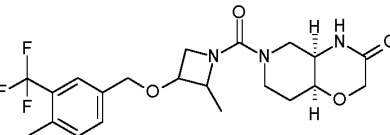
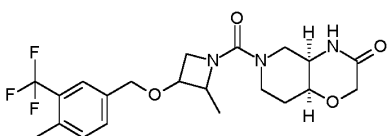
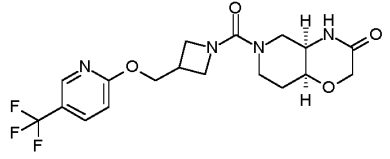
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
209	(4aR,8aS)-6-[4-[3-Pyrazol-1-yl-4-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB106	494.3 [M+H] ⁺	A4
210	(4aR,8aS)-6-[4-(4-Chlorophenoxy)piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and 4-(4-Chlorophenoxy)piperidine hydrochloride (CAS RN 63843-53-8)	394.1 [M+H] ⁺	A4
211	(4aR,8aS)-6-[4-[[2,6-Difluoro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB107	462.2 [M+H] ⁺	A4

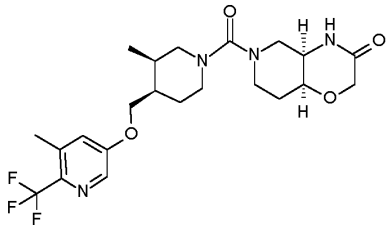
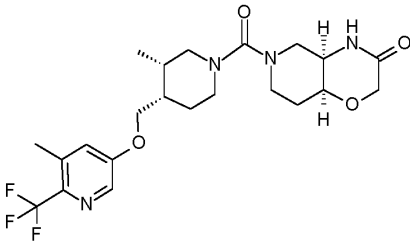
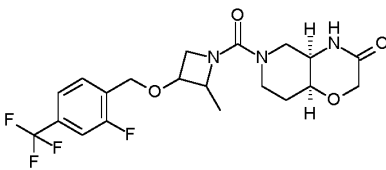
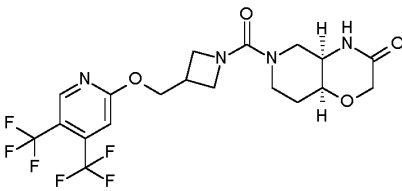
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
212	(4aR,8aS)-6-[4-[4-Chloro-3-(4-chlorophenyl)-2-fluorophenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB108	522.2 [M+H] ⁺	A4
213	(4aR,8aS)-6-[3-[2-Chloro-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB109	434.1 [M+H] ⁺	A4
214	(4aR,8aS)-6-[3-[[2-Fluoro-6-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB110	432.1 [M+H] ⁺	A4

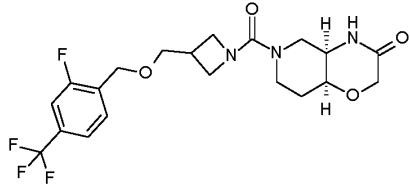
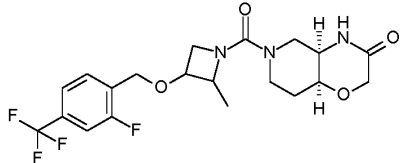
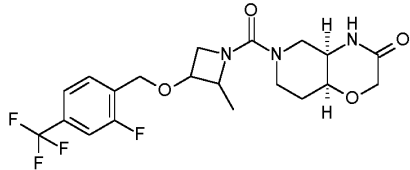
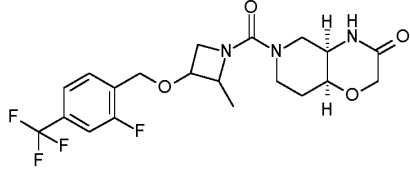
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
215	(4aR,8aS)-6-[3-[2-(2-Fluoro-4-methylphenyl)ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB111	376.0 [M+H] ⁺	A4
216	(4aR,8aS)-6-[3-[2-[4-Methoxy-2-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB112	442.3 [M+H] ⁺	A4
217	(4aR,8aS)-6-[3-[[4-Methyl-2-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB113	428.3 [M+H] ⁺	A4

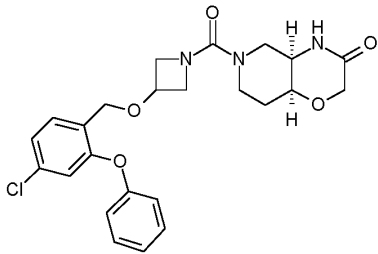
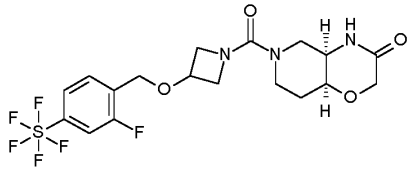
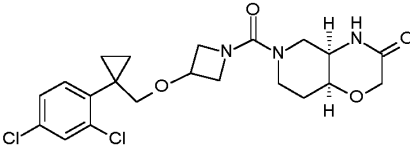
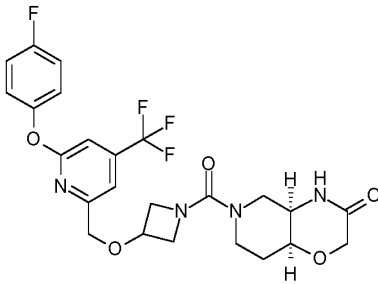
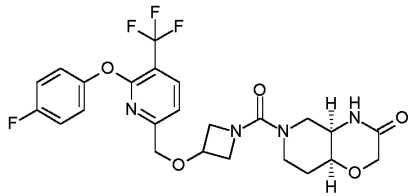
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
218	(4aR, 8aS)-6-[3-[2-[2-Methoxy-6-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB114	442.1 [M+H] ⁺	A4
219	(4aR,8aS)-6-[3-[2-[4-methyl-2-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB115	426.1 [M+H] ⁺	A4
220	(4aR,8aS)-6-[3-[2-[2-Acetyl-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB116	454.3 [M+H] ⁺	A4

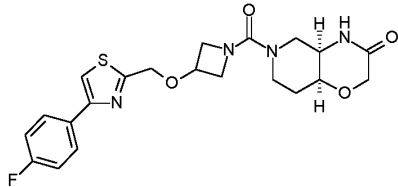
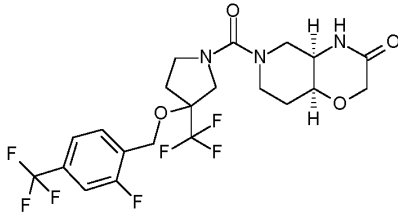
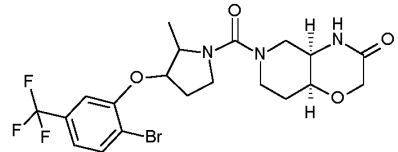
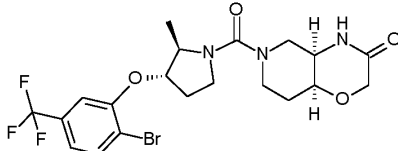
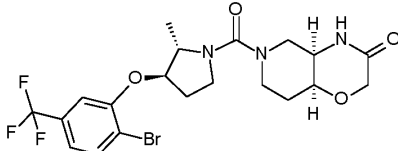
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
221	(4aR, 8aS)-6-[3-[2-[2-Bromo-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB117	491.0 [M+H] ⁺	A4
224		BB170 and BB1a	414.1 [M+H] ⁺	A3
225		BB171 and BB1a	414.1 [M+H] ⁺	A3
226		BB173 and BB1a	429.4 [M+H] ⁺	A3

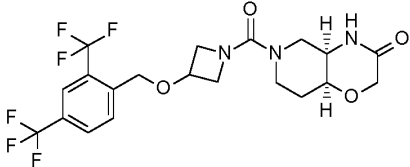
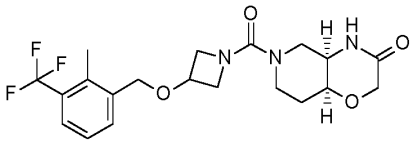
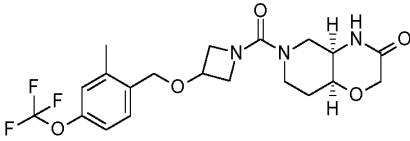
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
227		BB173 and BB1a	442.2 [M+H] ⁺	A3 Chiral HPLC (Reprosil Chiral NR, 60% n- heptane, 40% EtOH + NH ₄ Ac
228		BB173 and BB1a	442.2 [M+H] ⁺	A3 Chiral HPLC (Reprosil Chiral NR, 60% n- heptane, 40% EtOH + NH ₄ Ac
229		BB173 and BB1a	442.2 [M+H] ⁺	A3 Chiral HPLC (Reprosil Chiral NR, 60% n- heptane, 40% EtOH + NH ₄ Ac
230		BB174 and BB1a	415.2 [M+H] ⁺	A3

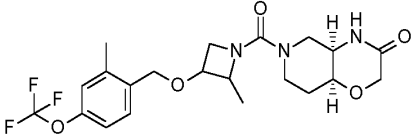
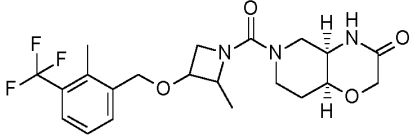
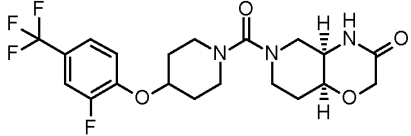
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
231		BB175 and BB1a	471.2 [M+H] ⁺	A3 SFC: OD- H column, 20% EtOH
232		BB175 and BB1a	471.2 [M+H] ⁺	A3 SFC: OD- H column, 20% EtOH
233		BB176 and BB1a	464.2 [M+H] ⁺	A3
234		BB177 and BB1a	483.2 [M+H] ⁺	A3

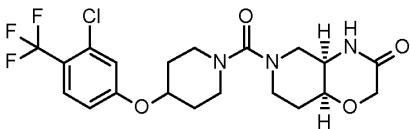
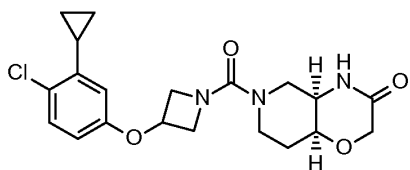
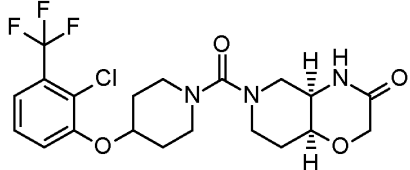
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
235		BB178 and BB1a	464.1 [M+H] ⁺	A3 HPLC: YMC- Triart C18, 25- 45-60- 100% ACN in water
236		Example 233	464.4 [M+H] ⁺	Reprosil Chiral NR, 70% Heptan, 30% EtOH + NH ₄ Ac
237		Example 233	464.3 [M+H] ⁺	Reprosil Chiral NR, 70% Heptan, 30% EtOH + NH ₄ Ac
238		Example 233	464.4 [M+H] ⁺	Reprosil Chiral NR, 70% n- heptane, 30% EtOH + NH ₄ Ac

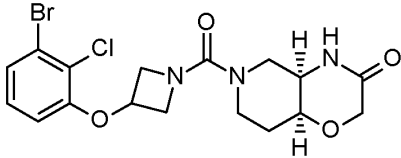
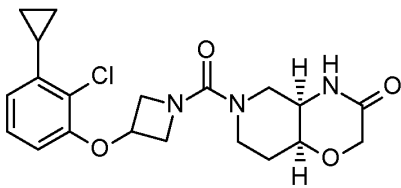
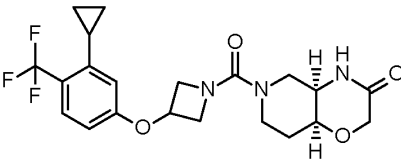
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
239		BB179 and BB1a	472.2 [M+H] ⁺	A3
240		BB180 and BB1a	490.1 [M+H] ⁺	A3
241		BB181 and BB1a	454.3 [M+H] ⁺	A3
242		BB182 and BB1a	525.3 [M+H] ⁺	A3
243		BB183 and BB1a	525.3 [M+H] ⁺	A3

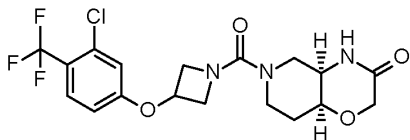
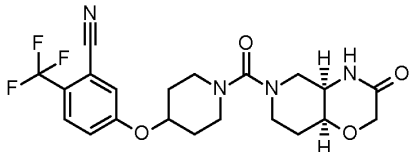
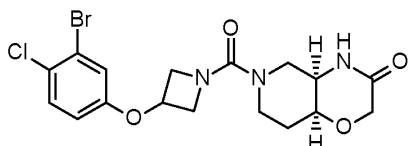
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
244		BB184 and BB1a	447.2 [M+H] ⁺	A3
245		BB185 and BB1a	514.2 [M+H] ⁺	A3
246		BB186 and BB1a	508.1 [M+H] ⁺	A3
247		Example 246	508.0 [M+H] ⁺	HPLC: Reprosil Chiral NR, 60% n- heptane, 40% EtOH + NH ₄ Ac
248		Example 246	508.0 [M+H] ⁺	HPLC: Reprosil Chiral NR, 60% n- heptane, 40% EtOH + NH ₄ Ac

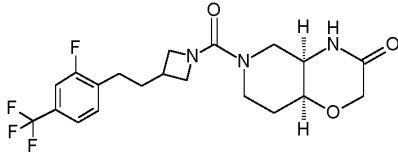
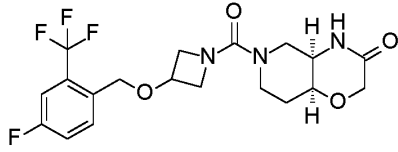
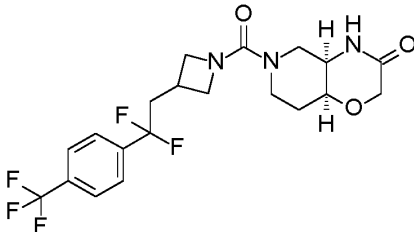
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
249	(+)-(4aR,8aS)-6-[3-[[2,4-bis(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB187	482.1 [M+H] ⁺	A10
250	(+)-(4aR,8aS)-6-(3-((2-Methyl-3-(trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB188	428.3 [M+H] ⁺	A10
251	(+)-(4aR,8aS)-6-(3-((4-Methyl-2-(trifluoromethoxy)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB189	444.2 [M+H] ⁺	A10

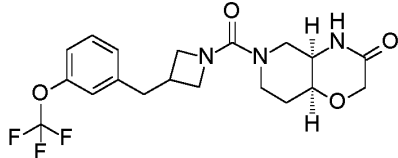
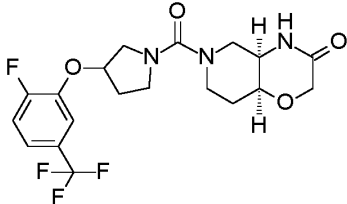
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
252	(4aR,8aS)-6-[2-Methyl-3-[[2-methyl-4-(trifluoromethoxy)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB190	458.2 [M+H] ⁺	A10
253	(4aR,8aS)-6-[2-Methyl-3-[[2-methyl-3-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB191	442.3 [M+H] ⁺	A10
254	(+)-(4aR,8aS)-6-[4-[2-Fluoro-4-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB192	446.3 [M+H] ⁺	A10

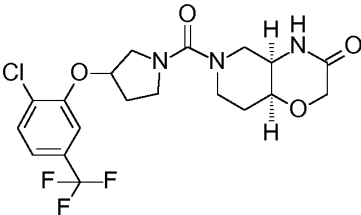
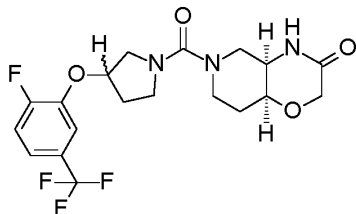
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
255	(+)-(4aR,8aS)-6-[4-[3-Chloro-4-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB193	462.3 [M+H] ⁺	A10
256	(+)-(4aR,8aS)-6-[3-(4-Chloro-3-cyclopropylphenoxy)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB194	406.4 [M+H] ⁺	A10
257	(+)-(4aR,8aS)-6-[4-[2-Chloro-3-(trifluoromethyl)phenoxy]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB195	462.3 [M+H] ⁺	A10

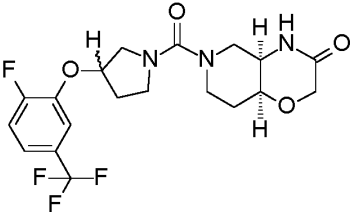
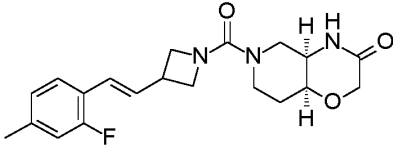
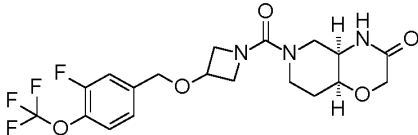
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
258	(+)-(4aR,8aS)-6-[3-(3-Bromo-2-chloro-phenoxy)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB196	446.0 [M+H] ⁺	A10
259	(+)-(4aR,8aS)-6-[3-(2-Chloro-3-cyclopropyl-phenoxy)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB197	406.4 [M+H] ⁺	A10
260	(+)-(4aR,8aS)-6-[3-[3-Cyclopropyl-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB199	440.1 [M+H] ⁺	A10

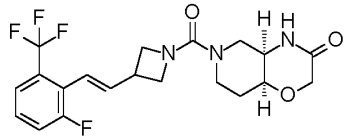
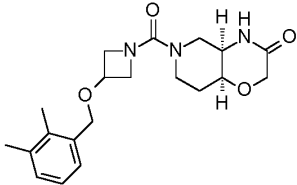
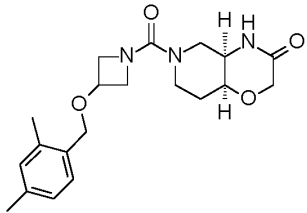
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
261	(+)-(4aR,8aS)-6-[3-[3-Chloro-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB200	434.1 [M+H] ⁺	A10
262	(+)-5-[[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]-4-piperidyl]oxy]-2-(trifluoromethyl)benzonitrile 	BB7a and BB202	453.4 [M+H] ⁺	A10
264	(+)-(4aR,8aS)-6-[3-(3-Bromo-4-chlorophenoxy)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB205	444.2 [M+H] ⁺	A10

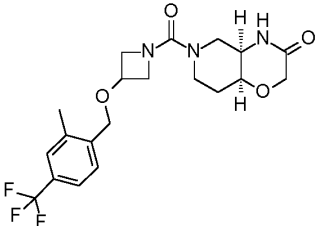
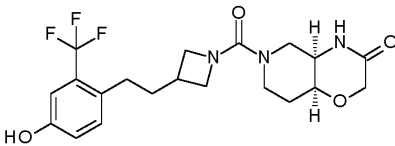
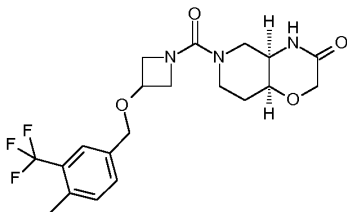
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
279	(4aR,8aS)-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB206	430.2 [M+H] ⁺	A4 ACN as solvent followed by prep-HPLC
280	(4aR,8aS)-6-[3-[[4-Fluoro-2-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB207	432.2 [M+H] ⁺	A4 ACN as solvent followed by prep-HPLC
281	(4aR,8aS)-6-[3-[2,2-Difluoro-2-[4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB208	448.3 [M+H] ⁺	A4 ACN as solvent followed by prep-HPLC

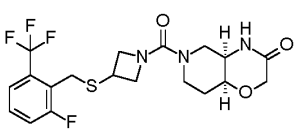
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
282	(4aR,8aS)-6-[3-[[3-(Trifluoromethoxy)phenyl]methyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and 3-(3-(Trifluoromethoxy)benzyl)azetidine hydrochloride (CAS RN 1354963-49-7)	414.3 [M+H]⁺	A4 ACN as solvent followed by prep-HPLC
283	(4aR,8aS)-6-[3-[2-Fluoro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB209	432.2 [M+H]⁺	A4 ACN as solvent followed by MPLC (n-heptane : EtOAc/EtOH 3/1 (70 : 30 to 10 : 90))

Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
284	(4aR,8aS)-6-[3-[2-Chloro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB7a and BB210	448.2 [M+H] ⁺	A4 ACN as solvent followe d by MPLC (n- heptane : EtOAc/Et OH 3/1 (70 : 30 to 10 : 90)
285	(4aR,8aS)-6-[(3R or 3S)-3-[2-Fluoro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 283	432.2 [M+H] ⁺	B3

Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
286	(4aR,8aS)-6-[(3S or 3R)-3-[2-Fluoro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 283	432.2 [M+H] ⁺	B3
287		BB1a and BB211	374.2 [M+H] ⁺	A3
288	(4aR,8aS)-6-(3-((3-Fluoro-4-(trifluoromethoxy)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB212	448.3 [M+H] ⁺	A4

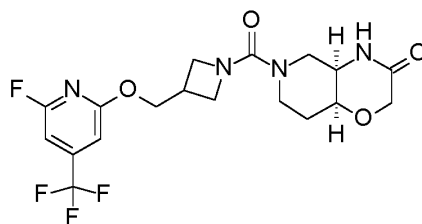
Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
289	(4aR,8aS)-6-(3-((E)-2-Fluoro-6-(trifluoromethyl)styryl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB1a and BB213	428.2 [M+H] ⁺	A3
290	(4aR,8aS)-6-(3-((2,3-Dimethylbenzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB214	374.2 [M+H] ⁺	A4 (ACN as solvent)
291	(4aR,8aS)-6-(3-((2,4-Dimethylbenzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB215	374.2 [M+H] ⁺	A4 (ACN as solvent)

Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
292	(4aR,8aS)-6-(3-((2-Methyl-4-(trifluoromethyl)benzyl)oxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB7a and BB 216	428.2 [M+H] ⁺	A4 (ACN as solvent)
293	(4aR,8aS)-6-(3-(4-Hydroxy-2-(Trifluoromethyl)phenethyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 216	427.2 [M+H] ⁺	G
294	(4aR,8aS)-6-[3-[[4-Methyl-3-(trifluoromethyl)phenyl]methoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB217	428.2 [M+H] ⁺	A3

Ex.	Systematic Name / Structure	Building block(s)	MS, m/z	Method
295	(4aR,8aS)-6-(3-((2-Fluoro-6-(trifluoromethyl)benzyl)thio)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	BB1a and BB218	448.1 [M+H] ⁺	A3

Example 222

(4aR,8aS)-6-[3-[[6-Fluoro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



5

Step a) *tert*-Butyl 3-[[6-chloro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate

To a solution of *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (CAS Nr. 142253-56-3) (2.60 g, 13.9 mmol) and 2,6-dichloro-4-(trifluoromethyl)pyridine (CAS Nr. 39890-98-7) (3.00 g, 13.9 mmol) in THF (60 mL) was added NaH (60%, 1.11 g, 27.8 mmol) and the mixture was stirred 3 h at 25 °C. The solution was poured into sat. aq. NH₄Cl (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were concentrated under vacuum to give crude *tert*-butyl 3-[[6-chloro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate (3.00 g, 59%) as colorless oil, which was used directly in the next step. LC-MS (ESI): m/z = 367.1 [M+H]⁺.

15 Step b) 2-(Azetidin-3-ylmethoxy)-6-chloro-4-(trifluoromethyl)pyridine

A solution of trifluoroacetic acid (6.3 mL, 81.8 mmol, 10 eq) and *tert*-butyl 3-[[6-chloro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate (3.00 g, 8.18 mmol) in DCM (30 mL) was stirred at 25 °C for 4 h. The solution was concentrated under vacuum to give a residue,

- 153 -

which was purified by Prep-HPLC (HCl condition) to give 2-(azetidin-3-ylmethoxy)-6-chloro-4-(trifluoromethyl)pyridine (1.00 g, 46%) as white solid. LC-MS (ESI): $m/z = 267.0$ $[M+H]^+$.

Step c) (4aR,8aS)-6-[3-[[6-Chloro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one

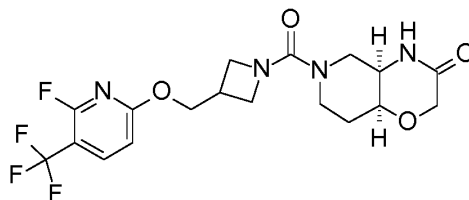
- 5 A solution of 2-(azetidin-3-ylmethoxy)-6-chloro-4-(trifluoromethyl)pyridine (150 mg, 0.560 mmol), *N,N*-diisopropylethylamine (0.29 mL, 1.69 mmol) and 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazine-6(5*H*)-carboxylate (BB7a) (199 mg, 0.620 mmol) in ACN (5 mL) was stirred at 25 °C for 16 h. The solution was concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA conditions) to give (4aR,8aS)-6-[3-[[6-chloro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (100 mg, 40%) as colorless oil. LC-MS (ESI): $m/z = 449.2$ $[M+H]^+$.

Step d) (4aR,8aS)-6-[3-[[6-Fluoro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one

- 15 A solution of (4aR,8aS)-6-[3-[[6-chloro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (75 mg, 0.17 mmol) and cesium fluoride (101 mg, 0.670 mmol) in DMSO (3 mL) was stirred at 80 °C for 16 h. The solution was filtered and purified by prep-HPLC (TFA conditions) to give (4aR,8aS)-6-[3-[[6-fluoro-4-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (22 mg, 28%) as white solid. LC-MS (ESI): $m/z = 433.0$ $[M+H]^+$.

Example 223

(4aR,8aS)-6-[3-[[6-Fluoro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one



25

Step a) *tert*-Butyl 3-[[6-chloro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate

- 154 -

To a solution of *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (CAS Nr. 142253-56-3) (1.56 g, 8.33 mmol) in THF (50 mL) was added NaH (60%, 741 mg, 18.5 mmol) followed by 2,6-dichloro-3-(trifluoromethyl)pyridine (CAS Nr. 55304-75-1) (2.00 g, 9.26 mmol). The resulting mixture was stirred at 25 °C for 3 h. The solution was poured into sat.aq. NH₄Cl (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were concentrated under vacuum to give a residue, which was purified by flash column chromatography (petroleum ether:EtOAc = 5:1) to give *tert*-butyl 3-[[6-chloro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate (1.10 g, 32%) as colorless oil. LC-MS (ESI): *m/z* = 311.0 [M-56+H]⁺.

10 Step b) 6-(Azetidin-3-ylmethoxy)-2-chloro-3-(trifluoromethyl)pyridine

A solution of trifluoroacetic acid (0.37 mL, 4.8 mmol) and *tert*-butyl 3-[[6-chloro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate (1.1 g, 3.0 mmol) in DCM (30 mL) was stirred at 25 °C for 4 h. The solution was concentrated under vacuum to give a residue, which was purified by Prep-HPLC (HCl condition) to give 6-(azetidin-3-ylmethoxy)-2-chloro-3-(trifluoromethyl)pyridine (600 mg, 75%) as white solid. LC-MS (ESI): *m/z* = 267.0 [M+H]⁺.

Step c) (4*aR*,8*aS*)-6-[3-[[6-Chloro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4*a*,5,7,8,8*a*-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one

To a solution of 6-(azetidin-3-ylmethoxy)-2-chloro-3-(trifluoromethyl)pyridine (100 mg, 0.380 mmol) and 4-nitrophenyl (4*aR*,8*aS*)-3-oxohexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazine-6(5*H*)-carboxylate (BB7a) (120 mg, 0.380 mmol) in ACN (5 mL) was added N,N-diisopropylethylamine (0.13 mL, 0.75 mmol) with stirring at 25 °C. The solution was stirred at 25 °C for 16 h. The solution was concentrated under vacuum to give a residue, which was purified by Prep-HPLC (TFA conditions) to give (4*aR*,8*aS*)-6-[3-[[6-chloro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4*a*,5,7,8,8*a*-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (76 mg, 45%) as white solid. LC-MS (ESI): *m/z* = 449.1 [M+H]⁺.

Step d) (4*aR*,8*aS*)-6-[3-[[6-Fluoro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4*a*,5,7,8,8*a*-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one

A solution of (4*aR*,8*aS*)-6-[3-[[6-chloro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4*a*,5,7,8,8*a*-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (70 mg, 0.16 mmol) and cesium fluoride (95 mg, 0.62 mmol) in DMSO (3 mL) was stirred at 60 °C for 24 h. The solution

- 155 -

was filtered and then purified by Prep-HPLC (TFA conditions) to give (4a*R*,8a*S*)-6-[3-[[6-fluoro-5-(trifluoromethyl)-2-pyridyl]oxymethyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-*b*][1,4]oxazin-3-one (38 mg, 49%) as white solid. LC-MS (ESI): m/z = 433.3 $[M+H]^+$.

5

Synthesis of building blocks

BB1a & BB1b

(+)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-*b*][1,4]oxazin-3-one

and

(-)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-*b*][1,4]oxazin-3-one

- 10 The enantiomers of rac-(4a*R*,8a*S*)-hexahydro-2H-pyrido[4,3-*b*][1,4]oxazin-3(4H)-one dihydrochloride (BB1, 500 mg, 2.18 mmol, ChemBridge Corporation) were separated by preparative chiral HPLC (ReprosilChiral NR column) using an isocratic mixture of EtOH (containing 0.05% of NH_4OAc) : n-heptane (30 : 70).

First eluting enantiomer: (+)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-*b*][1,4]oxazin-3-one

- 15 (BB1a). Yellow solid (0.150 g; 44.0%). MS (ESI): m/z = 157.1 $[M+H]^+$.

Second eluting enantiomer: (-)-cis-4a,5,6,7,8,8a-Hexahydro-4H-pyrido[4,3-*b*][1,4]oxazin-3-one.

(BB1b). Yellow solid (0.152 g; 44.6%). MS (ESI): m/z = 157.1 $[M+H]^+$.

BB2

(4-Nitrophenyl) 4-[[4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate

- 20 To a solution of 4-(4-(trifluoromethyl)benzyl)piperidine (100 mg, 411 μmol , CAS RN 192990-03-7) in DCM (1 mL), TEA (83.2 mg, 115 μL , 822 μmol) was added. On cooling to 0 °C, 4-nitrophenyl carbonochloridate (91.1 mg, 452 μmol , CAS RN 7693-46-1) was added, the reaction mixture was allowed to warm to RT and stirred for 18 hours. The reaction mixture was diluted with DCM and subsequently washed with H_2O and sat. aqueous NaHCO_3 solution. The
- 25 combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica 10 g, eluting with EtOAc/Heptane 0-50 %), to afford title compound as a light yellow solid. (0.165 g; 98.3%). MS (ESI): m/z = 409.3 $[M+H]^+$.

- 156 -

BB3**rac-(4aR,8aS)-6-(Piperazine-1-carbonyl)-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one**

To a mixture of rac-tert-butyl 4-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperazine-1-carboxylate (100 mg, 271 μ mol) in DCM (3 mL) was added TFA (155 mg, 105 μ L, 1.36 mmol) and the mixture was stirred at RT for 15 h under an argon atmosphere.

The reaction mixture was washed with a saturated aqueous NaHCO₃ solution. The H₂O layer was concentrated in vacuo to give a white solid which was triturated with DCM for 30 min. before it was filtered. The filtrate was concentrated to give a light yellow gum (70 mg, 96.1%).

MS (ESI): m/z = 269.3 [M+H]⁺.

Step a) *rac-tert-Butyl 4-((4aR,8aS)-3-oxooctahydro-2H-pyrido[4,3-b][1,4]oxazine-6-carbonyl)piperazine-1-carboxylate*

To a mixture of triphosgene (1.29 g, 4.36 mmol) and Na₂CO₃ (1.98 g, 18.7 mmol) in THF (3 mL) at 0 °C were added dropwise a solution of tert-butyl piperazine-1-carboxylate (1.16 g, 6.23 mmol, CAS RN 57260-71-6) in THF (90 mL). The reaction mixture was stirred for 10 min. at 0 °C, then allowed to warm up to RT and stirring was continued at RT for 5 h. The suspension was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in THF (40 mL) and added dropwise to a stirred suspension of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one hydrochloride (1200 mg, 6.23 mmol, Chembridge Corporation) and DIPEA (4.83 g, 6.53 mL, 37.4 mmol) in THF (40 mL) at 0 °C. After 30 min. at 0 °C, the reaction mixture was allowed to warm up to RT, and stirred at RT for 15 h. The mixture was filtered and the filtrate concentrated in vacuo. The residue was diluted with DCM and washed with water, aq. NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to give a white solid (1.13g, 58.6%). MS (ESI): m/z = 313.3 [M+H]⁺.

25

BB4**(4-Nitrophenyl) 4-(phenoxymethyl)piperidine-1-carboxylate**

The compound was prepared in analogy to BB2 using 4-(phenoxymethyl)piperidine (CAS N63614-86-8) to afford title compound as a white solid which was used in the next step without further purification.

- 157 -

BB5**2-(4-Piperidylmethyl)-5-(trifluoromethyl)pyridine; hydrochloride salt**

tert-Butyl 4-[[5-(trifluoromethyl)-2-pyridyl]methyl]piperidine-1-carboxylate (320 mg, 0.930 mmol) was dissolved in 4 M HCl in EtOAc (10.0 mL, 40 mmol) and the solution stirred at 20 °C for 2 h. The mixture was concentrated to yield the desired compound as light yellow solid (0.259, 94.8%). MS (ESI): $m/z = 245.0$ $[M-HCl+H]^+$.

Step a) *tert-Butyl 4-[[5-(trifluoromethyl)-2-pyridyl]methyl]piperidine-1-carboxylate*

2-Bromo-5-(trifluoromethyl)pyridine (500.0 mg, 2.21 mmol, CAS RN 1000773-62-5) was degassed before 9-BBN solution 0.5 M in THF (4.87 mL, 2.43 mmol, CAS RN 280-64-8) was added. The resulting solution was refluxed for 1 h. After cooling to RT, the solution was added to a solution of tert-butyl 4-methylenepiperidine-1-carboxylate (480.1 mg, 2.43 mmol, CAS RN 159635-49-1), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (161.89 mg, 0.220 mmol, CAS RN 72287-26-4) and K_2CO_3 (611.56 mg, 4.42 mmol) in DMF (5 mL) and water (0.5 mL). The resulting mixture was heated at 80 °C for 4 h. The mixture was cooled to RT and poured into water, the pH was adjusted to 11 with 10% aqueous NaOH and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and evaporated to give a crude oil, which was purified by column chromatography (silica adsorbent; gradient of PE : EtOAc 10 : 1 then 5 : 1) to yield the desired compound as a light yellow oil (320 mg, 0.930 mmol, 42%). MS (ESI): $m/z = 289.0$ $[M-C_4H_8+H]^+$.

BB6**rac-(4aS,8aS)-Hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one**

rac-Benzyl (4aS,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (125 mg, 431 μ mol) was dissolved in MeOH (5 mL). The reaction solution was degassed in vacuo and backfilled with argon. Pd-C (20 mg, 188 μ mol) was added under an argon atmosphere. Argon was evacuated from the reaction mixture and backfilled with hydrogen. The reaction mixture was stirred at RT for 15 h under a hydrogen atmosphere. The reaction mixture was filtered through a syringe filter and concentrated in vacuo to afford the desired product as a white solid (62 mg, 92.2%). MS (ESI): $m/z = 157.098$ $[M+H]^+$.

Step a) *rac-Benzyl (3S,4S)-3-(2-chloroacetamido)-4-hydroxypiperidine-1-carboxylate*

- 158 -

To a stirred suspension of rac-benzyl (3S,4S)-3-amino-4-hydroxypiperidine-1-carboxylate (317 mg, 1.27 mmol, synthesized according to patent US 2011/59118 A1) and sodium acetate (208 mg, 2.53 mmol, CAS RN 127-09-3) in a mixture of acetone (4 mL)/H₂O (0.5 mL) was added dropwise a solution of chloroacetyl chloride (150 mg, 107 μ L, 1.33 mmol, CAS RN 79-04-9) in acetone (3 mL) between 0-5°C. After the addition the reaction mixture was stirred at RT for 1 h and subsequently evaporated to dryness giving a yellow gum. The crude product was purified by silica gel chromatography to afford the desired product as a yellow solid (385 mg, 93%). MS (ESI): m/z = 325.2 [M-H].

Step b) *rac-Benzyl (4aS,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate*

To a stirred solution of rac-Benzyl (3S,4S)-3-(2-chloroacetamido)-4-hydroxypiperidine-1-carboxylate (385 mg, 1.18 mmol) in dry THF (4 mL) was added NaH (67.9 mg, 1.7 mmol) at 0°C. The mixture was allowed to reach RT and then stirred for 90 min under an argon atmosphere. H₂O (5 mL) was added and stirring was continued for 10 min at RT. THF was removed in vacuo from the reaction mixture. The residue was treated with DCM and the organic phase was washed with H₂O and brine, dried over Na₂SO₄, filtered and then concentrated in vacuo. The residue was purified by flash chromatography (12 g reversed phase column, gradient 0-100% ACN (0.1% FA) in water (0.1% FA) to afford the desired product as a white solid (133 mg, 38.9%). MS (ESI): m/z = 291.3 [M+H]⁺.

BB7a and BB7b

4-Nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (BB7a)
and
4-nitrophenyl (4aS,8aR)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (BB7b)

To a suspension of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one; dihydrochloride salt (4.5 g, 19.6 mmol, BB1) in dry DCM (125 mL) at 0 °C was added DIPEA (6.35 g, 8.58 mL, 49.1 mmol) followed by 4-nitrophenyl carbonochloridate (4.35 g, 21.6 mmol). The reaction mixture was stirred at 0 °C for 10 min and at RT for 2 h. The crude reaction was diluted with DCM and transferred into a separating funnel for extraction with sat. aq. Na₂CO₃ solution. The organic phase was collected and the aqueous phase was back-extracted with DCM. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness to yield 6.62 g of a crude racemic product (BB7) as a yellow solid. The crude material was directly

- 159 -

submitted for a chiral SFC separation to yield enantiomer BB7b (2.72 g, second eluting enantiomer) as a yellow solid and enantiomer BB7a (3.25 g, first eluting enantiomer) as a light beige solid but contaminated with BB7b. A further SFC chiral separation was carried out to yield 2.71 g of BB7a. MS (ESI): $m/z = 322.2$ $[M+H]^+$ for both enantiomers.

5

BB8**5-tert-Butyl-2-(4-piperidylmethyl)oxazole; hydrochloride salt**

A solution of tert-butyl 4-[(5-tert-butyloxazol-2-yl)methyl]piperidine-1-carboxylate (167 mg, 518 μmol) in HCl 2M in diethyl ether (2.59 mL, 5.18 mmol) was stirred at RT for 5 h before another 1.29 mL (2.59 mmol) of HCl 2M in diethyl ether was added. The white suspension was stirred at RT overnight. The mixture was cooled down in an ice-bath, then filtered and washed with diethyl ether to get the desired compound as a colorless solid (0.126 g, 94.0%). MS (ESI): $m/z = 223.2$ $[M+H]^+$.

Step a) (5-tert-Butyloxazol-2-yl)methyl-triphenyl-phosphonium bromide

To a solution of 2-(bromomethyl)-5-(tert-butyl)oxazole (600 mg, 2.75 mmol, CAS RN 1334492-54-4) in diethyl ether (5 mL) was added triphenylphosphine (722 mg, 2.75 mmol, CAS RN 603-35-0) and the mixture was stirred at RT for 64 h. The suspension was cooled down in an ice-bath and then filtered. The filter cake was washed a small volume of cold diethyl ether to give the desired compound as a light yellow solid (0.864 g, 65.4%). MS (ESI): $m/z = 400.2$ $[M-\text{Br}+H]^+$.

Step b) tert-Butyl 4-[(5-tert-butyloxazol-2-yl)methylene]piperidine-1-carboxylate

To an ice-cold suspension of (5-tert-butyloxazol-2-yl)methyl-triphenyl-phosphonium bromide (355 mg, 739 μmol) in THF (7 mL) was added potassium tert-butyrate 1M solution in THF (738 μL , 738 μmol) and the reaction stirred at this temperature for 15 min. Then, tert-butyl 4-oxopiperidine-1-carboxylate (162 mg, 813 μmol , CAS RN 79099-07-3) was added to the turbid, orange solution and stirring was continued at 0 °C for another 15 min., then at RT for 42 h. The reaction mixture was poured on half-saturated aqueous NH_4Cl solution and EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over MgSO_4 , filtered, treated with silica gel and evaporated. The compound was purified by silica gel chromatography on a 12 g column using an MPLC system eluting with a gradient of n-heptane : EtOAc (100 : 0 to 50 : 50) to provide the desired compound as a colorless solid (0.180 mg, 76.0%). MS (ESI): $m/z = 321.3$ $[M+H]^+$.

Step c) tert-Butyl 4-[(5-tert-butyloxazol-2-yl)methyl]piperidine-1-carboxylate

- 160 -

To a solution of tert-butyl 4-[(5-tert-butyloxazol-2-yl)methylene]piperidine-1-carboxylate (180 mg, 562 μ mol) in MeOH (1 mL) and EtOAc (1 mL) was added Pd/C 10% (17.9 mg, 16.9 μ mol) and the suspension was stirred under a hydrogen atmosphere at 1.3 bar for 2 h. The suspension was filtered over a microfilter and the filtrate was evaporated to get the desired compound as a colorless oil (0.167 g; 92.2%). MS (ESI): m/z = 323.3 $[M+H]^+$.

BB12**4-[(2-Chloro-4-fluoro-phenoxy)methyl]-4-methyl-piperidine; hydrochloride salt**

To a solution of tert-butyl 4-[(2-chloro-4-fluoro-phenoxy)methyl]-4-methyl-piperidine-1-carboxylate (186 mg, 0.520 mmol) in EtOAc (1.5 mL) was added HCl in EtOAc (4 M, 1.5 mL) at 0 °C. The solution was stirred at 15 °C for 3 h. The solution was concentrated under vacuum, then dried by lyophilization to give desired product as a white solid (64.0 mg, 0.220 mmol, 40.3% yield). MS (ESI): m/z = 258 $[M+H]^+$.

Step a) tert-Butyl 4-methyl-4-(methylsulfonyloxymethyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(hydroxymethyl)-4-methyl-piperidine-1-carboxylate (500 mg, 2.14 mmol, CAS RN: 614730-97-1) in DCM (5 mL) was added NEt₃ (0.45 mL, 3.22 mmol) and methanesulfonyl chloride (0.23 mL, 3.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was washed twice with water (3 mL each) at 0 °C, and dried over Na₂SO₄. The organic layer was concentrated in vacuum to yield the desired compound as colorless oil (766 mg, 2.46 mmol, 98.5%) which was used in the next step without further purification. MS (ESI): m/z = 256 $[M-56+H]^+$.

Step b) tert-Butyl 4-[(2-chloro-4-fluoro-phenoxy)methyl]-4-methyl-piperidine-1-carboxylate

To a solution of tert-butyl 4-methyl-4-(methylsulfonyloxymethyl)piperidine-1-carboxylate (450 mg, 1.46 mmol) in DMF (5 mL) was added Cs₂CO₃ (620 mg, 1.9 mmol) and 2-chloro-4-fluorophenol (0.14 mL, 1.46 mmol) at 15 °C. The mixture was heated to 90 °C and stirred for 16 h. The reaction solution was diluted by EtOAc (10 mL), washed twice with brine (10 mL each), and dried over Na₂SO₄. The organic layer was concentrated under vacuum to give the crude product (0.7 g) as light yellow oil. The crude product was purified by prep-HPLC and dried by lyophilization to give the desired compound as colorless solid (186 mg, 0.520 mmol, 35.5% yield). MS (ESI): m/z = 302 $[M-56+H]^+$.

- 161 -

BB15**4-[(2-Chloro-4-fluoro-phenoxy)methyl]-4-fluoro-piperidine; hydrochloride salt**

To a solution of tert-butyl 4-[(2-chloro-4-fluoro-phenoxy)methyl]-4-fluoro-piperidine-1-carboxylate (220 mg, 0.610 mmol) in EtOAc (2 mL) was added HCl/EtOAc (0.4 mL, 3.6 mmol) at 0 °C. The solution was stirred at 15 °C for 2.5 h. The solution was concentrated in vacuo, then dried by lyophilization to give desired product as a white solid (136.7 mg, 75.4%).

Step a) tert-Butyl 4-fluoro-4-(methylsulfonyloxymethyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate (500 mg, 2.14 mmol) in DCM (5 mL) was added NEt₃ (0.45 mL, 3.22 mmol) and methanesulfonyl chloride (0.23 mL, 3 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was washed twice with H₂O (3 mL each) at 0 °C, and dried over Na₂SO₄. The organic layer was concentrated to provide the compound as a colorless oil (766 mg, 98.5%) which was used in next step without further purification. MS (ESI): m/z = 256 [M-56+H]⁺.

Step b) tert-Butyl 4-[(2-chloro-4-fluoro-phenoxy)methyl]-4-fluoro-piperidine-1-carboxylate

To a solution of tert-butyl 4-fluoro-4-(methylsulfonyloxymethyl)piperidine-1-carboxylate (383 mg, 1.23 mmol) in DMF (4 mL) was added Cs₂CO₃ (601 mg, 1.85 mmol), 2-chloro-4-fluorophenol (0.13 mL, 1.35 mmol) and 2-chloro-4-fluorophenol (0.13 mL, 1.35 mmol) at 15 °C. The mixture was heated to 85 °C and stirred for 16 h. The mixture was extracted three times with EtOAc (5 mL each) at 15 °C, the combined organic layers washed three times with brine (5 mL each), dried over Na₂SO₄, filtered and evaporated. The crude product was purified by preparative HPLC and dried by lyophilization to give the desired compound as light yellow oil (275 mg, 0.760 mmol, 61.5%). MS (ESI): m/z = 306 [M-56+H]⁺.

BB16**rac-(4aR,8aS)-6-(4-(Hydroxymethyl)piperidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one**

To a suspension of rac-(4aR,8aS)-hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one; dihydrochloride salt (450 mg, 1.96 mmol, BB1) in dry DMF (9 mL) cooled down to 0 °C under an inert atmosphere was added DIPEA (787 mg, 1.06 mL, 6.09 mmol) and 4-nitrophenyl carbonochloridate (475 mg, 2.36 mmol). The reaction mixture was stirred at 0 °C for 30 min. Piperidin-4-ylmethanol (271 mg, 2.36 mmol, CAS RN 6457-49-4) and DIPEA (381 mg, 515 µL,

- 162 -

2.95 mmol) were added, and the reaction mixture was stirred at 100 °C for 14 h. Volatiles were removed in vacuo and the crude residue was purified by flash chromatography with a 24 g SiO₂ column using an eluent mixture of DCM and MeOH (5% to 25%). The crude product was submitted for SFC purification to yield the desired compound as a light yellow oil (338 mg). MS (ESI): $m/z = 298.3$ $[M+H]^+$.

BB17**4,4-Difluoro-1-(piperidin-4-ylmethyl)piperidine; dihydrochloride salt**

To a solution of tert-butyl 4-((4,4-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate (453 mg, 1.07 mmol) in dioxane (2.5 mL) was added HCl (4.0M solution in dioxane) (2.67 mL, 10.7 mmol) and the reaction mixture was stirred at room temperature for 14 h. Volatiles were removed in vacuo to yield the desired compound as a white solid (286 mg) which was used in the next step without further purification. MS (ESI): $m/z = 219.3$ $[M+H]^+$.

Step a) tert-Butyl 4-((4,4-difluoropiperidin-1-yl)methyl)piperidine-1-carboxylate

To a solution of a tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (0.5 g, 1.8 mmol, CAS RN: 158407-04-6) in dry DMF (4 mL) was added 4,4-difluoropiperidine; dihydrochloride salt (425 mg, 2.7 mmol) and Cs₂CO₃ (1.17 g, 3.59 mmol). The reaction mixture was then stirred at 80 °C under microwave radiation for 60 min. Insolubles were removed by filtration, the filtrate was then concentrated in vacuo, and the obtained crude residue was suspended in DCM and filtered through a pad of Celite to give a crude yellow oil, which was purified by flash chromatography on a SiO₂ column, using an eluent mixture of n-heptane and EtOAc (10% to 60%) to yield the desired product as a colorless oil (453 mg). The compound was carried forwards to the next step without further purification. MS (ESI): $m/z = 319.3$ $[M+H]^+$.

BB19**N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-amine; bis(trifluoroacetate) salt**

To a solution of tert-butyl 3-(((2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate (1 g, 2.42 mmol) in DCM (10mL) was added TFA (5.53 g, 3.74 mL, 48.5 mmol). The resulting reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* to yield the desired compound as colorless oil (1.29 g). MS (ESI): $m/z = 313.5$ $[M+H]^+$.

- 163 -

Step a) *tert*-Butyl 3-(((2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate

To a dry flask with septum was added under nitrogen *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (0.852 g, 4.57 mmol), triethylamine (1.39 g, 1.91 mL, 13.7 mmol), 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one (1.11 g, 780 μ L, 4.57 mmol), and dry DCM (28 mL).
Titanium tetrachloride 1 M in DCM (2.29 mL, 2.29 mmol) was added via a syringe to the ice-cooled flask (exothermic). The reaction was stirred overnight at RT, then carefully quenched with a solution of NaCNBH₃ (862 mg, 13.7 mmol) in MeOH (8.79 g, 11.1 mL, 274 mmol) and stirred overnight. The reaction was basified with sat. NaHCO₃ solution. The obtained insoluble material was filtered off over celite. Extraction of the filtrate with DCM, the organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in *n*-heptane to yield *tert*-butyl 3-(((2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate which was used in the next step without further purification.

15

BB26**3-Chloro-4-(4-piperidylmethoxy)benzonitrile; hydrochloride salt**

To a solution of *tert*-butyl 4-[(2-chloro-4-cyano-phenoxy)methyl]piperidine-1-carboxylate (300 mg, 0.860 mmol) in EtOAc (3 mL) was added HCl in EtOAc (4M, 2.0 mL) at 0 °C. The solution was stirred at 15 °C for 3 h. The solution was concentrated in vacuo, then dried by lyophilization to give desired product as a white solid (238 mg, 0.830 mmol, 96% yield). MS (ESI): m/z = 251 [M+H]⁺.

Step a) *tert*-Butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate

To a solution of *N*-Boc-4-piperidinemethanol (10.0 g, 46.5 mmol, 1 eq) in DCM (200 mL) was added NEt₃ (7.04 g, 69.7 mmol), then methanesulfonyl chloride (3.95 mL, 51.1 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 1 h. The mixture was poured into ice-water, the aqueous phase was extracted twice with DCM (50 mL each). The combined organic layers were washed with brine (50 mL), and concentrated under vacuum. The residue was directly used without any purification. MS (ESI): m/z = 238.1 [M+H]⁺.

Step b) *tert*-Butyl 4-[(2-chloro-4-cyano-phenoxy)methyl]piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(methylsulfonyloxymethyl)piperidine-1-carboxylate (700 mg, 2.39 mmol) in DMF (7 mL) was added Cs₂CO₃ (855 mg, 2.62 mmol) and 3-chloro-4-

- 164 -

hydroxybenzonitrile (0.25 mL, 2.39 mmol) at 15 °C. The mixture was heated to 85 °C and stirred for 16 h. The reaction mixture was diluted with EtOAc (8 mL) at 15 °C, washed three times with brine (8 mL each), the combined organic layers were dried over Na₂SO₄ and evaporated. The colorless residue (0.75 g) was purified by prep-HPLC and dried by lyophilization to give the desired product as a white solid (531 mg, 1.51 mmol, 53.4 %). MS (ESI): m/z = 295 [M-56+H]⁺.

BB27**4-((4-(Trifluoromethyl)-1H-imidazol-1-yl)methyl)piperidine; hydrochloride salt**

To a solution of tert-butyl 4-((4-(trifluoromethyl)-1H-imidazol-1-yl)methyl)piperidine-1-carboxylate (430 mg, 1.29 mmol) in dioxane (3 mL) was added HCl (4 M solution in dioxane; 3.22 mL, 12.9 mmol) and the reaction mixture was stirred at RT for 14 h. Volatiles were removed in vacuo to give the crude product (362 mg) which was used in the next step without further purification. MS (ESI): m/z = 234.2 [M+H]⁺.

Step a) *tert-Butyl 4-((4-(trifluoromethyl)-1H-imidazol-1-yl)methyl)piperidine-1-carboxylate*

To a solution of a tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (0.5 g, 1.8 mmol, CAS RN: 158407-04-6) in dry DMF (4 mL) was added 4-(trifluoromethyl)-1H-imidazole (293 mg, 2.16 mmol) and Cs₂CO₃ (1.17 g, 3.59 mmol). The reaction mixture was then stirred at 80 °C for 14 h. Insolubles were removed by filtration, and the filtrate was concentrated in vacuo. The crude residue was suspended in DCM and filtered through a pad of Celite to give a yellow oil, which was purified by flash chromatography with a SiO₂ column, using an eluent mixture of n-heptane and EtOAc (10% to 90%). This yielded the first fraction (301 mg) of the desired product as a colorless oil, and a second fraction (261 mg) of a mixture of the desired product with impurities. The second fraction was submitted for SFC purification, and the purified product was combined with the first fraction to yield 430 mg of the desired product as a colorless oil. MS (ESI): m/z = 334.2 [M+H]⁺.

BB29**3-((2-Chloro-4-(trifluoromethyl)phenoxy)methyl)azetidine**

Trifluoroacetic acid (2 g, 1.35 mL, 17.5 mmol) was added to a solution of tert-butyl 3-((2-chloro-4-(trifluoromethyl)phenoxy)methyl)azetidine-1-carboxylate (320 mg, 875 μmol) in DCM (4.37 mL) and the solution was stirred at RT for 2 h. The solvent was removed under reduced

- 165 -

pressure and the resulting pale oil (470 mg) was diluted with EtOAc and washed with aq. Na₂CO₃ solution. The aqueous phase was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford the compound as a yellow oil (259 mg, 877 µmol). MS (ESI): m/z = 266.1 [M+H]⁺.

Step a) *tert*-Butyl 3-((2-chloro-4-(trifluoromethyl)phenoxy)methyl)azetidine-1-carboxylate

To a solution of 2-chloro-4-(trifluoromethyl)phenol (525 mg, 357 µL, 2.67 mmol), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (500 mg, 2.67 mmol, CAS RN: 142253-56-3) and triphenylphosphine (770 mg, 2.94 mmol) in DCM (13.4 mL) was added DIAD (594 mg, 571 µL, 2.94 mmol) dropwise and the reaction was stirred at RT for 17 h. The reaction mixture was quenched by addition of sat. aq. NaHCO₃ solution (20 mL). The phases were separated and the aq. phase was extracted with DCM twice. The combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The residue was dissolved in EtOH (7 mL) and a homogeneous solution of zinc chloride (218 mg, 1.6 mmol) in EtOH (2 mL, 0.5 M) was added. The mixture was stirred for 30 min during which a white solid precipitated. The white solid was filtered off and washed with EtOH. The filtrate was concentrated to give a yellow oil with a white precipitate. The crude was immobilized on Isolute and purified by column chromatography (40 g, 0 to 30 % EtOAc in heptanes) to afford the title compound as a white solid (764.6 mg, 1.99 mmol, 74.4%). MS (ESI): m/z = 310.1 [M-56+H]⁺.

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BB30

N-benzyl-N-(2-hydroxyethyl)piperidine-4-carboxamide hydrochloride

To a solution of *tert*-butyl 4-(benzyl(2-hydroxyethyl)carbamoyl)piperidine-1-carboxylate (0.080 g, 221 µmol) in DCM (1 mL) was added HCl 2 M in diethyl ether (1.1 mL, 2.21 mmol). The resultant reaction mixture was stirred at RT for 1 h and then concentrated under vacuum at 22 °C to yield the desired compound as a colorless oil (63 mg) (BB30). MS (ESI): m/z = 263.18 [M+H]⁺.

Step a) *tert*-Butyl 4-(benzyl(2-hydroxyethyl)carbamoyl)piperidine-1-carboxylate

In a 10 mL glastube, to 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (0.1 g, 436 µmol) in DMF (2 mL) was added 2-(benzylamino)ethan-1-ol (72.5 mg, 480 µmol), DIPEA (169 mg, 229 µL, 1.31 mmol) and HATU (182 mg, 480 µmol), stirred at RT for 1 h and extracted with

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- 166 -

H₂O/DCM. The crude material was purified by flash chromatography (silica gel, 20 g, 50% to 100% EtOAc in n-heptane) to yield the compound as a light yellow oil (156 mg).

BB31

N-benzylpiperidine-4-carboxamide hydrochloride

- 5 tert-Butyl 4-(benzylcarbamoyl)piperidine-1-carboxylate (0.138 g, 433 μ mol) was dissolved in DCM (1 mL) and HCl 2M in diethyl ether (2.17 mL, 4.33 mmol) was added. The reaction mixture was stirred for 2 h. The residue was concentrated *in vacuo* to yield the compound (108 mg) as a colorless oil. MS (ESI): m/z = 219.15 [M+H]⁺.

Step a) *tert-Butyl 4-(benzylcarbamoyl)piperidine-1-carboxylate*

- 10 In a 10 mL glastube, to 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (0.1 g, 436 μ mol) in DMF (2 mL) was added phenylmethanamine (51.4 mg, 52.4 μ L, 480 μ mol), DIPEA (169 mg, 229 μ L, 1.31 mmol) and HATU (182 mg, 480 μ mol), stirred at RT for 2 h and extracted with H₂O/DCM. The crude material was purified by flash chromatography (silica gel, 20 g, 50% to 100% EtOAc in n-heptane) to yield the compound as a colorless oil (0.138 g).

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BB32

4-((4-(tert-Butyl)-1H-pyrazol-1-yl)methyl)piperidine; hydrochloride salt

- To a solution of tert-butyl 4-((4-(tert-butyl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate (100 mg, 311 μ mol) in dioxane (1 mL) was added HCl (4.0M solution in dioxane; 1.17 mL, 4.67 mmol) and the reaction mixture was stirred at RT for 14 h. Volatiles were removed *in vacuo* to give 84 mg of a crude product which was used in the next step without further purification. MS (ESI): m/z = 222.3 [M+H]⁺.
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Step a) *tert-Butyl 4-((4-(tert-butyl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate*

- To a solution of a tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (0.5 g, 1.8 mmol, CAS RN 158407-04-6) in dry DMF (4 mL) was added 4-(tert-butyl)-1H-pyrazole (268 mg, 2.16 mmol) and NaH (86.3 mg, 2.16 mmol). The reaction mixture was stirred at 80 °C for 14 h. The reaction was quenched by addition of few drops of sat. aq. NH₄Cl solution, and transferred into a separating funnel for partitioning between DCM and sat. aq. NaHCO₃ solution. The organic phase was collected and the aqueous phase was back-extracted with DCM. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness. The crude material was
- 25

- 167 -

purified by flash chromatography with a SiO₂ column, eluting with a mixture of n-heptane and EtOAc (5% to 60%) to yield the desired compound as a colorless oil (102 mg). MS (ESI): m/z = 322.3 [M+H]⁺.

BB33**5 (2R,4aR,8aS)-2-methyl-4a,5,6,7,8,8a-hexahydro-4H-pyrido[4,3-b][1,4]oxazin-3-one**

To a solution of 6-benzyl-2-methyl-5,6,7,8-tetrahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (Isomer A, 1.10 g, 4.26 mmol) in EtOAc (16 mL) and MeOH (16 mL) was added under argon Pd-C (227 mg, 213 μmol) and the suspension was stirred under a hydrogen atmosphere (balloon) at 1 bar for 24 h. The suspension was filtered over a microglass filter and washed with 20 mL EtOAc under inert gas. The filtrate was evaporated to give BB33 as a colorless solid (715 mg). MS (ESI): m/z = 170.8 [M+H]⁺. Note: Only the single enantiomer formed during the reduction.

Step a) 2-Methyl-4H-pyrido[4,3-b][1,4]oxazin-3-one

To a solution of 3-aminopyridin-4-ol (2.5 g, 22.7 mmol) in DMF (100 mL) was added dropwise 2-chloropropanoyl chloride (3.03 g, 2.31 mL, 23.8 mmol) and the mixture was stirred at RT for 30 min. After addition of K₂CO₃ (7.84 g, 56.8 mmol), the suspension was heated to 100 °C (oil bath) for 20 h. The DMF was removed in vacuo, then 100 mL EtOAc were added and stirred at RT for 10 min, and it was washed with 50 mL H₂O, extracted 3 times with EtOAc. The organic phases were combined, dried with MgSO₄ and concentrated under vacuo to yield 3.72 g of 2-methyl-4H-pyrido[4,3-b][1,4]oxazin-3-one which was used in the next step without further purification.

Step b) 6-Benzyl-2-methyl-3-oxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazin-6-ium bromide

A suspension of 2-methyl-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (3.72 g, 22.7 mmol) in DCM (32 mL) and MeOH (8 mL) was treated with (bromomethyl)benzene (4.65 g, 3.23 mL, 27.2 mmol) and the mixture was stirred at RT for 60 h. A suspension formed, which was cooled down to 0°C, 20 mL n-hexane were added and then the precipitate was filtered. The residue was washed with 15 mL of cold DCM/n-hexane to yield the compound as an off-white solid (5.2 g). MS (ESI): m/z = 255 [M+H]⁺.

Step c) 6-Benzyl-2-methyl-5,6,7,8-tetrahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one

To a suspension of 6-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazin-6-ium bromide (5.2 g, 15.5 mmol) in EtOH (38 mL) was added in portions NaBH₄ (763 mg, 20.2

- 168 -

mmol) (exothermic, 22°C to 30°C, yellow suspension). After the exothermic reaction faded out the mixture was stirred at room temperature for 3 h, then at 60 °C for 1h and at 22 °C for 1h. The reaction mixture was evaporated, partitioned between H₂O and EtOAc and the layers were separated. The aqueous layer was extracted once with EtOAc. The organic layers were washed
5 twice with H₂O, dried over MgSO₄, filtered, treated with silica gel and evaporated. The compound was purified by silica gel chromatography on a 120 g column using an MPLC system eluting with a gradient of n-heptane : EtOAc (50 to 100 in 30 min.) to provide the compound as a light yellow solid (2.48 g) which could be used in the following step without further purification.

10 Step d) *6-Benzyl-2-methyl-5,6,7,8-tetrahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one*

The enantiomers were separated by preparative chiral HPLC (Chiralcel OD column) using an isocratic mixture of EtOH (containing 0.05% of NH₄OAc) : n-heptane (10 : 90). The fractions were evaporated to provide the desired compounds as light yellow solids (Isomer A 1.17 g, Isomer B 1.10 g).

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BB34**N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)ethan-1-amine**

In a 100 mL two-necked flask, benzyl 3-(((2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate (0.913 g, 2.05 mmol) was dissolved in a mixture of THF (5 mL) and MeOH (5 mL). Pd/C 10% (109 mg, 102 µmol) was
20 added under argon. The flask was purged and backfilled with H₂ gas (3 times). The reaction mixture was then stirred at 25°C for 4 h. The suspension was filtered over decalite, concentrated and the resulting title compound (611 mg, colorless oil) used directly for the next step. MS (ESI): m/z = 313.4 [M+H]⁺.

25 Step a) *Benzyl 3-(((2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate*

To a dry flask with septum was added benzyl 3-(aminomethyl)azetidine-1-carboxylate (0.5 g, 2.27 mmol), NEt₃ (689 mg, 949 µL, 6.81 mmol), 2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)ethan-1-one (554 mg, 391 µL, 2.27 mmol), and dry DCM (15 mL). Titanium tetrachloride 1M in DCM (1.13 mL, 1.13 mmol) was added via a syringe and the flask
30 was cooled in an ice bath (exothermic). The reaction was stirred at RT overnight, carefully quenched with a solution of NaCNBH₃ (428 mg, 6.81 mmol) in MeOH (4.36 g, 5.51 mL, 136

- 169 -

mmol) and acetic acid (0.1 mL) and stirred at RT overnight. The reaction was basified with sat. aq. NaHCO₃ solution and the insoluble material obtained was filtered away over celite. The filtrate was extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in n-heptane) to yield the desired compound as a colorless oil (913 mg). MS (ESI): m/z = 447.2 [M+H]⁺.

BB35**N-(azetidin-3-ylmethyl)-1-(2,4-dichlorophenyl)-2,2,2-trifluoroethan-1-amine**

In a 100 mL two-necked flask, benzyl 3-(((1-(2,4-dichlorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carboxylate (0.660 g, 1.48 mmol) was dissolved in EtOAc (20 mL) to give a colorless solution. Pd/C 10% (78.5 mg, 73.8 μmol) was added under argon. The flask was purged and backfilled with H₂ gas (3 times). The reaction mixture was stirred at 25 °C for 4 h. LC-MS showed a mixture of the title product N-(azetidin-3-ylmethyl)-1-(2,4-dichlorophenyl)-2,2,2-trifluoroethan-1-amine together with the dehalogenated side-products N-(azetidin-3-ylmethyl)-1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-amine and N-(azetidin-3-ylmethyl)-1-phenyl-2,2,2-trifluoroethan-1-amine. The reaction mixture was filtered over decalite, concentrated *in vacuo* and used directly for the next step.

Step a) *Benzyl 3-[[[1-(2,4-dichlorophenyl)-2,2,2-trifluoro-ethylidene]amino]methyl]azetidine-1-carboxylate*

To a dry flask with septum was added under nitrogen benzyl 3-(aminomethyl)azetidine-1-carboxylate (0.500 g, 2.27 mmol, CAS RN 1016731-24-0), NEt₃ (689 mg, 949 μL, 6.81 mmol), 1-(2,4-dichlorophenyl)-2,2,2-trifluoroethan-1-one (556 mg, 2.27 mmol, and dry DCM (16.4 mL). Titanium tetrachloride (1 M solution in DCM; 1.13 mL, 1.13 mmol) was added via a syringe to the ice-cooled flask (exothermic). The reaction was stirred at RT overnight, carefully quenched with a solution of NaCNBH₃ (428 mg, 6.81 mmol) in MeOH (4.36 g, 5.51 mL, 136 mmol) and stirred for 6 h. LCMS indicated the reaction stopped at the imine.

The reaction was basified with sat. NaHCO₃. The obtained insoluble material was filtered over celite and the filtrate was extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in n-heptane) to give the desired compound as a colorless oil (1g).

- 170 -

Step b) *Benzyl 3-(((1-(2,4-dichlorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carboxylate*

In a 25 mL two-necked flask, benzyl 3-[[[1-(2,4-dichlorophenyl)-2,2,2-trifluoroethylidene]amino]methyl]azetidine-1-carboxylate (1 g, 2.25 mmol) was dissolved in THF (10 mL) and MeOH (1 mL) to give a colorless solution. Acetic acid (135 mg, 129 μ L, 2.25 mmol) and NaCNBH₃ (423 mg, 6.74 mmol) were added. The reaction mixture was stirred at 25°C for 6 h. The reaction was basified with sat. NaHCO₃. The obtained insoluble material was filtered over celite and the filtrate was extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in heptane) to afford the title compound as a colorless oil (660 mg) which used in the next step without further purification.

BB36

cis-4-((2-Chloro-4-fluorophenoxy)methyl)-3-methylpiperidine; hydrochloride salt

tert-Butyl cis-4-((2-chloro-4-fluorophenoxy)methyl)-3-methylpiperidine-1-carboxylate (115 mg, 321 μ mol) was dissolved in DCM (2 mL) and 2M HCl in ether (161 μ L, 321 μ mol) was added. The reaction was stirred at RT for 6 h, then the solvent was removed *in vacuo*. The crude product (94 mg, colorless foam) was used in the next step without purification. MS (ESI): m/z = 258.2 [M+H]⁺.

Step a) tert-Butyl cis-4-((2-chloro-4-fluorophenoxy)methyl)-3-methylpiperidine-1-carboxylate

Mitsunobu reaction: In a 50mL four-necked sulphonation flask under argon, tert-butyl cis-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (840 mg, 3.66 mmol) was dissolved in THF (15 mL), 2-chloro-4-fluorophenol (590 mg, 439 μ L, 4.03 mmol) and triphenylphosphine (1.06 g, 4.03 mmol) were added. The clear solution was stirred 5 min at RT, then cooled to 0-2°C and DEAD (702 mg, 638 μ L, 4.03 mmol) was added over 10 min. The reaction mixture was stirred at 2-4 °C for 1 h, then stirred over night at RT. 50 mL diethylether were added, the mixture was washed with 2x 25 mL water, 3x 20 mL 1 N NaOH, 1x 20 mL brine, the organic phase was dried with Mg₂SO₄, after removing the solvent *in vacuo* 2.7 g yellow oil were obtained. To remove the triphenylphosphin oxide, the residue was stirred in n-Heptane/diethylether for 30 min, the solids was filtered away, the filtrate was concentrated *in vacuo*, to obtain 1.8 g crude product that was purified by flash chromatography (silica gel, 50 g, 0% to 30% EtOAc in

- 171 -

heptane, 40 min): tert-butyl cis-4-((2-chloro-4-fluorophenoxy)methyl)-3-methylpiperidine-1-carboxylate, 1.21 g white solid.

BB39**3-((2-Fluoro-4-(trifluoromethoxy)benzyl)oxy)azetidine; trifluoroacetate salt**

5 To a solution of tert-butyl 3-((2-fluoro-4-(trifluoromethoxy)benzyl)oxy)azetidine-1-carboxylate (415 mg, 1.14 mmol) in DCM (5 mL) was added TFA (1.3 g, 875 μ L, 11.4 mmol) and the reaction mixture was stirred at RT for 3 h. Volatiles were removed in vacuo to yield 455 mg of a light yellow oil that was used in the next step without further purification. MS (ESI): m/z = 266.1 $[M+H]^+$.

10 Step a) *tert-Butyl 3-((2-fluoro-4-(trifluoromethoxy)benzyl)oxy)azetidine-1-carboxylate*

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (200 mg, 1.15 mmol) in dry THF (5 mL) was added potassium tert-butoxide (1.65 M solution in THF, 735 μ L, 1.21 mmol) and the reaction mixture was stirred at RT for 15 min followed by addition of 1-(bromomethyl)-2-fluoro-4-(trifluoromethoxy)benzene (315 mg, 1.15 mmol). The reaction mixture was then stirred
15 at room temperature for 14 h. The crude reaction was diluted with EtOAc and extracted with aq. 1 M NaHCO_3 solution, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over NaSO_4 and evaporated down to dryness to yield 418 mg of the crude product which was used in the next step without further purification. MS (ESI): m/z = 310.1 $[M-56+H]^+$.

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BB40**N-(azetidin-3-yl)-2-chloro-4-fluoro-benzamide; trifluoroacetate salt**

To a solution of tert-butyl 3-[(2-chloro-4-fluoro-benzoyl)amino]azetidine-1-carboxylate (346 mg, 1.05 mmol) in DCM (3.5 mL) was added TFA (0.7 mL) at 0 °C. The solution was stirred at 0 °C for 2 h. The reaction was concentrated in vacuum to give the crude product (600 mg) as
25 light yellow oil. The crude product was purified by prep-HPLC (0.1% TFA in H_2O and MeCN) and dried by lyophilization to give desired compound as colorless solid (223 mg, 0.650 mmol, 59.2% yield). MS (ESI): m/z = 229 $[M+H]^+$.

Step a) *tert-Butyl 3-[(2-chloro-4-fluoro-benzoyl)amino]azetidine-1-carboxylate*

- 172 -

To a solution of 2-chloro-4-fluorobenzoic acid (500 mg, 2.86 mmol), 1-Boc-3-(amino)azetidine (493 mg, 2.86 mmol) and DMAP (35.0 mg, 0.290 mmol) in THF (10 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (714 mg, 3.72 mmol) at 0 °C. The mixture was heated to 30 °C and stirred for 16 h. The reaction was diluted with EtOAc (5 mL),
 5 washed three times with brine (10 mL each) and dried over Na₂SO₄. The organic layer was concentrated in vacuum to give the crude product (0.72 g) as yellow oil. The crude product was purified by prep-HPLC and dried by lyophilization to give desired compound as a colorless solid (546 mg, 1.66 mmol, 57.9 % yield). MS (ESI): m/z = 273 [M-56+H]⁺.

BB41

10 **N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-N-methyl-1-[4-(trifluoromethyl)phenyl]ethanamine;
 trifluoroacetate salt**

To a solution of tert-butyl 3-((methyl(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate (0.256 g, 600 μmol) in DCM (5 mL) was added TFA (1.37 g, 925 μL, 12 mmol). The resulting reaction mixture was
 15 stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* to provide the desired compound as a colorless oil (268 mg). MS (ESI): m/z = 327.4 [M+H]⁺.

Step a) *tert-Butyl 3-((methyl(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)amino)methyl)azetidine-1-carboxylate*

To a dry flask with septum and 3 Å molecular sieves was added under nitrogen tert-butyl 3-
 20 ((methylamino)methyl)azetidine-1-carboxylate (0.300 g, 293 μL, 1.5 mmol), TEA (455 mg, 626 μL, 4.49 mmol), 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one (363 mg, 255 μL, 1.5 mmol), and dry DCM (9.86 mL). Titanium tetrachloride 1 M in DCM (749 μL, 749 μmol) was added via a syringe to the ice-cooled flask (exothermic). The reaction was stirred at RT overnight, carefully quenched with a solution of NaCNBH₃ (282 mg, 4.49 mmol) in MeOH
 25 (3.64 mL, 89.9 mmol) and stirred at RT for 2 h. The reaction was basified with sat. NaHCO₃ solution. The obtained insoluble material was filtered over celite and the filtrate was extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in n-heptane) and was used directly for the next step.

- 173 -

BB42**N-methyl-N-(piperidin-4-yl)-1-(3-(trifluoromethyl)phenyl)cyclopropane-1-carboxamide hydrochloride**

To a solution of tert-butyl 4-(N-methyl-1-(3-(trifluoromethyl)phenyl)cyclopropane-1-carboxamido)piperidine-1-carboxylate (0.301 g, 706 μ mol) in DCM (2 mL) was added HCl 2M in diethyl ether (3.53 mL, 7.06 mmol). The resulting reaction mixture was stirred at RT overnight and then concentrated under vacuum at 22°C to give 256 mg of BB42 as off white solid, MS (ESI): $m/z = 327.2 [M+H]^+$

Step a) *tert-butyl 4-(N-methyl-1-(3-(trifluoromethyl)phenyl)cyclopropane-1-carboxamido)piperidine-1-carboxylate*

In a 20 mL glastube, to 1-(3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (177 mg, 770 μ mol) in DMF (5 mL) was added HATU (293 mg, 770 μ mol) and DIPEA (271 mg, 367 μ L, 2.1 mmol). The reaction mixture was stirred for 15 min and then tert-butyl 4-(methylamino)piperidine-1-carboxylate (0.15 g, 700 μ mol) was added. The reaction mixture was stirred at RT for 2 hours. The reaction mixture was extracted with Water/DCM. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 100% EtOAc in heptane) to yield the desired compound as a light yellow oil (301mg). MS (ESI): $m/z = 371.2 [M-56+H]^+$

BB43

2-(2-chloro-3-(trifluoromethyl)phenyl)-N-methyl-N-(piperidin-4-yl)acetamide; hydrochloride salt

To a solution of tert-butyl 4-(2-(2-chloro-3-(trifluoromethyl)phenyl)-N-methylacetamido)piperidine-1-carboxylate (0.301 g, 692 μ mol) in DCM (2 mL) was added HCl (3.46 mL, 6.92 mmol). The resulting reaction mixture was stirred at RT for 2 days and then concentrated under vacuum at 22 °C to yield 252 mg of BB43 as off white solid. MS (ESI): $m/z = 335.1 [M+H]^+$.

Step a) *tert-butyl 4-(2-(2-chloro-3-(trifluoromethyl)phenyl)-N-methylacetamido)piperidine-1-carboxylate*

In a 20mL glass tube, to 2-(2-chloro-3-(trifluoromethyl)phenyl)acetic acid (184 mg, 770 μ mol) in DMF (5 mL) was added HATU (293 mg, 770 μ mol), DIPEA (271 mg, 367 μ L, 2.1 mmol).

- 174 -

The reaction mixture was stirred for 15 min and then tert-butyl 4-(methylamino)piperidine-1-carboxylate (0.150 g, 700 μ mol) was added. The reaction mixture was stirred at RT for 2 hours, and then extracted with Water/DCM. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 100% EtOAc in heptane) to yield tert-butyl 4-(2-(2-chloro-3-(trifluoromethyl)phenyl)-N-methylacetamido)piperidine-1-carboxylate as light yellow oil, 301 mg, MS (ESI): $m/z = 379.1$ $[M-56+H]^+$

BB44**2-(2-Chloro-5-(trifluoromethyl)phenyl)-N-methyl-N-(piperidin-4-yl)acetamide; hydrochloride salt**

10 Synthesized from 2-(2-chloro-5-(trifluoromethyl)phenyl)acetic and tert-butyl 4-(methylamino)piperidine-1-carboxylate. See synthesis of BB43 for details. MS (ESI): $m/z = 335.1$ $[M+H]^+$.

BB46**3-Methyl-5-(piperidin-4-ylmethoxy)-2-(trifluoromethyl)pyridine; dihydrochloride salt**

15 In a 25 mL tube tert-butyl 4-(((5-methyl-6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carboxylate (87 mg, 232 μ mol) was dissolved in DCM (2 mL) and then HCl in ether 2M (697 μ L, 1.39 mmol) was added, the reaction mixture was stirred 12 h at RT. The mixture was concentrated in vacuum, yielding 80 mg of BB46 as a white solid. MS (ESI): $m/z = 275.2$ $[M+H]^+$.

20 Step a) *tert-Butyl 4-(((5-methyl-6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carboxylate*

In a 5 mL tube, tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (80.7 mg, 375 μ mol) was dissolved in DMF (1.5 mL), then NaH in Oil 60% (18 mg, 450 μ mol) was added at room temperature, the mixture was stirred for 20 min, then 5-bromo-3-methyl-2-(trifluoromethyl)pyridine (90 mg, 60 μ L, 375 μ mol) was added, and it was stirred for 2 hr at RT, yielding a brown solution. 10 mL sat. NH_4Cl were added, it was extracted with water/ethyl acetate, dried over $MgSO_4$, the solvent was removed at 40 °C/150 mbar. The crude product was purified by flash chromatography (silica gel, 20 g, 0 to 40% EtOAc in n-heptane, in 35 min) to yield 87 mg of tert-butyl 4-(((5-methyl-6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carboxylate. MS (ESI): $m/z = 319.2$ $[M-56+H]^+$

- 175 -

BB58**N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-amine**

In a 100 mL two-necked flask, benzyl 3-(((1-(2-chloro-4-fluorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carboxylate (707 mg, 1.64 mmol) was combined with THF (5 mL) and MeOH (5 mL) to give a colorless solution. Pd/C 10% (87.3 mg, 82.1 μ mol) was added under argon. The flask was purged and backfilled with H₂ (3 times). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered over decalite, concentrated and used directly for the next step. Colorless oil (472 mg). MS (ESI): m/z = 263.2 [M+H]⁺ (the ortho-chlorine was lost during the hydrogenation).

Step a:) *Benzyl 3-(((1-(2-chloro-4-fluorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carboxylate*

To a dry flask under a stream of nitrogen was added benzyl 3-(aminomethyl)azetidine-1-carboxylate (0.5 g, 2.27 mmol), triethylamine (689 mg, 949 μ L, 6.81 mmol), 1-(2-chloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone (519 mg, 2.27 mmol), and dry DCM (15 mL). Titanium tetrachloride 1M in DCM (1.13 mL, 1.13 mmol) was added via a syringe to the ice-cooled flask (exothermic). The reaction was stirred overnight at RT, carefully quenched with a methanolic solution of sodium cyanoborohydride (428 mg, 6.81 mmol) in methanol (4.36 g, 5.51 mL, 136 mmol) + Acetic Acid (0.1 mL) and stirred overnight at RT. The reaction was basified with sat. NaHCO₃. The insoluble material obtained was filtered away over celite, the filtrate was extracted with DCM, the organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated. Purification: The crude material was purified by flash chromatography (silica gel, 50 g, 0% to 50% EtOAc in heptane) to yield 707 mg of Benzyl 3-(((1-(2-chloro-4-fluorophenyl)-2,2,2-trifluoroethyl)amino)methyl)azetidine-1-carboxylate as a colorless oil. MS (ESI): m/z = 431.2 [M+H]⁺.

BB59**2,2,2-Trifluoro-1-(piperidin-4-yl)-N-(3-(trifluoromethyl)benzyl)ethan-1-amine;
hydrochloride salt**

To a solution of tert-butyl 4-(2,2,2-trifluoro-1-((3-(trifluoromethyl)benzyl)amino)ethyl)piperidine-1-carboxylate (0.140 g, 318 μ mol) in DCM (2 mL) was added HCl 2M in diethyl ether (1.59 mL, 3.18 mmol). The resulting reaction mixture was stirred at RT overnight and then concentrated under vacuum at 22 °C to yield 119 mg of the title compound as off-white solid. MS (ESI): m/z = 340.8 [M+H]⁺.

- 176 -

Step a) *tert*-Butyl 4-(2,2,2-trifluoro-1-((3-(trifluoromethyl)benzyl)amino)ethyl)piperidine-1-carboxylate

A solution of *tert*-butyl 4-(1-amino-2,2,2-trifluoroethyl)piperidine-1-carboxylate (0.150 g, 531 μ mol) and 3-(trifluoromethyl)benzaldehyde (92.5 mg, 71.1 μ L, 531 μ mol) in 1,2-DCE (1 mL) was stirred for 1 hour at RT. Sodium triacetoxyborohydride (225 mg, 1.06 mmol) was then added at 0°C, and the reaction mixture was stirred at RT overnight. The reaction mixture was poured onto sat. NaHCO₃ and extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 100% EtOAc in heptane) to yield 145 mg of the desired compound as a colorless oil. MS (ESI): m/z = 383.1 [M-56+H]⁺

BB69**2-methyl-3-((4-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt**

To a solution of *tert*-butyl 2-methyl-3-((4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate (0.36 g, 1.04 mmol) in DCM (4 mL) was added trifluoroacetic acid (1.19 g, 10.4 mmol). The resulting reaction mixture was stirred at RT for 1 hour. The reaction mixture was concentrated on high vacuum to yield BB69 as a light yellow oil, 399 mg, mixture of all four stereoisomers. MS (ESI): m/z = 246.1 [M+H]⁺.

Step a) *tert*-Butyl 2-methyl-3-((4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate

In a 25 mL two-necked flask, *tert*-butyl-3-hydroxy-2-methylazetidine-1-carboxylate (215 mg, 1.15 mmol) was dissolved in DMF (5 mL) to give a colorless solution. At 0°C, sodium hydride (60 % dispersion in mineral oil) (41.8 mg, 1.05 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min. Then 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.250 g, 1.05 mmol) was added at 0°C. The reaction mixture was stirred at RT overnight. The reaction mixture was poured onto 20 mL sat. NH₄Cl and extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 20 g, 0% to 70% EtOAc in heptane) to yield 360 mg of *tert*-butyl 2-methyl-3-((4-(trifluoromethyl)benzyl)oxy)azetidine-1-carboxylate as a colorless oil. MS (ESI): m/z = 290.1 [M-56+H]⁺

BB87**3-Fluoro-5-(trifluoromethyl)benzyl 4-methylbenzenesulfonate**

- 177 -

To a solution of (3-fluoro-5-(trifluoromethyl)phenyl)methanol (100 mg, 72.5 μ L, 515 μ mol, Eq: 1) in DCM (2.58 mL) was added p-toluenesulfonic anhydride (185 mg, 567 μ mol), DIPEA (79.9 mg, 108 μ L, 618 μ mol) and DMAP (6.29 mg, 51.5 μ mol). The reaction mixture was stirred for 4 h at 0 °C and for 2 days at room temperature. The reaction mixture was taken up in EtOAc and washed with water and brine. The organic layers were dried over MgSO₄ and concentrated in vacuo to give a yellow oil (178 mg) which was used without further purification.

In analogy to BB39, and if not specified otherwise, the intermediates shown in the following table were prepared from commercially available benzyl bromides or the prepared tosylate intermediates and the corresponding *tert*-butyl 3-hydroxyazetidine-1-carboxylate building blocks.

BB No.	Systematic Name	Starting material	MS, m/z
BB37	3-((2-Chloro-4-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	1-(Bromomethyl)-2-chloro-4-(trifluoromethyl)benzene	266.1 [M+H] ⁺
BB38	3-((4-(Trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	1-(Bromomethyl)-4-(trifluoromethyl)benzene	232.1 [M+H] ⁺
BB45	3-((3-Methoxy-4-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	4-(Bromomethyl)-2-methoxy-1-(trifluoromethyl)benzene	262.2 [M+H] ⁺
BB56	3-((3-Fluoro-5-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	3-Fluoro-5-(trifluoromethyl)benzyl 4-methylbenzenesulfonate (BB87)	250.1 [M+H] ⁺
BB60	3-((3-Chloro-4-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	4-(Bromomethyl)-2-chloro-1-(trifluoromethyl)benzene	266.1 [M+H] ⁺
BB62	3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)azetidine; trifluoroacetate salt	1-(Bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene and Tert-butyl 3-hydroxy-3-(trifluoromethyl)azetidine-1-carboxylate (CAS: 398489-42-4)	318.3 [M+H] ⁺
BB63	3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)-3-methylazetidine; trifluoroacetate salt	1-(Bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene and Tert-butyl 3-hydroxy-3-methylazetidine-1-carboxylate (CAS: 1104083-23-9)	264.1 [M+H] ⁺
BB64	3-((2,4-Difluoro-5-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	1-(Bromomethyl)-2,4-difluoro-5-(trifluoromethyl)benzene	268.1 [M+H] ⁺

BB65	3-((2-Fluoro-5-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	2-(Bromomethyl)-1-fluoro-4-(trifluoromethyl)benzene	250.1 [M+H] ⁺
BB66	3-((2-Fluoro-5-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	4-(Bromomethyl)-2-fluoro-1-(trifluoromethyl)benzene	250.1 [M+H] ⁺
BB67	3-((2-Methoxy-4-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	1-(Bromomethyl)-2-methoxy-4-(trifluoromethyl)benzene	262.2 [M+H] ⁺
BB68	3-((4-Chloro-2-(trifluoromethyl)benzyl)oxy)azetidine; trifluoroacetate salt	1-(Bromomethyl)-4-chloro-2-(trifluoromethyl)benzene	266.2 [M+H] ⁺
BB88	3-[(2,4-dichlorophenyl)methoxy]azetidine	1-(Bromomethyl)-2,4-dichlorobenzene	232.1 [M+H] ⁺
BB170	3-((3,4-Dichlorobenzyl)oxy)azetidine; 2,2,2-trifluoroacetate	4-(Bromomethyl)-1,2-dichlorobenzene	232.1 [M+H] ⁺
BB171	3-((2,5-Dichlorobenzyl)oxy)azetidine; 2,2,2-trifluoroacetate	2-(Bromomethyl)-1,4-dichlorobenzene	232.1 [M+H] ⁺
BB172	3-((3-(Trifluoromethoxy)benzyl)oxy)azetidine; 2,2,2-trifluoroacetate	3-(Bromomethyl)-trifluoromethoxy-benzene	248.1 [M+H] ⁺
BB173	2-Methyl-3-((4-methyl-3-(trifluoromethyl)benzyl)oxy)azetidine; 2,2,2-trifluoroacetate	tert-Butyl 3-hydroxy-2-methylazetidine-1-carboxylate and 4-(bromomethyl)-1-methyl-2-(trifluoromethyl)benzene	266.2 [M+H] ⁺
BB178	3-(((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)methyl)azetidine; 2,2,2-trifluoroacetate	tert-Butyl 3-(hydroxymethyl)azetidine-1-carboxylate and 1-(Bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene	264.2 [M+H] ⁺
BB180	[4-(Azetidin-3-yloxymethyl)-3-fluoro-phenyl]-pentafluoro- $\square$ 6-sulfane; 2,2,2-trifluoroacetate	(4-(Bromomethyl)-3-fluorophenyl)pentafluoro- $\square$ 6-sulfane	308.2 [M+H] ⁺
BB185	3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)pyrrolidine; 2,2,2-trifluoroacetate	tert-Butyl 3-hydroxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate and 1-(Bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene	332.2 [M+H] ⁺
BB187	3-[[2,4-bis(Trifluoromethyl)phenyl]methoxy]azetidine	1-(Bromomethyl)-2,4-bis(trifluoromethyl)benzene	336.2 [M+H] ⁺
BB188	3-[[2-Methyl-3-(trifluoromethyl)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-3-(trifluoromethyl)benzene	246.1 [M+H] ⁺

BB189	3-[[2-Methyl-4-(trifluoromethoxy)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-4-(trifluoromethoxy)benzene	262.1 [M+H] +
BB190	2-Methyl-3-[[2-methyl-4-(trifluoromethoxy)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-4-(trifluoromethoxy)benzene and tert-butyl 3-hydroxy-2-methylazetidine-1-carboxylate	276.2 [M+H] +
BB191	2-Methyl-3-[[2-methyl-3-(trifluoromethyl)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-3-(trifluoromethyl)benzene and tert-Butyl 3-hydroxy-2-methylazetidine-1-carboxylate	260.2 [M+H] +
BB207	3-[[4-Fluoro-2-(trifluoromethyl)phenyl]methoxy]azetidine; 4-methylbenzenesulfonate	1-(Chloromethyl)-4-fluoro-2-(trifluoromethyl)benzene (CAS RN 248262-29-5)	250.2 [M +H] ⁺
BB212	3-[[3-Fluoro-4-(trifluoromethoxy)phenyl]methoxy]azetidine; 2,2,2-trifluoroacetate	4-(Bromomethyl)-2-fluoro-1-(trifluoromethoxy)benzene	Used without purifica tion
BB217	3-((4-Methyl-3-(trifluoromethyl)benzyl)oxy)azetidine; 2,2,2-trifluoroacetate	4-(Bromomethyl)-1-methyl-2-(trifluoromethyl)benzene. tBuOK as base	246.2 [M +H] ⁺

In analogy to BB29, intermediates BB20, BB25 and BB61 of the following table were prepared from the commercially available phenols. Where trifluoroacetate salts are indicated, the crude product resulting from concentration of the reaction mixture was used directly without further
5 neutralization or purification.

BB No.	Systematic Name	Starting material	MS, m/z
BB20	3-((2-Fluoro-4-(trifluoromethyl)phenoxy)methyl)azetidine; trifluoroacetate salt	2-Fluoro-4-(trifluoromethyl)phenol (CAS RN: 77227-78-2)	250.1 [M+H] ⁺
BB25	3-[(2-Chloro-4-fluorophenoxy)methyl]azetidine	2-Chloro-4-fluorophenol (CAS RN: 1996-41-4)	216.1 [M+H] ⁺ (purified by RP-HPLC)
BB61	3-((2-Chloro-4-fluorophenoxy)methyl)-3-fluoroazetidine; trifluoroacetate salt	2-Chloro-4-fluorophenol (CAS RN: 1996-41-4) and	234.1 [M+H] ⁺

- 180 -

		tert-Butyl 3-fluoro-3-(hydroxymethyl)azetidine-1-carboxylate (CAS: 1126650-66-5)	
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In analogy to BB26, intermediates BB21 – BB24 and BB28 of the following table were prepared from the commercially available phenols.

BB No.	Systematic Name	Starting material	MS, m/z
BB21	4-((4-Fluoro-2-(trifluoromethyl)phenoxy)methyl)piperidine; hydrochloride salt	4-Fluoro-2-(trifluoromethyl)phenol (CAS: 130047-19-7)	278.1 [M+H] ⁺
BB22	4-[[2-Fluoro-4-(trifluoromethyl)phenoxy]methyl]piperidine; hydrochloride salt	2-Fluoro-4-(trifluoromethyl)phenol (CAS: 77227-78-2)	278.0 [M+H] ⁺
BB23	4-((2-Chloro-4-(trifluoromethyl)phenoxy)methyl)piperidine; hydrochloride salt	2-Chloro-4-(trifluoromethyl)phenol (CAS: 35852-58-5)	294.1 [M+H] ⁺
BB24	5-Fluoro-2-(piperidin-4-ylmethoxy)benzonitrile; hydrochloride salt	5-Fluoro-2-hydroxybenzonitrile (CAS: 91407-41-9)	235.1 [M+H] ⁺
BB28	4-[(4-Fluoro-2-methylphenoxy)methyl]piperidine; hydrochloride salt	4-Fluoro-2-methylphenol (CAS: 452-72-2)	224.0 [M+H] ⁺
BB170	3-((3,4-Dichlorobenzyl)oxy)azetidine 2,2,2-trifluoroacetate	4-(Bromomethyl)-1,2-dichlorobenzene	232.1 [M+H] ⁺
BB171	3-((2,5-Dichlorobenzyl)oxy)azetidine 2,2,2-trifluoroacetate	2-(Bromomethyl)-1,4-dichlorobenzene	232.1 [M+H] ⁺
BB172	3-((3-(Trifluoromethoxy)benzyl)oxy)azetidine 2,2,2-trifluoroacetate	3-(Bromomethyl)-trifluoromethoxy-benzene	248.1 [M+H] ⁺
BB173	2-Methyl-3-((4-methyl-3-(trifluoromethyl)benzyl)oxy)azetidine 2,2,2-trifluoroacetate	tert-Butyl 3-hydroxy-2-methylazetidine-1-carboxylate and 4-(Bromomethyl)-1-methyl-2-(trifluoromethyl)benzene	266.2 [M+H] ⁺
BB178	3-(((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)methyl)azetidine 2,2,2-trifluoroacetate	tert-Butyl 3-(hydroxymethyl)azetidine-1-carboxylate and 1-(Bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene	264.2 [M+H] ⁺
BB180	[4-(Azetidin-3-ylloxymethyl)-3-fluoro-phenyl]-pentafluoro- $\square$ 6-sulfane 2,2,2-trifluoroacetic acid	(4-Bromomethyl)-3-fluorophenyl pentafluoro- $\square$ 6-sulfane	308.2 [M+H] ⁺

BB185	3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)pyrrolidine 2,2,2-trifluoroacetate	tert-Butyl 3-hydroxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate and 1-(Bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene	332.2 [M+H] ⁺
BB187	3-[[2,4-bis(Trifluoromethyl)phenyl]methoxy]azetidine	1-(Bromomethyl)-2,4-bis(trifluoromethyl)benzene	336.2 [M+H] ⁺
BB188	3-[[2-Methyl-3-(trifluoromethyl)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-3-(trifluoromethyl)benzene	246.1 [M+H] ⁺
BB189	3-[[2-Methyl-4-(trifluoromethoxy)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-4-(trifluoromethoxy)benzene	262.1 [M+H] ⁺
BB190	2-Methyl-3-[[2-methyl-4-(trifluoromethoxy)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-4-(trifluoromethoxy)benzene and tert-butyl 3-hydroxy-2-methylazetidine-1-carboxylate	276.2 [M+H] ⁺
BB191	2-Methyl-3-[[2-methyl-3-(trifluoromethyl)phenyl]methoxy]azetidine	1-(Bromomethyl)-2-methyl-3-(trifluoromethyl)benzene and tert-Butyl 3-hydroxy-2-methylazetidine-1-carboxylate	260.2 [M+H] ⁺
BB207	3-[[4-Fluoro-2-(trifluoromethyl)phenyl]methoxy]azetidine; 4-methylbenzenesulfonate	1-(Chloromethyl)-4-fluoro-2-(trifluoromethyl)benzene (CAS RN 248262-29-5)	250.2 [M+H] ⁺
BB212	3-[[3-Fluoro-4-(trifluoromethoxy)phenyl]methoxy]azetidine; 2,2,2-trifluoroacetate	4-(Bromomethyl)-2-fluoro-1-(trifluoromethoxy)benzene	Used without purification
BB217	3-((4-Methyl-3-(trifluoromethyl)benzyl)oxy)azetidine; 2,2,2-trifluoroacetate	4-(Bromomethyl)-1-methyl-2-(trifluoromethyl)benzene. tBuOK as base	246.2 [M+H] ⁺
BB218	3-((2-Fluoro-6-(trifluoromethyl)benzyl)thio)azetidine 2,2,2-trifluoroacetate	tert-Butyl 3-mercaptoazetidine-1-carboxylate and 2-(Bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene	266.2 [M+H] ⁺

Method D1**BB9****4-[2-Chloro-4-(trifluoromethyl)phenoxy]piperidine; trifluoroacetate salt**

- 182 -

A mixture of tert-butyl 4-[2-chloro-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (750.0 mg, 1.97 mmol) in DCM (20 mL) and TFA (0.76 mL) was stirred at 20 °C for 12 h. The mixture was concentrated. The residue was dissolved in H₂O (20 mL) and washed twice with PE : EA = 10 : 1 (20 mL each). The aqueous layer was lyophilized to give the desired product as light yellow solid (716 mg, 1.82 mmol, 87.8%). MS (ESI): m/z = 280.1 [M+H]⁺.

Step a) *tert-Butyl 4-[2-chloro-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate*

A mixture of 2-chloro-4-(trifluoromethyl)phenol (500 mg, 2.54 mmol), 1-Boc-4-hydroxypiperidine (768 mg, 3.82 mmol) and triphenylphosphine (1334 mg, 5.09 mmol) in THF (10 mL) was stirred at 0 °C until completely dissolved. DIAD (1542 mg, 7.63 mmol) was slowly added dropwise at 0 °C. The mixture was stirred at 20 °C for 3 h and then concentrated under vacuum. The residue was purified by prep-HPLC to give the desired compound as light yellow solid (760 mg, 2 mmol, 78.7% yield). MS (ESI): m/z = 324.0 [M-56+H]⁺.

BB57

3-(((2-Fluoro-6-(trifluoromethyl)benzyl)oxy)methyl)azetidine; trifluoroacetate salt

To a solution of tert-butyl 3-(((2-fluoro-6-(trifluoromethyl)benzyl)oxy)methyl)azetidine-1-carboxylate (158 mg, 435 µmol) in DCM (1.74 mL) was added TFA (793 mg, 536 µL, 6.96 mmol) and the reaction was stirred at room temperature for 3 h. The reaction mixture was concentrated to give 3-(((2-fluoro-6-(trifluoromethyl)benzyl)oxy)methyl)azetidine; trifluoroacetate salt (202 mg, 434 µmol, 99.7 % yield) as a colorless oil. The crude was used without further purification. MS (ESI): m/z = 264.1 [M+H]⁺.

Step a) *Tert-butyl 3-(((2-fluoro-4-(trifluoromethyl)benzyl)oxy)methyl)azetidine-1-carboxylate*

To a solution of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (100 mg, 534 µmol) in dry THF (2.67 mL) was added potassium tert-butoxide 1.65 M solution in THF (340 µL, 561 µmol) and the turbid reaction mixture was stirred at RT for 15 min followed by addition of 1-(bromomethyl)-2-fluoro-6-(trifluoromethyl)benzene (137 mg, 534 µmol). The reaction mixture was then stirred at room temperature for 3 h. The crude reaction was diluted with ethyl acetate and extracted with sat. aq. NaHCO₃ solution, the organic phase was collected and the aqueous phase was back-extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated down to dryness to yield a clear oil. The crude was immobilized on Isolute and purified by column chromatography eluting with 0 to 30 % EtOAc in heptanes to

- 183 -

afford tert-butyl 3-(((2-fluoro-6-(trifluoromethyl)benzyl)oxy)methyl)azetidine-1-carboxylate (158 mg, 413 μ mol, 77.3 % yield) as a colorless oil. MS (ESI): m/z = 308.1 $[M-56+H]^+$

Method D2

BB10

5 **4-[[2-Cyclopentyl-4-(trifluoromethyl)phenyl]methyl]piperidine; formic acid salt**

A mixture of tert-butyl 4-[[2-cyclopentyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate (440 mg, 0.610 mmol) and 5.0 mL of 4 M HCl in EtOAc in EtOAc (10 mL) was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum. The residue was re-dissolved in H₂O (5 mL), washed twice with PE : EA (3 : 1; 10 mL each) and the layers were
10 separated. The aqueous layer was purified by prep-HPLC to give the desired compound as light yellow solid (124 mg, 0.350 mmol, 65.3% yield). MS (ESI): m/z = 312.2 $[M+H]^+$.

Step a) *tert-Butyl 4-[[2-cyclopentyl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate*

A solution of tert-butyl 4-[[2-bromo-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (500 mg, 1.19 mmol), cyclopentyl bromide (266 mg, 1.78 mmol),
15 Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (13.4 mg, 0.010 mmol, CAS RN 870987-63-6), NiCl₂.glyme (0.77 mg, 0.060 mmol), dtbbpy (19.2 mg, 0.070 mmol, CAS RN 72914-19-3), TTMS (296 mg, 1.19 mmol, CAS RN 1873-77-4) and Na₂CO₃ (252 mg, 2.38 mmol) in DMF (20 mL) was degassed by bubbling argon stream for 20 min. The reaction mixture was irradiated with Blue LED (4×1) at 25 °C for 16 h. The mixture was diluted with H₂O and then extracted three times with EtOAc
20 (100 mL each). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC to give the compound as a colorless oil (460 mg, 1.12 mmol, 53.8%). MS (ESI): m/z = 354.1 $[M-56+H]^+$.

Step b) *tert-Butyl 4-[[2-cyclopentyl-4-(trifluoromethyl)phenyl]methyl] piperidine-1-carboxylate*

To a mixture of tert-butyl 4-[[2-cyclopentyl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (460 mg, 0.640 mmol) in EtOAc (10 mL) was added wet Pd/C (40 mg), and then the
25 mixture was stirred at 20 °C for 12 h under H₂ (1520 mmHg). The mixture was filtered and the filtrate was concentrated to give the compound as colorless oil (460 mg, 1.12 mmol, 99.5%). MS (ESI): m/z = 356.1 $[M+H-56]^+$.

BB11

30 **2-(4-Piperidylmethyl)-1,3-benzoxazole; formic acid salt**

- 184 -

- A solution of 2-aminophenol (1.0 g, 9.16 mmol) and 1-Boc-4-piperidylacetic acid (2.68 g, 11 mmol) in polyphosphoric acid (2.2 g) was stirred at 180 °C for 2 h. The mixture was diluted with a mixture of 12M aqueous NH₄OH solution and ice to reach pH > 7, and then extracted three times with EtOAc (10 mL each). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated, and the residue was purified by prep-HPLC to give the desired compound as a brown oil (251 mg, 0.960 mmol, 9.7%). MS (ESI): m/z = 217.2 [M+H]⁺.

Method D3**BB13****4-[4-Chloro-3-(4-chlorophenyl)phenoxy]piperidine; hydrochloride salt**

- A solution of tert-butyl 4-[4-chloro-3-(4-chlorophenyl)phenoxy]piperidine-1-carboxylate (1000 mg, 2.37 mmol) in a 4 M solution of HCl in dioxane (50 mL) was stirred at 20 °C for 12 h. The mixture was concentrated to give the title compound as a white solid (845 mg, 2.35 mmol, 96.2%). MS (ESI): m/z = 322.0 [M+H]⁺.

Step a) tert-Butyl 4-(3-bromo-4-chloro-phenoxy) piperidine-1-carboxylate

- A mixture of 3-bromo-4-chlorophenol (1000 mg, 4.82 mmol), 1-Boc-4-hydroxypiperidine (1164 mg, 5.78 mmol) and triphenylphosphine (2529 mg, 9.64 mmol) was stirred in THF (10 mL) until completely dissolved. Then DIAD (1948 mg, 9.64 mmol) was slowly added drop wise at 0 °C. The mixture was stirred at 20 °C for 12 h, concentrated and the residue was purified by reversed flash chromatography to give the compound as yellow oil (1300 mg, 3.33 mmol, 69.0%). MS (ESI): m/z = 336.0 [M-56+H]⁺.

Step b) tert-Butyl 4-[4-chloro-3-(4-chlorophenyl)phenoxy]piperidine-1-carboxylate

- To a solution of tert-butyl 4-(3-bromo-4-chloro-phenoxy)piperidine-1-carboxylate (1150 mg, 2.94 mmol) and 4-chlorophenylboronic acid (506 mg, 3.24 mmol), Na₂CO₃ (1248 mg, 11.8 mmol) in 1,4-dioxane (20 mL) and H₂O (5 mL) was added tetrakis(triphenylphosphine)palladium(0) (340 mg, 0.290 mmol, CAS RN 14221-01-3), and the mixture was stirred at 110 °C under N₂ atmosphere for 12 h. The mixture was filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography, eluting with a 5 - 20% EtOAc - PE gradient to give the desired compound as light yellow oil (1100 mg, 2.6 mmol, 88.5%). MS (ESI): m/z = 366.1 [M-56+H]⁺.

- 185 -

BB14**4-[[2-(1H-Pyrazol-4-yl)-4-(trifluoromethyl)phenyl]methyl]piperidine; trifluoroacetate salt**

To a mixture of tert-butyl 4-[[2-(1-tert-butoxycarbonylpyrazol-4-yl)-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate (150.0 mg, 0.290 mmol) in DCM (5 mL) was added
5 TFA (1.0 mL). The mixture was stirred at 20 °C for 15 h. The mixture was concentrated under vacuum and then lyophilized to give the title compound as light yellow gum (149 mg, 0.280 mmol, 85.1% yield). MS (ESI): $m/z = 310.0$ $[M+H]^+$.

Step a) *tert-Butyl 4-[[2-(1-tert-butoxycarbonylpyrazol-4-yl)-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate*

10 A mixture of tert-butyl 4-[[2-bromo-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (600 mg, 1.43 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)pyrazole-1-carboxylate (846 mg, 2.86 mmol) and K_2CO_3 (592 mg, 4.28 mmol) in DMF (10 mL) and H_2O (0.5 mL) was stirred at 80 °C for 12 h. The mixture was poured into H_2O (30 mL) and extracted twice with EtOAc (50 mL each). The combined organic layers were washed with brine (30 mL),
15 dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give the compound as light yellow oil (520 mg, 1.02 mmol, 71.8% yield). MS (ESI): $m/z = 308.1$ $[M+H]^+$.

Step b) *tert-Butyl 4-[[2-(1-tert-butoxycarbonylpyrazol-4-yl)-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate*

A mixture of tert-butyl 4-[[2-(1-tert-butoxycarbonylpyrazol-4-yl)-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (180 mg, 0.350 mmol) and wet Pd/C (18 mg) in EtOAc (10 mL) was stirred at 30 °C for 24 h under H_2 atmosphere (~1520 mm Hg). The mixture was
20 filtered and concentrated under vacuum to give the compound as brown oil (150 mg, 0.290 mmol, 83%). MS (ESI): $m/z = 354.1$ $[M-56-100+H]^+$.

BB18**4-[2-(2-Chlorophenyl)ethynyl]piperidine**

25 To a suspension of *tert*-butyl 4-((2-chlorophenyl)ethynyl)piperidine-1-carboxylate (0.05 g, 0.156 mmol) in MeOH (3 mL) was added 4 M HCl in dioxane (0.391 mL, 1.56 mmol) and the reaction mixture was stirred at room temperature for 2 h. The mixture was evaporated to dryness and the residue triturated in diisopropyl ether, filtered off and further dried under high vacuum to give
30 the title compound as a white solid as the hydrochloride salt (0.02 g, 50%). MS (ESI): $m/z = 220.1$ $[M+H]^+$.

- 186 -

Step a) *tert*-Butyl 4-[2-(2-chlorophenyl)ethynyl]piperidine-1-carboxylate

In a sealed tube, a mixture of *tert*-butyl 4-ethynylpiperidine-1-carboxylate (0.1 g, 0.478 mmol, CAS RN 287192-97-6), 1-bromo-2-chlorobenzene (0.084 mL, 0.717 mmol), copper (I) iodide (0.002 g, 0.009 mmol), TEA (0.666 mL, 4.78 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.027 g, 0.038) in THF (2.8 mL) was degassed for 5 min under Argon. The reaction mixture was then heated to 70 °C and stirred for 4 h. The mixture was filtered off over a pad of Dicalite, washed with EtOAc and the mother liquors were evaporated to dryness. The residue was purified by silica gel flash chromatography, eluting with a gradient of 0-50% EtOAc/n-heptane to give the title compound as a white solid (0.05 g, 33%). MS (ESI): $m/z = 264.1$ [$M+H$]⁺.

BB48a***tert*-Butyl 4-[[2-fluoro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate**

A degassed solution of *tert*-butyl 4-methylenepiperidine-1-carboxylate (4465 mg, 22.6 mmol, CAS RN 159635-49-1) in 9-BBN (45.3 mL, 22.6 mmol) was refluxed for 1 h. After cooling to room temperature, the solution was added into a solution of 4-bromo-3-fluorobenzotrifluoride (5.0 g, 20.6 mmol, CAS RN 40161-54-4), Pd(dppf)Cl₂ (1514 mg, 2.06 mmol) and K₂CO₃ (5687 mg, 41.1 mmol) in DMF (50 mL) and water (5 mL). The resulting mixture was heated at 80 °C for 5 h. After the mixture was cooled to room temperature and poured into water, the pH was adjusted to 11 with 10% aqueous NaOH solution, and the mixture was extracted with EtOAc. The combined organic extracts were dried with brine and Na₂SO₄, filtered, and evaporated to give a residue, which was further purified by column chromatography (silica gel, PE : EtOAc = 10 : 1 to 5 : 1) to give the compound as light yellow solid (240 mg, 3.2%). MS (ESI): $m/z = 306$ [$M+H-56$]⁺.

BB51a

A mixture of *tert*-butyl 4-[[2-cyclopropyl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (1000 mg, 2.62 mmol) and PtO₂ (100 mg, 0.440 mmol) in EtOAc (20 mL) was stirred at 20 °C for 12 h under H₂ atmosphere (1520 mmHg). The mixture was filtered and the filtrate concentrated to furnish the compound as light yellow solid (940 mg, 93.5%). MS (ESI): $m/z = 328.2$ [$M+H$]⁺.

Step a) *2-Bromo-1-(bromomethyl)-4-(trifluoromethyl)benzene*

- 187 -

A mixture of 2-bromo-1-methyl-4-(trifluoromethyl)benzene (5.5 g, 23.0 mmol, CAS RN 128-08-5), benzoyl peroxide (835 mg, 3.45 mmol) and NBS (4.07 g, 23.01 mmol) in CCl₄ (50.0 mL, 23.0 mmol) was stirred at 70 °C for 5 h. The mixture was poured into water (20 mL) and extracted twice with DCM (20 mL each). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give the desired compound as light yellow oil which was used in the next step without further purification (7.1 g, 97%).

Step b) *2-Bromo-1-(diethoxyphosphorylmethyl)-4-(trifluoromethyl)benzene*

A mixture of 2-bromo-1-(bromomethyl)-4-(trifluoromethyl)benzene (7.1 g, 22.3 mmol) and triethyl phosphite (30 mL) was stirred at 155 °C for 5 h. The mixture was concentrated in vacuum to remove triethyl phosphite, the residue was diluted with water (100 mL) and extracted three times with EtOAc (100 mL each). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (PE : EtOAc = 100 : 1 to 10:1) to give the compound as light yellow oil which was used without further purification in the next step (8 g, 95.5%).

Step c) *tert-Butyl 4-(2-bromo-4-(trifluoromethyl)benzylidene)piperidine-1-carboxylate*

To a mixture of 2-bromo-1-(diethoxyphosphorylmethyl)-4-(trifluoromethyl)benzene (6.9 g, 18.4 mmol) in THF (100 mL) was added sodium hydride (2.21 g, 55.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then 1-Boc-4-piperidone (7.33 g, 36.79 mmol, CAS RN 79099-07-3) was added and the mixture was stirred at 20 °C for 12 h. The mixture was poured into water (100 mL) and extracted three times with EtOAc (100 mL each). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (PE : EA = 100 : 1 to 50 : 1) to yield the desired compound as off-white solid (4 g, 51.7%). MS (ESI): m/z = 365.9 [M-56+H]⁺.

Step d) *tert-butyl 4-[[2-cyclopropyl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate*

A mixture of tert-butyl 4-[[2-bromo-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (2.0 g, 4.76 mmol), cyclopropylboronic acid (818 mg, 9.52 mmol, CAS RN 411235-57-9) and potassium carbonate (1973 mg, 14.3 mmol) in DMF (10 mL) and water (0.5 mL) was stirred at 80 °C under nitrogen atmosphere for 12 h. The mixture was poured into water (50 mL), extracted three times with EtOAc (50 mL each). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by

- 188 -

prep-HPLC to give the compound as light yellow oil (1020 mg, 56.2% yield). MS (ESI): m/z = 326.0 $[M-56+H]^+$.

BB53a

tert-Butyl 3-[(4-chlorophenyl)methoxy]pyrrolidine-1-carboxylate

5 A solution of N-Boc-3-hydroxypyrrolidine (1.0 g, 5.34 mmol) and 4-chlorobenzyl bromide (1.32 g, 6.41 mmol) in ACN (10 mL) was added potassium carbonate (1.48 g, 10.68 mmol). The mixture was stirred at 80 °C for 15 h. Then the mixture was concentrated and diluted with water and extracted three times with EtOAc (10 mL each). The combined organic layers were concentrated to give the desired compound as colorless oil (326 mg, 19.6% yield) MS (ESI): m/z = 256.0 $[M-56+H]^+$.

Method D4

BB70

3-[4-(Trifluoromethyl)phenoxy]azetidine

To a solution of tert-butyl 3-[4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate (500 mg, 1.58 mmol, BB70a) in DCM (3 mL) was added TFA (1.0 mL, 0.950 mmol) at 25 °C, the reaction was stirred at this temperature for 12 h. The mixture was concentrated and the residue was purified via prep-HPLC to provide the compound as colorless solid (150 mg, 0.690 mmol, 43.8%). MS (ESI): m/z = 218.1 $[M+H]^+$.

BB72a

tert-Butyl 4-(4-chloro-3-cyclopropyl-phenoxy)piperidine-1-carboxylate

20 To a solution of tert-butyl 4-(3-bromo-4-chloro-phenoxy)piperidine-1-carboxylate (500 mg, 1.28 mmol, BB90), potassium carbonate (354 mg, 2.56 mmol) and cyclopropylboronic acid (121 mg, 1.41 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium(II) (187.28 mg, 0.260 mmol). The mixture
25 was stirred at 100 °C under nitrogen atmosphere for 12 h. The reaction mixture was filtered and the filtrate was diluted with EtOAc (30 mL), washed with water and then brine, the organic phase was dried over Na₂SO₄, concentrated. The residue was purified by silica gel column (eluting with a gradient of 5% - 10% EtOAc-PE) to give the compound as light yellow oil (220 mg, 48.9%). MS (ESI): m/z = 296.1 $[M-56+H]^+$.

- 189 -

BB73a**tert-Butyl 4-(4-chloro-3-morpholino-phenoxy) piperidine-1-carboxylate**

To a solution of tert-butyl 4-(3-bromo-4-chloro-phenoxy)piperidine-1-carboxylate (500 mg, 1.28 mmol, BB90), cesium carbonate (834 mg, 2.56 mmol), (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (159 mg, 0.260 mmol) and morpholine (112 mg, 1.28 mmol) in DMF (10 mL) was added tris(dibenzylideneacetone)dipalladium(0) (187 mg, 0.260 mmol) and the mixture was stirred at 110 °C under nitrogen atmosphere for 12 h. The reaction mixture was filtered, the filtrate was diluted with EtOAc (30 mL), washed with water and then brine, the organic phase was dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column (eluting with a gradient of 5% - 10% EtOAc-PE) to give the desired compound (360 mg, 70.9% yield) as light yellow oil. MS (ESI): m/z = 397.1 [M + H]⁺.

BB74a**tert-Butyl 4-[2-methyl-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate**

To a solution of tert-butyl 4-[2-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (2.0 g, 4.71 mmol, BB74b) in THF (40 mL) was added lithium methide (11.8 mL, 18.9 mmol) dropwise at -70 °C. The mixture was stirred at -70 °C for 1 h and then stirred at 20 °C for 12 h. The mixture was poured into ice water (100 mL) and extracted three times with EtOAc (50 mL each). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum to yield the compound as light yellow solid (780 mg, 46%). MS (ESI): m/z = 260.1 [M-100+H]⁺.

BB75a**tert-Butyl 4-[2-cyano-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate**

To a solution of zinc cyanide (2214 mg, 18.9 mmol) and tert-butyl 4-[2-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (1600 mg, 3.77 mmol, BB74b) in DMA (30 mL) was added dppf (627 mg, 1.13 mmol), N,N-diisopropylethylamine (1.97 mL, 11.3 mmol), Zinc dust (245 mg, 3.77 mmol) and Pd₂(dba)₃ (1036 mg, 1.13 mmol) at 20 °C, then the mixture was stirred at 140 °C under nitrogen atmosphere for 4 h. The mixture was filtered. The filtrate was poured into water (100 mL) and extracted three times with EtOAc (50 mL each). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated over vacuum to give the title compound as light brown solid (2.3 g, crude). MS (ESI): m/z = 315.0 [M-56+H]⁺.

- 190 -

BB76a**tert-Butyl 4-(oxazolo[5,4-c]pyridin-2-ylmethyl)piperidine-1-carboxylate**

To a solution of hexachloroethane (2.47 g, 10.4 mmol) in toluene (20 mL) was added triphenylphosphine (3.28 g, 12.5 mmol) and NEt₃ (4.65 mL, 33.4 mmol). The mixture was stirred at 80 °C for 5 min, then tert-butyl 4-[2-[(3-hydroxy-4-pyridyl)amino]-2-oxo-ethyl]piperidine-1-carboxylate (1.4 g, 4.17 mmol) was added and stirred at 80 °C for 12 h. The mixture was concentrated to remove toluene, then diluted with water (100 mL) and extracted three times with EtOAc (50 mL each). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was purified by silica gel chromatography (PE : EtOAc = 10 : 1 to 1 : 0) to give the compound as a yellow oil (814 mg, 21% yield). MS (ESI): m/z = 318.1 [M+H]⁺.

Step a) tert-Butyl 4-[2-[(3-hydroxy-4-pyridyl)amino]-2-oxo-ethyl]piperidine-1-carboxylate

A solution of 4-aminopyridin-3-ol (3.0 g, 27.3 mmol) and 1-Boc-4-piperidylacetic acid (7.95 g, 32.7 mmol) in DMF (30 mL) was added HOBt (6.26 g, 40.9 mmol), EDCI (6.34 g, 40.87 mmol) and NEt₃ (11.39 mL, 81.74 mmol). The mixture was stirred at 20 °C for 15 h. Then the mixture was concentrated, the residue taken up in water (100 mL), and then extracted three times with EtOAc (20 mL each). The organic phase was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by reversed phase chromatography and lyophilized to give two batches of the desired compound. Batch 1 as colorless solid (1.2 g, 85% purity, 11.1%), and batch 2 as colorless solid (520 mg, 76.7% purity, 4.4% yield). MS (ESI): m/z = 336.1 [M+H]⁺ for both batches.

BB77**4-Chloro-3-(2-piperidin-4-ylethynyl)pyridine**

Intermediate BB77 was prepared in analogy to BB18, but using 3-bromo-4-chloro-pyridine in step a), to give the title compound as an orange solid. MS (ESI): m/z = 221.1 [M+H]⁺.

BB78**3-Chloro-2-(2-piperidin-4-ylethynyl)pyridine**

Intermediate BB78 was prepared in analogy to BB18, but using 2-bromo-3-chloro-pyridine in step a), to give the title compound as a yellow solid. MS (ESI): m/z = 221.1 [M+H]⁺.

- 191 -

BB79**4-[2-(2-Chloro-4-fluorophenyl)ethynyl]piperidine**

Intermediate BB79 was prepared in analogy to BB18, but using 1-bromo-2-chloro-4-fluorobenzene in step a), to give the title compound as a white solid. MS (ESI): $m/z = 238.1$ $[M+H]^+$.

5

BB80**4-[2-(3-Chlorophenyl)ethynyl]piperidine**

Intermediate BB80 was prepared in analogy to BB18, but using 1-bromo-3-chlorobenzene in step a), to give the title compound as a colorless amorphous solid. MS (ESI): $m/z = 220.2$ $[M+H]^+$.

10

BB81**4-[2-(4-Chlorophenyl)ethynyl]piperidine**

Intermediate BB81 was prepared in analogy to BB18, but using 1-bromo-4-chlorobenzene in step a), to give the title compound as a yellow amorphous solid. MS (ESI): $m/z = 220.2$ $[M+H]^+$.

BB82

15

4-[2-(2-Chloro-4-chlorophenyl)ethynyl]piperidine

Intermediate BB82 was prepared in analogy to BB18, but using 1-bromo-2,4-dichlorobenzene in step a), to give the title compound as a light yellow amorphous solid. MS (ESI): $m/z = 254.1$ $[M+H]^+$.

BB83

20

4-[2-(2-Chlorophenyl)ethynyl]piperidin-4-ol

Intermediate BB83 was prepared in analogy to BB18, but using *tert*-butyl 4-ethynyl-4-hydroxypiperidine-1-carboxylate (CAS RN 275387-83-2) in step a), to give the title compound as a yellow amorphous solid. MS (ESI): $m/z = 218.1$ $[M-H_2O+H]^+$.

BB84

25

3-[2-(2-Chlorophenyl)ethynyl]azetidine

To a solution *tert*-butyl 3-[2-(2-chlorophenyl)ethynyl]azetidine-1-carboxylate (0.035 g, 0.120 mmol) in DCM (0.6 mL) was added TFA (0.924 mL, 1.2 mmol) and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with DCM, poured into a saturated

- 192 -

aq. NaHCO₃ solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, evaporated and further dried on the high vacuum to give the crude title compound (0.02 g, 87%) as a light yellow oil. MS (ESI): m/z = 192.0 [M+H]⁺.

Step a) *tert*-Butyl 3-[2-(2-chlorophenyl)ethynyl]azetidine-1-carboxylate

- 5 The compound was prepared in analogy to intermediate BB18, but using *tert*-butyl 3-ethynylazetidine-1-carboxylate (CAS RN 287193-01-5) in step a), to give the title compound as a white solid. MS (ESI): m/z = 236.1 [M-56+H]⁺.

BB85

3-[2-(2,4-Dichlorophenyl)ethynyl]azetidine

- 10 Intermediate BB85 was prepared in analogy to intermediate BB84, but using 1-bromo-2,4-dichloro-benzene in step a), to give the title compound as a light yellow oil. MS (ESI): m/z = 226.1 [M+H]⁺.

BB86

3-[2-(2-Chloro-4-fluoro-phenyl)ethynyl]azetidine

- 15 Intermediate BB86 was prepared in analogy to intermediate BB84, but using 1-bromo-2-chloro-4-fluoro-benzene in step a), to give the title compound as a yellow oil. MS (ESI): m/z = 210.1 [M+H]⁺.

In analogy to BB9a the following building blocks were prepared from the respective building blocks

BB No.	Systematic Name	Starting materials	MS, m/z
BB54a	<i>tert</i> -Butyl 4-[[2-methyl-4-(trifluoromethyl)phenyl]methyl] piperidine-1-carboxylate	<i>tert</i> -Butyl 4-methylenepiperidine-1-carboxylate 4-Bromo-3-methyl benzotrifluoride	302.1 [M+H-56] ⁺
BB55a	<i>tert</i> -Butyl 4-[[2-chloro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate	<i>tert</i> -Butyl 4-methylenepiperidine-1-carboxylate 4-Bromo-3-chlorobenzotrifluoride	322.0 [M+H-56] ⁺

In analogy to BB15a the following building blocks were prepared from the respective building blocks.

BB No.	Systematic Name	Starting materials	MS, m/z
BB49a	tert-Butyl 3-[(2-chlorophenyl)methoxy]pyrrolidine-1-carboxylate	2-Chlorobenzyl bromide N-Boc-3-hydroxypyrrolidine	256.0 [M-56+H] ⁺
BB50a	tert-Butyl 3-[(3-chlorophenyl)methoxy]pyrrolidine-1-carboxylate	3-Chlorobenzyl bromide N-BOC-3-hydroxypyrrolidine	256.0 [M-56+H] ⁺

In analogy to BB9 step a, the following building blocks were prepared from the respective starting materials.

BB No.	Systematic Name	Starting materials	MS, m/z
BB47a	tert-Butyl 3-[(2-chlorophenoxy)methyl]pyrrolidine-1-carboxylate	2-Chlorophenol tert-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate	256.0 [M-56+H] ⁺
BB52a	tert-Butyl 3-[(4-chlorophenoxy)methyl]pyrrolidine-1-carboxylate	4-Chlorophenol tert-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate	256.0 [M-56+H] ⁺
BB70a	tert-Butyl 3-[4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate	4-(Trifluoromethyl)phenol tert-Butyl 3-hydroxyazetidine-1-carboxylate	Used without further purification
BB71a	tert-Butyl 4-[4-chloro-3-(trifluoromethyl)phenoxy]piperidine-1-carboxylate	1-Boc-4-hydroxypiperidine 4-Chloro-3-(trifluoromethyl)phenol	324.0 [M-56+H] ⁺
BB74b	tert-Butyl 4-[2-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate	2-Bromo-4-(trifluoromethyl)phenol 1-BOC-4-hydroxypiperidine	369.9 [M-56+H] ⁺
BB89a	tert-Butyl 3-[(3-chlorophenoxy)methyl]pyrrolidine-1-carboxylate	3-Chlorophenol tert-Butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate	256.0 [M-56+H] ⁺

BB90	tert-Butyl 4-(3-bromo-4-chloro-phenoxy) piperidine-1-carboxylate	3-Bromo-4-chlorophenol 1-BOC-4-hydroxypiperidine	336.0 [M-56+H] ⁺
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Method D5**BB51****4-[[2-Cyclopropyl-4-(trifluoromethyl)phenyl]methyl]piperidine formic acid salt**

- 5 To a mixture of tert-butyl 4-[[2-cyclopropyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate (940 mg, 2.45 mmol, BB51a) in DCM (10 mL) was added TFA (2.0 mL, 2.45 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum. The residue was purified twice by prep-HPLC to furnish the desired compound as light yellow gum (111 mg, 12.4%). MS (ESI): m/z = 284.2 [M+H]⁺.

10 Step a) *2-Bromo-1-(bromomethyl)-4-(trifluoromethyl)benzene*

- A mixture of 2-bromo-1-methyl-4-(trifluoromethyl)benzene (5.5 g, 23.0 mmol, CAS RN 128-08-5), benzoyl peroxide (835 mg, 3.45 mmol) and NBS (4.07 g, 23.0 mmol) in CCl₄ (50.0 mL, 23.0 mmol) was stirred at 70 °C for 5 h. The mixture was poured into water (20 mL) and extracted twice with DCM (20 mL each). The combined organic layers were washed with brine
 15 (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give the compound as light yellow oil (7.1 g, 97%) which was used in the next step without further purification.

Step b) *2-Bromo-1-(diethoxyphosphorylmethyl)-4-(trifluoromethyl)benzene*

- A mixture of 2-bromo-1-(bromomethyl)-4-(trifluoromethyl)benzene (7.1 g, 22.3 mmol,) and triethyl phosphite (30.0 mL) was stirred at 155 °C for 5 h. The mixture was concentrated in
 20 vacuum to remove triethyl phosphite. The residue was diluted with water (100 mL) and extracted three times with EtOAc (100 mL each). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (PE : EA = 100 : 1 to 10 : 1) to give the title compound as light yellow oil (8 g, 21.3 mmol, 95.5%) which was used in the subsequent step without further purification.

25 Step c) *tert-Butyl 4-(2-bromo-4-(trifluoromethyl)benzylidene)piperidine-1-carboxylate*

A mixture of 2-bromo-1-(diethoxyphosphorylmethyl)-4-(trifluoromethyl)benzene (6.9 g, 18.4 mmol) in THF (100 mL) was added NaH (2.21 g, 55.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then 1-Boc-4-piperidone (7.33 g, 36.8 mmol, CAS RN 79099-07-3) was added and

- 195 -

the mixture was stirred at 20 °C for 12 h. The mixture was poured into water (100 mL) and extracted three times with EtOAc (100 mL each). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (PE : EA = 100 : 1 to 50 : 1) to yield the desired compound as off-white solid (4 g, 9.52 mmol, 51.7%). MS (ESI): m/z = 365.9 [M-56+H]⁺.

Step d) *tert-Butyl 4-[[2-cyclopropyl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate*

A mixture of *tert*-butyl 4-[[2-bromo-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (2.0 g, 4.76 mmol), cyclopropylboronic acid (818 mg, 9.52 mmol, CAS RN 411235-57-9) and potassium carbonate (1973 mg, 14.3 mmol) in DMF (10 mL) and water (0.5 mL) was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was poured into water (50 mL) and extracted three times with EtOAc (50 mL each). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by prep-HPLC to give the compound as light yellow oil (1020 mg, 56.2% yield) MS (ESI): m/z = 326.0 [M-56+H]⁺.

Step e) *tert-Butyl 4-[[2-cyclopropyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate*

A mixture of *tert*-butyl 4-[[2-cyclopropyl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (1000 mg, 2.62 mmol) and PtO₂ (100 mg, 0.440 mmol) in EtOAc (20 mL) was stirred at 20 °C for 12 h under hydrogen atmosphere (1520 mm Hg). Then the mixture was filtered and the filtrate was concentrated to yield the compound as light yellow solid (940 mg, 93.5% yield). MS (ESI): m/z = 328.2 [M+H]⁺.

Method D6

BB92

N-methyl-N-[4-(trifluoromethyl)phenyl]piperidin-4-amine; trifluoroacetate salt

To a solution of *tert*-butyl 4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carboxylate (150 mg, 0.420 mmol) in DCM (1 mL) was added TFA (0.1 mL) at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated in vacuum. The residue was purified by pre-HPLC (in the presence of TFA) to give the desired product as yellow solid (120 mg, 77.0%). MS (ESI): m/z = 259.2 [M+H]⁺.

- 196 -

Step a) *tert-Butyl 4-[4-(trifluoromethyl)anilino]piperidine-1-carboxylate*

To a solution of p-trifluoromethylaniline (1.17 mL, 9.31 mmol, CAS RN 455-14-1) in DCM (30 mL) was added AcOH (0.560 g, 9.31 mmol) and 1-BOC-4-piperidone (2.78 g, 14.0 mmol, CAS RN 79099-07-3). Then 1M BH₃/THF solution (27.9 mL, 27.9 mmol) was added
5 carefully at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 12 h. The mixture was poured into saturated aqueous NH₄Cl solution (30 mL) and extracted three times with EtOAc. The combined organic layers were washed twice with water H₂O, and then brine, dried over Na₂SO₄ and concentrated in vacuum to afford yellow residue, which was purified by silica gel column eluting with a gradient of PE : EtOAc (20 : 1 to 5 : 1) to give the
10 desired product as white solid (2.0 g, 62.4%). MS (ESI): m/z = 289.1 [M-56+H]⁺.

Step b) *tert-Butyl 4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carboxylate*

To a solution of NaH (52.3 mg, 60.0% wt%, 1.31 mmol) in DMF (5 mL) was added *tert*-butyl 4-[4-(trifluoromethyl)anilino]piperidine-1-carboxylate (300 mg, 0.870 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 15 min, and then iodomethane
15 (371 mg, 2.61 mmol) was added. The reaction mixture was stirred at 80 °C for 12 hrs. The reaction mixture was poured into water (20 mL) and extracted three times with EtOAc, the combined organic layers were washed twice with water and brine, dried over sodium sulfate and concentrated in vacuum to afford light yellow residue, which was purified by silica gel column eluting with a gradient of PE : EtOAc (20 : 1 to 5 : 1) to give the desired product as white solid
20 (160 mg, 51.3%). MS (ESI): m/z = 303.1 [M-56+H]⁺.

BB93

N-methyl-N-(4-(trifluoromethyl)phenyl)azetidin-3-amine (trifluoroacetic acid salt)

The title compound was prepared in analogy to method D6 from *tert*-butyl 3-[N-methyl-4-(trifluoromethyl)anilino]azetidine-1-carboxylate (48%). MS (ESI): m/z = 231.1 [M+H]⁺.

25 Step a) *tert-Butyl 3-[4-(trifluoromethyl)anilino]azetidine-1-carboxylate*

To a solution of p-trifluoromethylaniline (0.780 mL, 6.21 mmol, CAS RN 455-14-1), AcOH (1.86 g, 31.0 mmol) and 1-BOC-3-azetidinone (2.13 g, 12.4 mmol, CAS RN 398489-26-4) in EtOH (10 mL) was added NaBH₃CN (1.95 g, 31.0 mmol) at 25 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into saturated aqueous NH₄Cl solution (20 mL)
30 and extracted twice with EtOAc. The combined organic layers were washed twice with H₂O and

- 197 -

brine, dried over sodium sulfate and concentrated in vacuum to afford yellow residue, which was purified by silica gel column eluting with a gradient of PE : EtOAc (10 : 1 to 5 : 1) to give the desired product as white solid (340 mg, 17.3%). MS (ESI): $m/z = 261.1$ $[M-56+H]^+$.

Step b) *tert-Butyl 3-[N-methyl-4-(trifluoromethyl)anilino]azetidine-1-carboxylate*

- 5 To a solution of *tert-butyl 3-[4-(trifluoromethyl)anilino]azetidine-1-carboxylate* (300 mg, 0.950 mmol) in DMF (5 mL) was added NaH (45.5 mg, 60% wt%, 1.14 mmol) at 0 °C. The mixture was stirred for 15 min, and then iodomethane (404 mg, 2.85 mmol) was added. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into H₂O (20 mL) and extracted twice with EtOAc. The combined organic layers were washed three times with H₂O
10 and brine, dried over Na₂SO₄ and concentrated in vacuum to afford yellow residue. The residue was purified by silica gel column eluting with a gradient of PE : EtOAc (10 : 1 to 5 : 1) to give the desired product as white solid (310 mg, 98.9%). MS (ESI): $m/z = 275.2$ $[M-56+H]^+$.

Method D7

BB94

- 15 **N-methyl-N-(piperidin-4-yl)-2-(3-(trifluoromethyl)phenyl)acetamide hydrochloride**

To a solution of *tert-butyl 4-[methyl-[2-[3-(trifluoromethyl)phenyl]acetyl]amino]piperidine-1-carboxylate* (0.080 g, 200 µmol) in DCM (1 mL) was added a 2 M HCl solution in diethyl ether (999 µL, 2 mmol). The reaction mixture was stirred at RT overnight and then concentrated in vacuo to afford the title compound (67 mg, 199 µmol) as an off-white solid. MS (ESI): $m/z =$
20 301.2 $[M+H]^+$.

Step a) *tert-Butyl 4-[methyl-[2-[3-(trifluoromethyl)phenyl]acetyl]amino]piperidine-1-carboxylate*

- To a stirred mixture of 2-(3-(trifluoromethyl)phenyl)acetic acid (105 mg, 513 µmol, CAS RN 351-35-9) in DMF (5 mL) was added HATU (195 mg, 513 µmol) and DIPEA (181 mg, 244 µL,
25 1.4 mmol). After 15 min. stirring, *tert-butyl 4-(methylamino)piperidine-1-carboxylate* (0.100 g, 467 µmol, CAS RN 147539-41-1) was added and the reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted with DCM and washed with H₂O. The org. phase was concentrated to give a crude product which was purified by flash chromatography on a 20 g SiO₂ column, using an eluent mixture of n-heptane and EtOAc (0% to 100%) to afford the desired

- 198 -

compound as a light yellow oil (85 mg, 213 μ mol). MS (ESI): m/z = 459.259 [M + $\text{CH}_3\text{CN}+\text{NH}_4$] $^+$.

Method D8

BB194

5

3-(4-Chloro-3-cyclopropylphenoxy)azetidine

To a solution of *tert*-butyl 3-(4-chloro-3-cyclopropylphenoxy)azetidine-1-carboxylate (0.023 g, 0.057 mmol) in DCM (1 mL) was added TFA (0.088 mL, 1.14 mmol) and the reaction mixture stirred at room temperature for 18 hours. The mixture was diluted with DCM, poured into a sat. aq. NaHCO_3 solution and extracted with DCM. The combined organic layers were washed with
10 brine, dried over Na_2SO_4 , filtered and evaporated to dryness to yield the crude title compound (0.007 g, 35%) as a colorless oil. MS (ESI): m/z = 224.1 [M + H] $^+$.

Step a) *tert*-Butyl 3-(3-bromo-4-chlorophenoxy)azetidine-1-carboxylate

In a sealed tube, 3-bromo-4-chlorophenol (0.1 mg, 0.482 mmol) and *tert*-butyl 3-hydroxyazetidine-1-carboxylate (0.083 g, 0.482 mmol) were dissolved in toluene (1.5 mL). The
15 vial was degassed with argon, then (tributylphosphoranylidene)acetonitrile (CAS RN 157141-27-0, 0.195 mL, 0.723 mmol) was added and the reaction mixture heated to 100°C for 30 minutes. The mixture was diluted with EtOAc, poured into sat. aq. NaHCO_3 solution and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel
20 flash chromatography eluting with a 0 to 20% EtOAc/heptane gradient to give the title compound (0.116 g, 53%) as a yellow oil. MS (ESI): m/z = 308.1 [M -56+ H] $^+$.

Step b) *tert*-Butyl 3-(4-chloro-3-cyclopropylphenoxy)azetidine-1-carboxylate

In a microwave vial, *tert*-butyl 3-(3-bromo-4-chlorophenoxy)azetidine-1-carboxylate (0.075 g, 0.165 mmol), cyclopropylboronic acid (0.021 g, 0.248 mmol) and K_2CO_3 (0.046 g, 0.331 mmol)
25 were mixed in dioxane (1.6 mL). Then, water (0.4 mL) was added followed by bis(triphenylphosphine)palladium (II) chloride (0.012 g, 0.016 mmol) and the reaction mixture heated at 130°C under microwave irradiation for 1 hour. The reaction mixture was diluted with EtOAc, poured into water and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica

- 199 -

gel flash chromatography, eluting with a 0 to 10% EtOAc/heptane gradient to give the title compound (0.023 g, 43%) as a colorless oil. MS (ESI): $m/z = 268.2$ $[M-56+H]^+$.

Method D9

BB197

5 **3-(2-Chloro-3-cyclopropylphenoxy)azetidine, trifluoroacetate salt**

To a solution of *tert*-butyl 3-(2-chloro-3-cyclopropyl-phenoxy)azetidine-1-carboxylate (0.1 g, 0.310 mmol) in DCM (2.5 mL) was added TFA (0.25 mL) and the reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo* to give the crude title compound (0.083 g, 80% yield) as a dark brown oil. MS (ESI): $m/z = 224.6$ $[M+H]^+$.

10 **Step a) *tert*-Butyl 3-(3-bromo-2-chloro-phenoxy)azetidine-1-carboxylate**

To a solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (0.5 g, 2.89 mmol) and 3-bromo-2-chloro-phenol (0.5 g, 2.41 mmol) in THF (10 mL) were added PPh_3 (0.948 g, 3.62 mmol) followed by diethyl azodicarboxylate (0.47 mL, 3.62 mmol) and the reaction mixture was stirred at room temperature for 12 hours. The mixture was purified by reversed phase HPLC to give the
15 title product (0.4 g, 46%) as a light yellow oil. MS (ESI): $m/z = 308.3$ $[M-56+H]^+$.

Step b) *tert*-Butyl 3-(2-chloro-3-cyclopropylphenoxy)azetidine-1-carboxylate

In a sealed tube, cyclopropylboronic acid (0.071 g, 0.830 mmol), *tert*-butyl 3-(3-bromo-2-chloro-phenoxy)azetidine-1-carboxylate (0.2 g, 0.550 mmol) and Na_2CO_3 (0.117 g, 1.1 mmol) were mixed in 1,4-dioxane (5 mL) and water (1 mL). Then, $Pd(dppf)Cl_2$ (0.040 g, 0.060 mmol)
20 was added and the mixture was stirred to 110 °C for 12 hours. The mixture was purified by reversed phase HPLC to give the title compound (0.12 g, 67%) as a light yellow oil. MS (ESI): $m/z = 268.1$ $[M-56+H]^+$.

Method D10

BB202

25 **5-(4-Piperidyloxy)-2-(trifluoromethyl)benzonitrile, trifluoroacetate**

To a solution of *tert*-butyl 4-[3-cyano-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (0.05 g, 0.140 mmol) in DCM (1.5 mL) was added TFA (0.2 mL) and the reaction mixture

- 200 -

stirred at room temperature for 12 hours. The mixture was concentrated *in vacuo* to give the crude title compound (0.051 g, 98%) as a light brown oil. MS (ESI): $m/z = 271.6$ $[M+H]^+$.

Step a) *tert*-Butyl 4-[3-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

To a solution of 3-bromo-4-(trifluoromethyl)phenol (0.5 g, 2.54 mmol) and 1-Boc-4-hydroxypiperidine (0.512 g, 2.54 mmol) in THF (8.5 mL) were added PPh₃ (1 g, 3.82 mmol) followed by diethyl azodicarboxylate (0.665 g, 3.82 mmol) and the reaction mixture was stirred at room temperature for 12 hours. The mixture was purified by silica gel flash chromatography, eluting with with PE:EtOAc 5:1 to give the title compound (0.5 g, 47%) as a light yellow oil. MS (ESI): $m/z = 370.2$ $[M-56 + H]^+$.

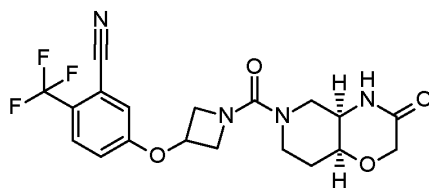
Step b) *tert*-Butyl 4-[3-cyano-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

In a sealed tube, *tert*-butyl 4-[3-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (0.2 g, 0.470 mmol), Zn(CN)₂ (0.111 g, 0.940 mmol), CuI (0.09 g, 0.470 mmol) were mixed in DMF (10 mL). Then, Pd(PPh₃)₄ (0.109 g, 0.090 mmol) was added and the reaction mixture stirred to 130 °C for 16 hours. The mixture was purified by reversed phase HPLC to give the title product (0.05 g, 29%) as a colorless oil. MS (ESI): $m/z = 315.5$ $[M-56+H]^+$.

Method E

Example 263

(+)-5-[1-[(4aR,8aS)-3-Oxo-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazine-6-carbonyl]azetidin-3-yl]oxy-2-(trifluoromethyl)benzonitrile



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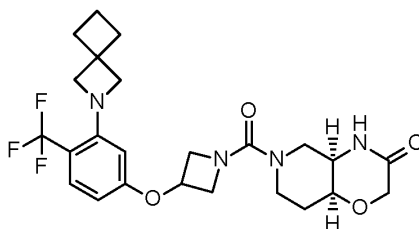
In a sealed tube, (+)-(4aR,8aS)-6-[3-[3-bromo-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB 205, 0.2 g, 0.420 mmol), Zn(CN)₂ (0.098 g, 0.840 mmol), Zn (0.027 g, 0.420 mmol), dppf (0.232 g, 0.420 mmol), Hünig's base (0.108 g, 0.840 mmol) were mixed in DMA (10 mL) and the mixture was degassed. Then, Pd₂(dba)₃ (76.59 mg, 0.080 mmol) was added and the reaction mixture was stirred at 130°C for 16 h. The mixture was purified by reversed phase HPLC to give the title compound (0.055 g, 30%) as a light yellow solid. MS (ESI): $m/z = 425.3$ $[M+H]^+$.

25

- 201 -

Method F**Example 265**

(+)-(4aR,8aS)-6-[3-[3-(2-Azaspiro[3.3]heptan-2-yl)-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one



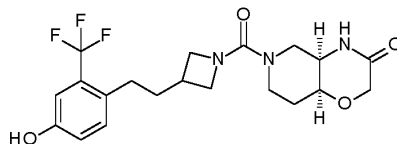
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In a sealed tube, (+)-(4aR,8aS)-6-[3-[3-bromo-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one (BB203, 0.2 g, 0.420 mmol), 2-azaspiro[3.3]heptane (CAS RN 665-04-03, 0.117 g, 0.630 mmol), BINAP (0.052 g, 0.080 mmol) and K₂CO₃ (0.173 g, 1.25 mmol) were mixed in DMF (10 mL) and the mixture was degassed. Then, Pd₂(dba)₃ (76.59 mg, 0.080 mmol) was added and the reaction mixture was stirred to 110 °C for 16 hours. The reaction mixture was filtered off, the filtrate diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL). Combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by reversed phase HPLC to give the title compound (0.06 g, 29%) as a white solid. MS (ESI): m/z = 495.1 [M+H]⁺.

15

Method G**Example 293**

(4aR,8aS)-6-(3-(4-Hydroxy-2-(trifluoromethyl)phenethyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one



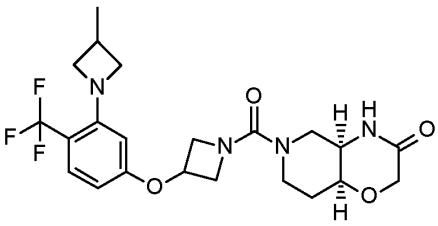
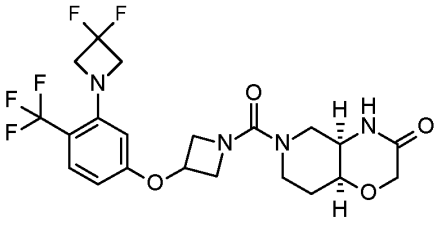
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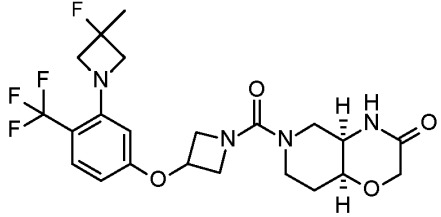
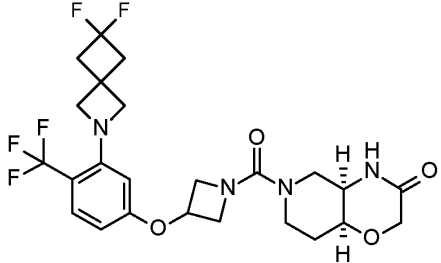
Boron tribromide (11.3 mg, 4.29 μL, 45.3 μmol) was added to an ice cooled solution of (4aR,8aS)-6-(3-(4-methoxy-2-(trifluoromethyl)phenethyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (Example 216, 20 mg, 45.3 μmol) in DCM (0.5 mL). The reaction mixture was stirred at ambient temperature for 3 h. A saturated solution of aqueous

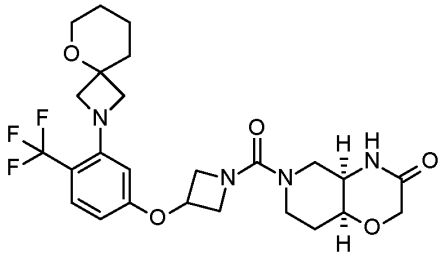
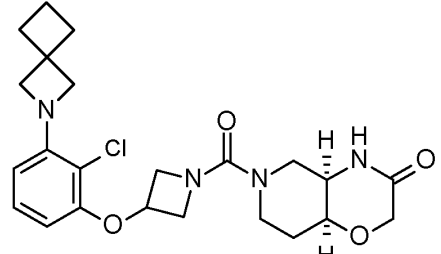
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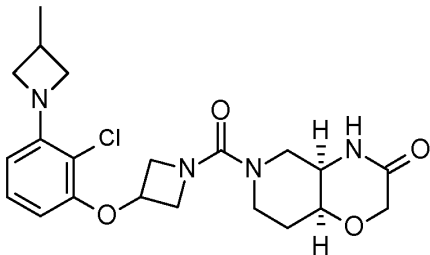
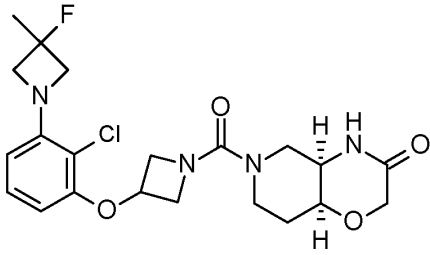
NaHCO₃ was added and the mixture was extracted with AcOEt. The layers were separated, the organic layer was dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude product was purified by prep. HPLC to give the title compound (19%) as colorless solid. MS (ESI): m/z = 427.2 [M+H]⁺.

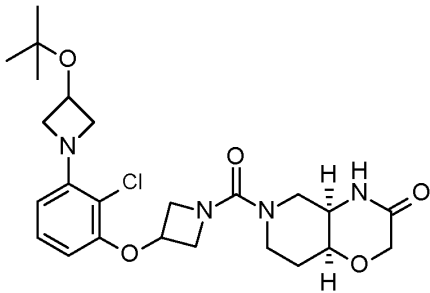
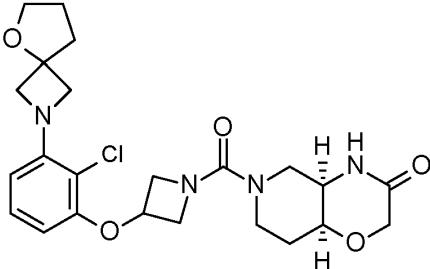
- 5 The following examples listed in the table below were prepared in analogy to the procedure described for the preparation of Example 265 by using the indicated intermediates and/or commercially available compounds and using the mentioned purification method such as reversed-phase HPLC or silica gel flash chromatography.

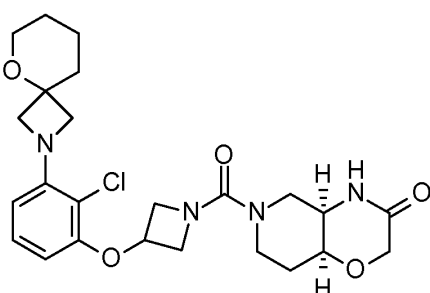
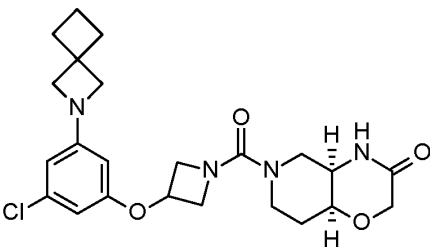
Ex	Systematic Name / Structure	Intermediates	MS, m/z
266	(+)-(4aR,8aS)-6-[3-[3-(3-Methylazetidin-1-yl)-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB203 BH66 and 3-Methylazetidine hydrochloride (CAS RN 935669-28-6)	469.2 [M+H]⁺
267	(+)-(4aR,8aS)-6-[3-[3-(3,3-Difluoroazetidin-1-yl)-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB203 and Difluoroazetidine hydrochloride (CAS RN 288315-03-7)	491.2 [M+H]⁺

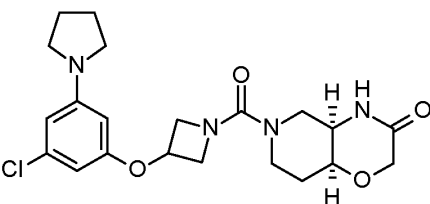
268	(+)-(4aR,8aS)-6-[3-[3-(3-Fluoro-3-methyl-azetidin-1-yl)-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB203 and 3-Fluoro-3-methyl-azetidine hydrochloride (CAS RN 1427379-42-7)	487.3 [M+H]⁺
269	(+)-(4aR,8aS)-6-[3-[3-(6,6-Difluoro-2-azaspiro[3.3]heptan-2-yl)-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB203 and 6,6-Difluoro-2-azaspiro[3.3]heptane (CAS RN 1354952-05-8)	531.1 [M+H]⁺

270	(+)-(4aR,8aS)-6-[3-[3-(5-oxa-2-azaspiro[3.5]nonan-2-yl)-4-(trifluoromethyl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB203 and 5-Oxa-2-azaspiro[3.5]nonane (CAS RN 138387-19-6)	525.3 [M+H]⁺
271	(+)-(4aR,8aS)-6-[3-[3-(2-Azaspiro[3.3]heptan-2-yl)-2-chlorophenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 258 and 2-Azaspiro[3.3]heptane (CAS RN 665-04-03)	461.1 [M+H]⁺

272	(+)-(4aR,8aS)-6-[3-[2-Chloro-3-(3-methylazetidin-1-yl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 258 and 3-Methylazetidine hydrochloride (CAS RN 935669-28-6)	435.1 [M+H]⁺
273	(+)-(4aR,8aS)-6-[3-[2-Chloro-3-(3-fluoro-3-methyl-azetidin-1-yl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 258 and 3-Fluoro-3-methyl- azetidine hydrochloride (CAS RN 1427379-42-7)	453.2 [M+H]⁺

274	(+)-(4aR,8aS)-6-(3-(3-(3-(tert-Butoxy)azetidin-1-yl)-2-chlorophenoxy)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one 	Example 258 and 3-<i>tert</i>-Butoxyazetidine (CAS RN 1147530-63-9)	493.2 [M+H]⁺
275	(+)-(4aR,8aS)-6-[3-[2-Chloro-3-(5-oxa-2-azaspiro[3.4]octan-2-yl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 258 and 5-Oxa-2-azaspiro[3.4]octane (CAS RN 145309-24-6)	477.2 [M+H]⁺

276	(+)-(4aR,8aS)-6-[3-[2-chloro-3-(5-oxa-2-azaspiro[3.5]nonan-2-yl)phenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	Example 258 and 5-Oxa-2-azaspiro[3.5]nonane (CAS RN 138387-19-6)	491.2 [M+H]⁺
277	(+)-(4aR,8aS)-6-[3-[3-(2-Azaspiro[3.3]heptan-2-yl)-5-chlorophenoxy]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB204 and 2-Azaspiro[3.3]heptane (CAS RN 665-04-03)	461.3 [M+H]⁺

278	(+)-(4aR,8aS)-6-[3-(3-Chloro-5-pyrrolidin-1-yl-phenoxy)azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one 	BB204 and Pyrrolidine	435.3 [M+H] ⁺
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In analogy to the methods described herein above, the following building blocks were prepared from the respective starting material indicated in the table below.

BB No.	Systematic Name	Starting material	Method	MS, m/z
BB47	3-[(2-Chlorophenoxy)methyl]pyrrolidine; hydrochloride salt	tert-Butyl 3-[(2-chlorophenoxy)methyl]pyrrolidine-1-carboxylate BB47a	D3	212.1 [M+H] ⁺
BB48	4-[[2-Fluoro-4-(trifluoromethyl)phenyl]methyl]piperidine; formic acid salt	tert-Butyl 4-[[2-fluoro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate BB48a	D2	262.1 [M+H] ⁺
BB49	3-[(2-Chlorophenyl)methoxy]pyrrolidine; hydrochloride salt	tert-Butyl 3-[(2-chlorophenyl)methoxy]pyrrolidine-1-carboxylate BB49a	D3	212.1 [M+H] ⁺
BB50	3-[(3-Chlorophenyl)methoxy]pyrrolidine; hydrochloride salt	tert-Butyl 3-[(3-chlorophenyl)methoxy]pyrrolidine-1-carboxylate BB50a	D3	212.1 [M+H] ⁺
BB52	3-[(4-Chlorophenoxy)methyl]pyrrolidine; hydrochloride salt	tert-Butyl 3-[(4-chlorophenoxy)methyl]pyrrolidine-1-carboxylate BB52a	D3	212.1 [M+H] ⁺
BB53	3-[(4-Chlorophenyl)methoxy]pyrrolidine formic acid salt	tert-Butyl 3-[(4-chlorophenyl)methoxy]pyrrolidine-1-carboxylate BB53a	D2	Used without further purification

BB54	4-[[2-Methyl-4-(trifluoromethyl)phenyl]methyl]piperidine; formic acid salt	tert-Butyl 4-[[2-methyl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate BB54a	D2	258.2 [M+H] ⁺
BB55	4-[[2-Chloro-4-(trifluoromethyl)phenyl]methyl]piperidine; trifluoroacetate salt	tert-Butyl 4-[[2-chloro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate BB55a	D1	278.0 [M+H] ⁺
BB71	4-[4-Chloro-3-(trifluoromethyl)phenoxy]piperidine; hydrochloride salt	tert-Butyl 4-[4-chloro-3-(trifluoromethyl)phenoxy]piperidine-1-carboxylate BB71a	D3	280.0 [M+H] ⁺
BB72	4-(4-Chloro-3-cyclopropylphenoxy) piperidine; trifluoroacetate salt	tert-Butyl 4-(4-chloro-3-cyclopropylphenoxy)piperidine-1-carboxylate BB72a	D1	Used without further purification
BB73	4-[2-Chloro-5-(4-piperidyloxy) phenyl] morpholine hydrochloride	tert-Butyl 4-(4-chloro-3-morpholino-phenoxy)piperidine-1-carboxylate BB73a	D3	Used without further purification
BB74	4-[2-Methyl-4-(trifluoromethyl)phenoxy]piperidine; trifluoroacetate salt	tert-Butyl 4-[2-methyl-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate BB74a	D1	260.2 [M+H] ⁺
BB75	2-(4-Piperidyloxy)-5-(trifluoromethyl)benzonitrile	tert-Butyl 4-[2-cyano-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate BB75a	D4	271.1 [M+H] ⁺
BB76	2-(4-Piperidylmethyl)oxazolo[5,4-c]pyridine; trifluoroacetate salt	tert-Butyl 4-(oxazolo[5,4-c]pyridin-2-ylmethyl)piperidine-1-carboxylate BB76a	D1	218.1 [M+H] ⁺
BB89	3-[(3-Chlorophenoxy)methyl]pyrrolidine; hydrochloride salt	tert-Butyl 3-[(3-chlorophenoxy)methyl]pyrrolidine-1-carboxylate BB89a	D3	212.1 [M+H] ⁺
BB192	4-[2-Fluoro-4-(trifluoromethyl)phenoxy]piperidine; hydrochloride salt	tert-Butyl 4-hydroxypiperidine-1-carboxylate	D3	264.2 [M+H] ⁺
BB193	4-[3-Chloro-4-(trifluoromethyl)phenoxy]piperidine; hydrochloride salt	tert-Butyl 4-[3-chloro-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate	D3	280.1 [M+H] ⁺
BB195	4-[2-Chloro-3-(trifluoromethyl)phenoxy]piperidine; hydrochloride salt	tert-Butyl 4-[2-chloro-3-(trifluoromethyl)phenoxy]piperidine-1-carboxylate	D8	280.1 [M+H] ⁺

BB196	3-(3-Bromo-2-chloro-phenoxy)azetidine; trifluoroacetate salt	<i>tert</i> -Butyl 3-(3-bromo-2-chloro-phenoxy)azetidine-1-carboxylate	D1	263.0 [M+H] ⁺
BB198	3-[3-Bromo-4-(trifluoromethyl)phenoxy]azetidine; trifluoroacetate salt	<i>tert</i> -Butyl 3-[3-bromo-4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate	D9	296.4 [M+H] ⁺
BB199	3-[3-Cyclopropyl-4-(trifluoromethyl)phenoxy]azetidine; trifluoroacetate salt	<i>tert</i> -Butyl 3-[3-cyclopropyl-4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate	D9	258.1 [M+H] ⁺
BB200	3-[3-Chloro-4-(trifluoromethyl)phenoxy]azetidine; trifluoroacetate salt	<i>tert</i> -Butyl 3-[3-chloro-4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate	D1	252.5 [M+H] ⁺
BB201	3-(3-Bromo-5-chloro-phenoxy)azetidine; trifluoroacetate salt	<i>tert</i> -Butyl 3-(3-bromo-5-chloro-phenoxy)azetidine-1-carboxylate	D1	263.9 [M+H] ⁺
BB205	3-(3-Bromo-4-chloro-phenoxy)azetidine; trifluoroacetate salt	<i>tert</i> -Butyl 3-(3-bromo-4-chlorophenoxy)azetidine-1-carboxylate	D1	263.9 [M+H] ⁺

BB91**4-[[2-Pyrrolidin-1-yl-4-(trifluoromethyl)phenyl]methyl]piperidine; formic acid salt**

A solution of *tert*-butyl 4-[[2-pyrrolidin-1-yl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate (500 mg, 1.21 mmol) in 6 M HCl in MeOH solution (10.0 mL) was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum, purified by reversed phase column to give the title compound as an orange oil (84.4 mg, 21.8% yield). MS (ESI): *m/z* = 313.2 [M+H]⁺.

Step a) *Tert-butyl 4-[[2-pyrrolidin-1-yl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate*

To a solution of *tert*-butyl 4-[[2-bromo-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (800 mg, 1.90 mmol; BB51, step c), pyrrolidine (163 mg, 2.28 mmol), Ruphos (4.25 mg, 0.010 mmol) and potassium *tert*-butoxide (320 mg, 2.86 mmol) in toluene (15 mL) was added palladium(II) acetate (1.28 mg, 0.010 mmol). The mixture was stirred at 80 °C for 15 h under N₂ atmosphere. The mixture was filtered and concentrated under vacuum to remove toluene. The mixture was diluted with H₂O (40 mL) and extracted three times with EtOAc (40

- 212 -

mL each). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (PE / EtOAc = 1:0 to 8:1) to give the compound as light yellow oil (552 mg, 1.34 mmol, 36.7%) MS (ESI): m/z = 411.1 [M+H]⁺.

5 Step b) *Tert-butyl 4-[[2-pyrrolidin-1-yl-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate*

To a solution of *tert-butyl 4-[[2-pyrrolidin-1-yl-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate* (525 mg, 0.660 mmol) in MeOH (20 mL) was added wet Pd/C (~52 mg) and the mixture was stirred at 20 °C under H₂ atmosphere (balloon) for 1 h. The mixture was filtered
10 and concentrated under vacuum to give the desired compound as colorless oil (500 mg) which was used in the next step without further purification.

BB95

3-[2-[2-fluoro-6-(trifluoromethyl)phenyl]ethyl]azetidine 4-methylbenzenesulfonate

To an solution of *3-[2-[2-fluoro-6-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate* (50
15 mg, 144 µmol, Eq: 1) in EtOAc (0.8 mL) was added 4-methylbenzenesulfonic acid monohydrate (29.7 mg, 173 µmol, Eq: 1.2) and the mixture was heated at reflux for 1.5 hours. The clear, colorless solution was allowed to cool down to RT. No precipitation occurred. The solution was evaporated to give the desired product as a colorless foam. MS (ESI): m/z = 248.1 [M-TsOH+H]⁺.

20 Step a) *tert-butyl 3-[(E)-2-[2-fluoro-6-(trifluoromethyl)phenyl]ethenyl]azetidine-1-carboxylate*

To an ice-cold solution of diethyl (2-fluoro-4-(trifluoromethyl)benzyl)phosphonate (300 mg, 955 µmol) in THF (2 mL) was added sodium hydride 55% in mineral oil (41.7 mg, 955 µmol) and the mixture was stirred at this temperature for 30 minutes. To the light brown mixture was added dropwise a solution of *tert-butyl 3-formylazetidine-1-carboxylate* (177 mg, 955 µmol) in THF (1
25 mL). This led to an immediate discolouration of the reaction mixture. Stirring was continued for 1 hours at ice-bath temperature followed by stirring at RT for 1.5 hours. The reaction mixture was poured into water and ethyl acetate and the layers were separated. The aqueous layer was extracted twice with ethyl acetate. The organic layers were washed once with brine, dried over MgSO₄, filtered, treated with silica gel and evaporated. The compound was purified by silica gel
30 chromatography on a 12 g column using an MPLC system eluting with a gradient of n-heptane :

- 213 -

ethyl acetate (100 : 0 to 25 : 75) to get the desired compound as a colorless solid (0.108 g; 32.8%). MS (ESI): $m/z = 290.2$ $[M-56+H]^+$.

Step b) *tert-butyl 3-[2-[2-fluoro-6-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

To a solution of *tert-butyl (E)-3-(2-fluoro-4-(trifluoromethyl)styryl)azetidine-1-carboxylate* (105 mg, 304 μ mol) in MeOH (1 mL) and Ethyl acetate (1 mL) was added Pd/C 10% (11 mg, 304 μ mol) and the mixture was stirred under a hydrogen atmosphere at 1.7 bar and RT for 30 minutes. The suspension was filtered. The filtrate was evaporated to get the desired compound as a colorless oil (0.104 g; 98.5%). MS (ESI): $m/z = 292.2$ $[M-56+H]^+$.

BB96

10 **4-((2-chloro-4-fluorophenoxy)methyl)azepane hydrochloride**

To a solution of *tert-butyl 4-((2-chloro-4-fluorophenoxy)methyl)azepane-1-carboxylate* (620 mg, 1.73 mmol) in DCM (7.5 ml) was added HCl in ether 2M (10 ml, 20 mmol) and the reaction mixture was stirred overnight at rt. The mixture was concentrated in vacuo, the crude material collected as a white solid (490 mg, 1.67 mmol, 96.1 %) and used directly on the next step. LC-MS (ESI): m/z : 258.2 $[M+H]^+$

Step a) *tert-butyl 4-((2-chloro-4-fluorophenoxy)methyl)azepane-1-carboxylate*

In a 25ml four-necked sulphonation flask under argon, *tert-butyl 4-(hydroxymethyl)azepane-1-carboxylate* (480 mg, 2.09 mmol) was dissolved in THF (10 ml). Subsequently, 2-chloro-4-fluorophenol (337 mg, 2.3 mmol) and triphenylphosphine (604 mg, 2.3 mmol) were added and the clear solution was stirred for 5 min at rt.. The mixture was cooled to 0°C and DEAD (401 mg, 2.3 mmol) was added in portions over 10min. The mixture was stirred for 1 hr at 0°C, then overnight at rt. The mixture was taken up into EtOAc (50 ml), washed with water (2x25 ml), organic phase washed with 1M NaOH (3x25 ml), brine (20 ml), dried with Na₂SO₄, filtered and concentrated in vacuo. Residue was dissolved in n-Heptane/diethylether and the mixture stirred for 30 min, the TPPO precipitate filtered and the crude concentrated in vacuo. The crude material was adsorbed on Isolute® and purified by flash column chromatography (0 – 30% EtOAc/Heptane) over silica gel (50 g) to afford the desired product (630 mg, 1.76 mmol, 84.1%) as a yellow oil. LC-MS (ESI): m/z : 302.1 $[M-56+H]^+$

- 214 -

BB97

4-[[4-(trifluoromethyl)phenyl]methyl]azepane hydrochloride

To a solution of tert-butyl 4-(4-(trifluoromethyl)benzyl)azepane-1-carboxylate (88 mg, 246 μ mol, Eq: 1) in DCM (1.5 ml) was added HCl in ether 2M (3.08 ml, 6.16 mmol) and the reaction mixture was stirred overnight at room temperature. The mixture was concentrated in vacuo, the crude material collected as a white solid (71 mg, 0.24 mmol, 98.2 %) and used directly on the next step. LC-MS (ESI): m/z: 258.2 [M+H]⁺

Step a: Triphenyl(4-(trifluoromethyl)benzyl)phosphonium bromide

Triphenylphosphine (1.84 g, 7 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.61 g, 6.74 mmol) were dissolved in xylene (35 ml). The reaction mixture was heated to reflux at 155 °C for 3.5 h and then cooled to room temperature. The precipitated white crystalline solid was collected by filtration, washed with diethyl ether and dried *in vacuo*. The final compound (3.30 g, 6.58 mmol, 97.7 % yield) was obtained as a white powder and directly used on the next step. LC-MS (ESI): m/z: 421.2 [M+H]⁺

Step b: tert-butyl (E)-4-(4-(trifluoromethyl)benzylidene)azepane-1-carboxylate

A suspension of sodium hydride (88.6 mg, 2.22 mmol) in DMF (7.5 ml) was cooled in an ice bath, then triphenyl(4-(trifluoromethyl)benzyl)phosphonium bromide (1.11 g, 2.22 mmol) was added. The suspension was stirred at 0 °C for 5 min. then for 25 min at rt. tert-butyl 4-oxoazepane-1-carboxylate (315 mg, 1.48 mmol) was added and the resulting mixture was stirred at 80 °C for 28 h. The mixture was concentrated in vacuo, diluted with water (50 ml) and EtOAc (40 ml) and extracted EtOAc (3x 30ml). The combined organic fractions were washed with water, 10% LiCl solution, dried with Na₂SO₄ and concentrated in vacuo. The residual oil was treated with Et₂O in order to precipitate the triphenylphosphoxide that was filtered off. The solution was concentrated in vacuo and the residue was purified by flash column chromatography (0 – 35% EtOAc/Heptane) over silica gel (50 g) to afford the desired product (92 mg, 259 μ mol, 17.5 % yield) as a yellow oil. LC-MS (ESI): m/z: 300.2 [M-56+H]⁺

Step c: tert-butyl 4-(4-(trifluoromethyl)benzyl)azepane-1-carboxylate

A solution of tert-butyl (E)-4-(4-(trifluoromethyl)benzylidene)azepane-1-carboxylate (90 mg, 253 μ mol) was dissolved in MeOH (2.5 ml). The reaction vessel was evacuated and back-filled with argon 5 times. Under argon, Pd-C (13.5 mg, 12.7 μ mol) was added and the atmosphere was

- 215 -

replaced with hydrogen three times. The reaction was stirred under a hydrogen atmosphere at 1 bar for 24h. The atmosphere was replaced with argon and the reaction mixture was filtered over a pad of Dicalite. The filter cake was washed with methanol. The filtrate was concentrated in vacuo to give the desired product (89 mg, 249 μ mol, 98.3 % yield) as a colorless oil which was used without further purification. LC-MS (ESI): m/z: 302.2 [M-56+H]⁺

BB98

3-((2-Chloro-4-(trifluoromethyl)phenyl)thio)azetidine 2,2,2-trifluoroacetate

tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxylate (110 mg, 299 μ mol) was dissolved in DCM (2 mL) and TFA (273 mg, 184 μ L, 2.39 mmol) was added. The reaction mixture was stirred at RT for 3 h. Volatiles were removed in vacuo to yield 110 mg of a light yellow solid (96%). MS (ESI): m/z = 268.1 [M+H]⁺.

Step a) *tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxylate*

In a 20 mL glastube, a solution of 2-chloro-4-(trifluoromethyl)benzenethiol (440 mg, 2.07 mmol) in dry THF (6 mL) was added potassium tert-butoxide 1M solution in THF (2.17 mL, 2.17 mmol) and the yellow reaction mixture was stirred at RT for 15 min followed by addition of tert-butyl 3-bromoazetidine-1-carboxylate (489 mg, 2.07 mmol). The reaction mixture was then stirred at RT for 5 h and over night at 70°C. The crude reaction was diluted with EtOAc and extracted with H₂O, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness. The residue was purified by chromatography (SiO₂, n-heptane / EtOAc (0 to 40% over 40 min) yielded the product as a viscous oil (467 mg, 61%). MS (ESI): m/z = 312.1 [M-56]⁺.

BB99

3-((2-Chloro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine 2,2,2-trifluoroacetate

tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-carboxylate (100 mg, 250 μ mol) was dissolved in DCM and TFA (228 mg, 154 μ L, 2 mmol) was added. The reaction mixture was stirred at RT for 8 h. Volatiles were removed in vacuo to yield the desired compound as light yellow solid (102 mg, 98%). MS (ESI): m/z = 300.0 [M+H]⁺.

Step a) *tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxylate*

- 216 -

In a 20 mL glastube, a solution of 2-chloro-4-(trifluoromethyl)benzenethiol (440 mg, 2.07 mmol) in dry THF (6 mL) was added potassium tert-butoxide 1M solution in THF (2.17 mL, 2.17 mmol) and the yellow reaction mixture was stirred at r.t for 15 min followed by addition of tert-butyl 3-bromoazetidine-1-carboxylate (489 mg, 2.07 mmol). The reaction mixture was then stirred at r.t for 5 h and over night at 70°C. The crude reaction was diluted with EtOAc and extracted with H₂O, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness. The residue was purified by column chromatography (SiO₂, n-heptane / EtOAc (0 to 40% over 40 min) to yield the desired product as a viscous oil (467 mg, 61%). MS (ESI): m/z = 312.1 [M-56+H]⁺.

Step b) *tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)azetidine-1-carboxylate*

mCPBA (347 mg, 1.41 mmol) was added in one portion to a stirred solution of tert-butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxylate (345 mg, 938 μmol) in DCM (6 mL) in an ice bath. The reaction was stirred at RT for 20 min. The reaction mixture was poured into 5 mL saturated Na₂CO₃ solution and extracted twice with DCM (20 mL each). The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by preparative HPLC (YMC-Triart C18, ACN / H₂O+0.1% HCOOH) to furnish the product as a white powder (253 mg, 67.5%) MS (ESI): m/z = 344.0 [M-56+H]⁺.

20

BB100**3-((2-Chloro-4-(trifluoromethyl)phenyl)sulfinyl)azetidine 2,2,2-trifluoroacetate**

tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)sulfinyl)azetidine-1-carboxylate (50 mg, 130 μmol) was dissolved in DCM (1.5 mL), TFA (149 mg, 100 μL, 1.3 mmol) was added and the reaction mixture was stirred at RT for 8 h. Volatiles were removed in vacuo to yield the compound as white solid (51 mg, 98%). MS (ESI): m/z = 284.1 [M+H]⁺.

Step a) *tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)thio)azetidine-1-carboxylate*

The compound was prepared in analogy to BB99, step a, and used in the next step without further purification.

Step b) *tert-Butyl 3-((2-chloro-4-(trifluoromethyl)phenyl)sulfinyl)azetidine-1-carboxylate*

- 217 -

The sulfoxide intermediate was isolated from the the synthesis of the according sulfone building block BB99, step b. The product was obtained as a white lyophilized powder (50 mg, 13.9%)
MS (ESI): $m/z = 328.1$ $[M-56+H]^+$.

BB101

5 3-(((2-Chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine 2,2,2-trifluoroacetate

To a solution of tert-butyl 3-(((2-chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine-1-carboxylate (0.200 g, 524 μ mol) in DCM (3 mL) was added TFA (478 mg, 323 μ L, 4.19 mmol) and the reaction mixture was stirred at RT for 3 h. Volatiles were removed in vacuo to yield the compound as light yellow oil that was used in the next step without further purification
10 (267 mg). MS (ESI): $m/z = 282.2$ $[M+H]^+$.

Step a) *tert-Butyl 3-[[2-chloro-4-(trifluoromethyl)phenyl]sulfanylmethyl]azetidine-1-carboxylate*

To a solution of 2-chloro-4-(trifluoromethyl)benzenethiol (0.400 g, 1.88 mmol) in dry THF (6 mL) was added potassium tert-butoxide 1M solution in THF (1.98 mL, 1.98 mmol) and the turbid reaction mixture was stirred at RT for 15min followed by addition of tert-butyl 3-
15 (bromomethyl)azetidine-1-carboxylate (471 mg, 1.88 mmol). The reaction mixture was then stirred at RT for 19 h. The crude reaction was diluted with EtOAc and extracted with aq. 1 M NaHCO₃ solution, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness to yield the crude product which was used in the next step without further purification
20 (762 mg). MS (ESI): $m/z = 326.1$ $[M-56+H]^+$.

BB102

3-((2-Fluoro-6-(trifluoromethyl)benzyl)sulfonyl)azetidine 2,2,2-trifluoroacetate

tert-Butyl 3-((2-fluoro-6-(trifluoromethyl)phenyl)methylsulfonyl)azetidine-1-carboxylate (0.047 g, 118 μ mol) was dissolved in DCM (0.5 mL) and TFA (108 mg, 72.9 μ L, 946 μ mol) was
25 added. The reaction mixture was stirred at RT for 2 h. Volatiles were removed in vacuo to yield the compound as a yellow oil (56 mg) that was used in the next step without further purification. MS (ESI): $m/z = 298.2$ $[M+H]^+$.

tep a) *tert-Butyl 3-((2-fluoro-6-(trifluoromethyl)benzyl)thio)azetidine-1-carboxylate*

- 218 -

To a solution of tert-butyl 3-mercaptoazetidine-1-carboxylate (0.400 g, 2.11 mmol) in dry THF (5 mL) was added potassium tert-butoxide 1M solution in THF (2.22 mL, 2.22 mmol) and the reaction mixture was stirred at RT for 15 min followed by addition of 2-(bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene (CAS RN 239087-08-2). The reaction mixture was then stirred at RT for 14 h. The crude reaction was diluted with EtOAc and extracted with aq. 1 M NaHCO₃ solution, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over NaSO₄ and evaporated down to dryness to yield the crude product (805 mg) which was used in the next step without further purification. MS (ESI): m/z = 310.2 [M-56+H]⁺.

10 Step b) *tert-Butyl 3-[[2-fluoro-6-(trifluoromethyl)phenyl]methylsulfonyl]azetidine-1-carboxylate*

3-Chlorobenzoperoxoic acid (283 mg, 1.64 mmol) was added in portion to a stirred solution of tert-butyl 3-((2-fluoro-6-(trifluoromethyl)benzyl)thio)azetidine-1-carboxylate (0.300 g, 821 μmol) in DCM (5 mL) in an ice bath. The reaction mixture was stirred at RT for 15 min and poured into 5 mL saturated aqueous NaHCO₃ solution and extracted twice with DCM (10 mL each). The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, 20 g, 0% to 100% EtOAc in n-heptane) to furnish the desired product as a colorless oil (47 mg, 15%). MS (ESI): m/z = 415.1 [M+NH₄]⁺.

BB103

20 3-((2-Fluoro-6-(trifluoromethyl)benzyl)sulfinyl)azetidine 2,2,2-trifluoroacetate

tert-Butyl 3-[[2-fluoro-6-(trifluoromethyl)phenyl]methylsulfinyl]azetidine-1-carboxylate (0.086 g, 225 μmol) was dissolved in DCM (1 mL) and TFA (206 mg, 139 μL, 1.8 mmol) was added. The reaction mixture was stirred at RT for 2 h. Volatiles were removed *in vacuo* to yield the compound as a yellow oil (93 mg) that was used in the next step without further purification. MS (ESI): m/z = 282.2 [M+H]⁺.

Step a) *tert-Butyl 3-[[2-fluoro-6-(trifluoromethyl)phenyl]methylsulfinyl]azetidine-1-carboxylate*

The sulfoxide intermediate was isolated from the synthesis of BB102, step b, as a colorless oil (86 mg, 28%). MS (ESI): m/z = 404.1 [M+Na]⁺.

BB104

- 219 -

3-(((2-Chloro-4-(trifluoromethyl)phenyl)sulfonyl)methyl)azetidine 2,2,2-trifluoroacetate
tert-Butyl 3-(((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)methyl)azetidine-1-carboxylate
(0.145 g, 350 μ mol) was dissolved in DCM (2 mL) and TFA (320 mg, 216 μ L, 2.8 mmol) was
added. The reaction mixture was stirred at RT for 2 h. Volatiles were removed *in vacuo* to yield
5 the compound as a yellow oil (181 mg) that was used in the next step without further
purification. MS (ESI): $m/z = 314.1$ $[M+H]^+$.

Step a) *tert-Butyl 3-(((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)methyl)azetidine-1-*
carboxylate

3-Chlorobenzoperoxoic acid (352 mg, 1.57 mmol) was added in portions to a stirred solution of
10 tert-butyl 3-(((2-chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine-1-carboxylate (BB101,
step a) (0.300 g, 786 μ mol) in DCM (5 mL) in an ice bath. The reaction mixture was stirred at
RT for 15 min and poured into 5 mL saturated aqueous NaHCO_3 solution and extracted twice
with DCM (10 mL each). 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
15 (silica gel, 20 g, 0% to 100% EtOAc in n-heptane) to provide the desired product as a colorless
oil (145 mg, 45%). MS (ESI): $m/z = 314.0$ $[M-56+H]^+$.

BB105

3-(((2-Chloro-4-(trifluoromethyl)phenyl)sulfinyl)methyl)azetidine 2,2,2-trifluoroacetate
tert-Butyl 3-(((2-chloro-4-(trifluoromethyl)phenyl)sulfinyl)methyl)azetidine-1-carboxylate
20 (0.086 g, 216 μ mol) was dissolved in DCM (1 mL) and TFA (197 mg, 133 μ L, 1.73 mmol) was
added. The reaction mixture was stirred at RT for 2 h. Volatiles were removed *in vacuo* to yield
the compound as a yellow oil (99 mg) that was used in the next step without further purification.
MS (ESI): $m/z = 298.1$ $[M+H]^+$.

Step a) *tert-Butyl 3-(((2-chloro-4-(trifluoromethyl)phenyl)sulfinyl)methyl)azetidine-1-*
25 *carboxylate*

The sulfoxide intermediate was isolated from the synthesis of BB104, step a. The desired
product was obtained as a yellow oil (80 mg, 25.6%). MS (ESI): $m/z = 398.1$ $[M+H]^+$.

BB106

3-((2-Fluoro-4-(trifluoromethyl)benzyl)thio)azetidine 2,2,2-trifluoroacetate

- 220 -

To a solution of tert-butyl 3-((2-fluoro-4-(trifluoromethyl)benzyl)thio)azetidine-1-carboxylate (0.282 g, 772 μmol) in DCM (3 mL) was added TFA (880 mg, 595 μL , 7.72 mmol) and the reaction mixture was stirred at RT for 3 h. Volatiles were removed *in vacuo* to yield the desired compound as a colorless oil (302 mg) that was used in the next step without further purification.

5 MS (ESI): $m/z = 266.2$ $[\text{M}+\text{H}]^+$.

Step a) *tert-Butyl 3-[[2-fluoro-4-(trifluoromethyl)phenyl]methylsulfanyl]azetidine-1-carboxylate*

To a solution of tert-butyl 3-mercaptoazetidine-1-carboxylate (0.200 g, 1.06 mmol) in dry THF (2 mL) was added potassium tert-butoxide 1M solution in THF (1.11 mL, 1.11 mmol) and the reaction mixture was stirred at RT for 15 min followed by addition of 1-(bromomethyl)-2-
 10 fluoro-4-(trifluoromethyl)benzene (272 mg, 1.06 mmol, CAS RN 239087-07-1). The reaction mixture was then stirred at RT for 14 h. The crude reaction was diluted with EtOAc and extracted with aq. 1 M NaHCO_3 solution, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over NaSO_4 and evaporated down to dryness and purified by flash chromatography (silica gel, 20 g, 0% to 80%
 15 EtOAc in n-heptane) to furnish the desired product as a colorless oil (288 mg, 75%). MS (ESI): $m/z = 310.2$ $[\text{M}-56+\text{H}]^+$.

In analogy to BB84, the following intermediates were prepared from the respective commercially available starting materials.

BB No.	Systematic Name	Starting material	MS, m/z
BB107	3-[2-(2,6-Dichlorophenyl)ethynyl]azetidine	1,3-Dichloro-2-iodobenzene	226.1 $[\text{M}+\text{H}]^+$
BB108	3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine	1-Bromo-2-fluoro-4-(trifluoromethyl)benzene	244.2 $[\text{M}+\text{H}]^+$
BB109	3-[2-(2,6-Difluorophenyl)ethynyl]azetidine	1,3-Difluoro-2-iodobenzene	194.2 $[\text{M}+\text{H}]^+$

BB110	3-[2-[3-Chloro-4-(trifluoromethyl)phenyl]ethynyl]azetidine	4-Bromo-2-chloro-1-(trifluoromethyl)benzene	260.2 [M+H] ⁺
BB111	3-[2-(2-Chloro-6-fluorophenyl)ethynyl]azetidine	2-Bromo-1-chloro-3-fluorobenzene	210.1 [M+H] ⁺
BB112	3-[2-(2-Chloro-4-cyclopropylphenyl)ethynyl]azetidine	1-Bromo-2-chloro-4-cyclopropylbenzene	232.2 [M+H] ⁺
BB113	3-[2-(2-Methoxyphenyl)ethynyl]azetidine	1-Bromo-2-methoxybenzene	188.2 [M+H] ⁺
BB114	3-[2-[4-Chloro-2-(trifluoromethyl)phenyl]ethynyl]azetidine	4-Chloro-1-iodo-2-(trifluoromethyl)benzene	260.1 [M+H] ⁺
BB115	3-[2-(3-Chlorophenyl)ethynyl]azetidine	1-Bromo-3-chlorobenzene	192.1 [M+H] ⁺
BB116	3-[2-[4-(Trifluoromethoxy)phenyl]ethynyl]azetidine	1-bromo-4-(Trifluoromethoxy)benzene	242.2 [M+H] ⁺
BB117	3-[2-[4-(Trifluoromethyl)phenyl]ethynyl]azetidine	1-Bromo-4-(trifluoromethyl)benzene	226.2 [M+H] ⁺
BB118	3-[2-(3-Fluoro-2-methylphenyl)ethynyl]azetidine	1-Bromo-3-fluoro-2-methylbenzene	190.2 [M+H] ⁺
BB119	3-[2-(2,6-Dimethylphenyl)ethynyl]azetidine	2-Iodo-1,3-dimethylbenzene	186.2 [M+H] ⁺

BB120	3-[2-[2-(Trifluoromethoxy)phenyl]ethynyl]azetidine	1-Bromo-2-(trifluoromethoxy)benzene	242.2 [M+H] ⁺
BB121	3-[2-(2-Bromophenyl)ethynyl]azetidine	1-Bromo-2-iodobenzene	236.1 [M+H] ⁺
BB122	3-[2-(2-Chloro-3-fluorophenyl)ethynyl]azetidine	1-Bromo-2-chloro-3-fluorobenzene	210.1 [M+H] ⁺
BB123	3-[2-(o-Tolyl)ethynyl]azetidine	1-Bromo-2-methylbenzene	172.2 [M+H] ⁺
BB124	3-[2-(4-Chloro-2-fluorophenyl)ethynyl]azetidine	4-Chloro-2-fluoro-1-iodobenzene	210.1 [M+H] ⁺
BB125	3-[2-[2-(Difluoromethoxy)phenyl]ethynyl]azetidine	1-(Difluoromethoxy)-2-iodobenzene	224.2 [M+H] ⁺
BB126	2-[2-(Azetidin-3-yl)ethynyl]-3-chlorobenzonitrile	2-Bromo-3-chlorobenzonitrile	217.2 [M+H] ⁺
BB127	3-[2-[4-(Difluoromethoxy)phenyl]ethynyl]azetidine	1-(Difluoromethoxy)-4-iodobenzene	224.2 [M+H] ⁺

BB128	1-[4-[2-(Azetidin-3-yl)ethynyl]phenyl]cyclopropanecarbonitrile	1-(4-Bromophenyl)cyclopropane-1-carbonitrile	223.2 [M+H] ⁺
BB129	3-[2-(4-Cyclopropylphenyl)prop-1-ynyl]azetidine	1-Bromo-4-cyclopropylbenzene	198.2 [M+H] ⁺
BB130	1-[4-[2-(Azetidin-3-yl)ethynyl]phenyl]cyclopropanol	1-(4-Bromophenyl)cyclopropanol	214.2 [M+H] ⁺
BB131	3-[2-(3-Methoxyphenyl)ethynyl]azetidine	1-Iodo-3-methoxybenzene	188.2 [M+H] ⁺
BB132	3-[2-[2-(Difluoromethyl)phenyl]ethynyl]azetidine	1-Bromo-2-(difluoromethyl)benzene	208.2 [M+H] ⁺
BB133	3-[2-(3-Methoxy-2-methylphenyl)ethynyl]azetidine	1-Iodo-3-methoxy-2-methylbenzene	202.2 [M+H] ⁺
BB134	3-[2-(2-Chloro-6-methylphenyl)ethynyl]azetidine	1-Chloro-2-iodo-3-methylbenzene	206.1 [M+H] ⁺
BB135	3-[2-(2-Chloro-5-fluorophenyl)ethynyl]azetidine	2-Bromo-1-chloro-4-fluorobenzene	210.1 [M+H] ⁺
BB136	3-[2-(4-Methylsulfonylphenyl)ethynyl]azetidine	1-Bromo-4-methylsulfonylbenzene	236.2 [M+H] ⁺

BB137	3-[2-(5-Chloro-2-thienyl)ethynyl]azetidine	2-Bromo-5-chlorothiophene	198.1 [M+H] ⁺
BB138	3-[2-(5-Chloro-3-thienyl)ethynyl]azetidine	4-Bromo-2-chlorothiophene	198.1 [M+H] ⁺
BB139	3-[2-[2-Chloro-6-fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine	2-Bromo-1-chloro-3-fluoro-5-(trifluoromethyl)benzene	278.1 [M+H] ⁺
BB140	3-[2-(2-Chlorophenyl)ethynyl]azetidin-3-ol	Chloro-2-iodobenzene and <i>tert</i> -butyl 3-ethynyl-3-hydroxyazetidine-1-carboxylate (CAS RN 1259034-35-9)	208.1 [M+H] ⁺
BB141	3-[2-[2-(Methoxymethyl)phenyl]ethynyl]azetidine	1-Iodo-2-(methoxymethyl)benzene	202.2 [M+H] ⁺
BB142	3-[2-[2-Chloro-4-(trifluoromethyl)phenyl]ethynyl]azetidine	2-Chloro-1-iodo-4-(trifluoromethyl)benzene	260.2 [M+H] ⁺

In analogy to BB18, the following intermediates were prepared from the respective commercially available starting materials.

BB No.	Systematic Name	Starting material	MS, m/z
BB143	4-[2-[2-(Trifluoromethyl)phenyl]ethynyl]piperidine	1-Bromo-2-(trifluoromethyl)benzene	254.3 [M+H] ⁺
BB144	4-[2-(2-Methoxyphenyl)ethynyl]piperidine	1-Bromo-2-methoxybenzene	216.3 [M+H] ⁺
BB145	4-[2-(o-Tolyl)ethynyl]piperidine	1-Bromo-2-methylbenzene	200.3 [M+H] ⁺
BB146	4-[2-(2,6-Dimethylphenyl)ethynyl]piperidine	2-Iodo-1,3-dimethylbenzene	214.3 [M+H] ⁺
BB147	4-[2-(2,4-Dichlorophenyl)ethynyl]-4-methyl-piperidine	Bromo-2,4-dichlorobenzene and <i>tert</i> -Butyl 4-ethynyl-4-methylpiperidine-1-carboxylate (CAS RN 1363383-17-8)	268.2 [M+H] ⁺
BB148	4-[2-(2-Chloro-4-fluorophenyl)ethynyl]-4-methyl-piperidine	2-Chloro-4-fluoro-1-iodobenzene and <i>tert</i> -Butyl 4-ethynyl-4-methylpiperidine-1-carboxylate	252.2 [M+H] ⁺

- 226 -

		(CAS RN 1363383-17-8)	
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BB149**1-[2-(Azetidin-3-yl)ethynyl]cyclopentanol hydrochloride**

To a solution of *tert*-butyl 3-[2-(1-hydroxycyclopentyl)ethynyl]azetidine-1-carboxylate (0.02 g, 0.075 mmol) in dioxane (0.5 mL) was added 4 M HCl in dioxane (0.094 mL, 0.377 mmol) and the reaction mixture was stirred at RT for 18 h. The mixture was evaporated to dryness and the residue triturated in diisopropyl ether, filtered off and further dried under high vacuum to give the title compound as a white solid as the hydrochloride salt (0.013 g, 87%). MS (ESI): m/z = 166.1 $[M+H]^+$.

10 **Step a) *tert*-Butyl 3-[2-(1-hydroxycyclopentyl)ethynyl]azetidine-1-carboxylate**

To a solution of *tert*-butyl 3-ethynylazetidine-1-carboxylate (0.2 g, 1.1 mmol) in THF (6.5 mL) at -78°C was added *n*BuLi (0.759 mL, 1.21 mmol) dropwise and the reaction mixture was stirred at this temperature for 1 h. Then, cyclopentanone (0.107 mL, 1.21 mmol) in THF (3 mL) was added dropwise to the mixture which was stirred at -78°C for 2 h. The mixture was allowed to warm up to 0°C, poured into a sat. NH₄OH aqueous solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by silica gel flash chromatography, eluting with a gradient of EtOAc : *n*-heptane (0 to 100%) to yield the title compound as a light yellow oil (0.020 g, 7%). MS (ESI): m/z = 192.2 $[M-56-18+H]^+$.

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BB150**4-[3-Pyrazol-1-yl-5-(trifluoromethyl)phenoxy]piperidine formate**

A mixture of *tert*-butyl 4-[3-pyrazol-1-yl-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (400.0 mg, 0.970 mmol) and TFA (1.0 mL, 0.970 mmol) in DCM (10 mL) was stirred at 20 °C for 12 h. The mixture was purified by prep-HPLC (ACN and water containing 0.225% v/v FA) to give the desired product (300 mg, 94.4%) as colorless gum. MS (ESI): m/z = 312.1 $[M+H]^+$.

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Step a: tert-Butyl 4-[3-bromo-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

- 227 -

To a solution of 3-bromo-5-(trifluoromethyl)phenol (2.0 g, 8.3 mmol), 1-BOC-4-hydroxypiperidine (1.84 g, 9.13 mmol, CAS RN 106-52-5) and PPh₃ (2.61 g, 9.96 mmol) in THF (32.6 mL) was added diisopropyl azodicarboxylate (1.96 mL, 9.96 mmol) and the mixture was stirred at 20 °C for 15 h. The mixture was concentrated under vacuum. The residue was purified by prep-HPLC (ACN and water containing 0.225% v/v FA) and concentrated under vacuum to give the desired product (2.6 g, 73.9% yield) as light yellow oil. MS (ESI): $m/z = 367.9$ [M-56+H]⁺.

Step b) *tert-Butyl 4-[3-pyrazol-1-yl-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate*

A mixture of *tert*-butyl 4-[3-bromo-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (500.0 mg, 1.18 mmol), pyrazole (160.47 mg, 2.36 mmol), CuI (22.37 mg, 0.120 mmol), cesium carbonate (1152 mg, 3.54 mmol) and *N,N'*-dimethylethylenediamine (519.15 mg, 5.89 mmol) in DMF (5 mL) was stirred at 110 °C for 12 h. The mixture was poured into H₂O water (30 mL) and extracted three times with EtOAc (50 mL). The combined organic layer was washed with ammonia (10 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum to give the desired product (400 mg, 82.5% yield) as light yellow oil. MS (ESI): $m/z = 356.2$ [M-56+H]⁺.

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BB151**4-[[2-(2,2,2-Trifluoroethoxy)-4-(trifluoromethyl)phenyl]methyl]piperidine**

A mixture of 4-[[2-(2,2,2-trifluoroethoxy)-4-(trifluoromethyl)phenyl]methylene]piperidine (250.0 mg, 0.740 mmol) and Pd/C (50.0 mg, wt.10%) in THF (10 mL) was stirred at 20 °C for 12 h under H₂ (1520 mmHg). The mixture was filtered and concentrated under vacuum to give the desired compound (240 mg, 95.4%) as light brown gum. MS (ESI): $m/z = 342.1$ [M+H]⁺.

20

Step a) *tert-Butyl 4-(p-tolylsulfonylhydrazono)piperidine-1-carboxylate*

To a solution of 4-methylbenzenesulfonylhydrazide (9.35 g, 50.19 mmol, CAS RN 1576-35-8) in MeOH (100 mL) was added 1-BOC-4-piperidone (10.0 g, 50.19 mmol, CAS RN 17502-28-8) and the mixture was stirred at 25 °C for 12 h. The mixture was concentrated to give the desired product (18.4 g, 99.8%) as off-white solid. MS (ESI): $m/z = 368.2$ [M+H]⁺.

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Step b) *2-(2,2,2-Trifluoroethoxy)-4-(trifluoromethyl)benzaldehyde*

A mixture of NaH (187.39 mg, 60% dispersion in mineral oil, 4.68 mmol,) in 2,2,2-trifluoroethanol (16.67 mL, 228.74 mmol, CAS RN75-89-8) was stirred at 0 °C. The cooling bath was removed and the mixture was stirred at 20 °C for 2 h, and then 2-fluoro-4-(trifluoromethyl)benzaldehyde (1.0 g, 5.21 mmol, CAS RN 763-93-9) was added and the mixture was stirred at 20 °C for 12 h. The mixture was poured into H₂O (30 mL) and extracted twice with EtOAc (30 mL each). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and filtered. The filtrate was

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- 228 -

concentrated under vacuum to give the desired product (1.2 g, 84.7%) as light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.44 - 10.34 (m, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.75 (s, 1H), 7.55 (d, *J*=8.1 Hz, 1H), 5.11 (q, *J*=8.7 Hz, 2H).

Step c) *tert*-Butyl 4-[2-(2,2,2-trifluoroethoxy)-4-(trifluoromethyl)benzoyl]piperidine-1-carboxylate

- 5 A mixture of 2-(2,2,2-trifluoroethoxy)-4-(trifluoromethyl)benzaldehyde (1000.0 mg, 3.67 mmol), *tert*-butyl 4-(*p*-tolylsulfonylhydrazono)piperidine-1-carboxylate (1350.3 mg, 3.67 mmol) and cesium carbonate (1795.9 mg, 5.51 mmol) in 1,4-dioxane (30 mL) was stirred at 110 °C for 12 h under N₂ atmosphere. The mixture was poured into H₂O (50 mL) and extracted three times with EtOAc (50 mL each). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and filtered. The
10 filtrate was concentrated under vacuum and the residue was purified by prep-HPLC (MeCN and water containing 0.225% v/v FA) to give the desired product (980 mg, 58.6%) as light yellow gum. MS (ESI): *m/z* = 400.1 [M-56+H]⁺.

Step d) *tert*-Butyl 4-[hydroxy-[2-(2,2,2-trifluoroethoxy)-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate

- 15 To a solution of *tert*-butyl 4-[2-(2,2,2-trifluoroethoxy)-4-(trifluoromethyl)benzoyl]piperidine-1-carboxylate (900.0 mg, 1.98 mmol) in MeOH (45 mL) was added NaBH₄ (149.54 mg, 3.95 mmol) at 0 °C and the mixture was stirred at 20 °C for 12 h. The mixture was purified by prep-HPLC (MeCN and water containing 0.225% v/v FA) (650 mg, 71.9%) as light yellow oil. MS (ESI): *m/z* = 384.0 [M-56-OH+H]⁺.

- 20 Step e) 4-[[2-(2,2,2-Trifluoroethoxy)-4-(trifluoromethyl)phenyl]methylene]piperidine

- A mixture of *tert*-butyl 4-[hydroxy-[2-(2,2,2-trifluoroethoxy)-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate (400.0 mg, 0.870 mmol) and MsOH (840.43 mg, 8.74 mmol) in DCM (4 mL) was stirred at 40 °C for 24 h. The mixture was poured into saturated aqueous Na₂CO₃ solution (5 mL) and extracted three times with EtOAc (10 mL each). The combined organic layers were washed with
25 brine (10 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum to give the desired compound as light yellow oil (260 mg, 76.2%). MS (ESI): *m/z* = 340.1 [M+H]⁺.

BB152

4-[3-(1,2,4-Triazol-1-yl)-5-(trifluoromethyl)phenoxy]piperidine trifluoroacetate

- To a mixture of *tert*-butyl 4-[3-(1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenoxy]piperidine-1-
30 carboxylate (240.0 mg, 0.580 mmol) in DCM (10 mL) was added TFA (1.0 mL). The mixture was stirred at 20 °C for 12 h and then concentrated under vacuum to give 4-[3-(1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenoxy]piperidine 2,2,2-trifluoroacetic acid salt (240 mg, 96.7%) as light yellow gum. MS (ESI): *m/z* = 313.1 [M+H]⁺.

- 229 -

Step a) *tert-Butyl 4-[3-(1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate*

A mixture of *tert*-butyl 4-[3-bromo-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (500.0 mg, 1.18 mmol, BB98, intermediate a), 1,2,4-triazole (162.8 mg, 2.36 mmol) and CuI (22.37 mg, 0.120 mmol) in DMF (5 mL) was stirred at 110 °C for 12 h. The mixture was poured into H₂O (20 mL) and
5 extracted three times with EtOAc (30 mL each). The combined organic layers were washed with ammonia (20 mL), brine (20 mL, three times), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (PE : EA = 50 : 1 ~ 3 : 1) to give the desired product (240 mg, 49.4%) as light yellow solid. MS (ESI): *m/z* = 357.1 [M-56+H]⁺.

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BB153**3-[4-Chloro-3-(trifluoromethyl)phenoxy]azetidine trifluoroacetate**

To a solution of *tert*-butyl 3-[4-chloro-3-(trifluoromethyl)phenoxy]azetidine-1-carboxylate (300.0 mg, 0.530 mmol) in DCM (7.5 mL) was added TFA (1.04 mL) at 0 °C and the mixture was stirred at 20 °C for 2 h. The mixture was concentrated to give the title compound as yellow oil (280 mg, 97%). MS (ESI): *m/z* = 252.0 [M+H]⁺.

15 Step a) *tert-Butyl 3-[4-chloro-3-(trifluoromethyl)phenoxy]azetidine-1-carboxylate*

To a solution of 2-chloro-5-hydroxybenzotrifluoride (1 g, 5.1 mmol CAS RN 6294-93-5), *tert*-butyl 3-hydroxyazetidine-1-carboxylate (0.97 g, 5.6 mmol CAS RN 141699-55-0) and triphenylphosphine (1.6 g, 6.11 mmol) in THF (20 mL) was added diisopropyl azodicarboxylate (1.2 mL, 6.11 mmol) and the mixture was stirred at 20 °C for 15 h. The mixture was concentrated and purified by reversed phase
20 chromatography (MeCN and water containing 0.225% v/v FA) to give the title compound (820 mg, 28.7%) as brown solid. MS (ESI): *m/z* = 295.9 [M-56+H]⁺.

BB154**4-(4-Chloro-3-pyrazol-1-yl-phenoxy)piperidine trifluoroacetate**

To a solution of *tert*-butyl 4-(4-chloro-3-pyrazol-1-yl-phenoxy)piperidine-1-carboxylate (260.0 mg, 0.690
25 mmol) in DCM (5.38 mL) was added TFA (1.34 mL, 17.46 mmol) at 0 °C and the mixture was stirred at 20 °C for 1 h. The mixture was concentrated to give the title compound as an orange oil (250 mg, 92.7 yield). MS (ESI): *m/z* = 278.1 [M+H]⁺.

Step a) *tert-Butyl 4-(3-bromo-4-chloro-phenoxy)piperidine-1-carboxylate*

To a solution of 1-BOC-4-hydroxypiperidine (2.04 g, 10.12 mmol, CAS RN 106-52-5), 3-bromo-4-chlorophenol (2.0 g, 9.64 mmol, CAS RN 2402-82-6) and triphenylphosphine (3.03 g, 11.57 mmol) in THF (50 mL) was added diisopropyl azodicarboxylate (2.28 mL, 11.57 mmol) and the mixture was stirred at 20 °C for 15
30 h. Then the mixture was concentrated and the residue was purified by reversed flash chromatography (MeCN and

- 230 -

water containing 0.1% v/v FA) to give the desired product (2.8 g, 74.3%) as light yellow oil. MS (ESI): $m/z = 335.9$ $[M-56+H]^+$.

Step b) *tert-Butyl 4-(4-chloro-3-pyrazol-1-yl-phenoxy)piperidine-1-carboxylate*

To a mixture of *tert*-butyl 4-(3-bromo-4-chloro-phenoxy)piperidine-1-carboxylate (1.0 g, 2.56 mmol), pyrazole (139.4 mg, 2.05 mmol), cesium carbonate (2501.8 mg, 7.68 mmol) and 1,10-phenanthroline (225.49 mg, 2.56 mmol) in DMF (20 mL) was added CuI (48.59 mg, 0.260 mmol) and the mixture was stirred at 110 °C for 12 h under N₂ atmosphere. The mixture was concentrated, diluted with H₂O (20 mL) and extracted three times with EtOAc (10 mL). The combined organic layers were concentrated and the residue purified by reversed phase chromatography (ACN and water containing 0.1% v/v FA) to give the desired product (265 mg, 22.5%, 82% purity) as yellow oil. MS (ESI): $m/z = 378.1$ $[M+H]^+$.

BB155

4-[5-(4-Piperidyloxy)-2-(trifluoromethyl)phenyl]morpholine trifluoroacetate

To a solution of *tert*-butyl 4-[3-morpholino-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (400.0 mg, 0.93 mmol) in DCM (3 mL) was added TFA (1.0 mL) and the reaction mixture was stirred at 25 °C for 12 h. The reaction was concentrated in vacuum to provide the crude product (300 mg) as yellow oil, which was used in next step without further purification. MS (ESI): $m/z = 331.2$ $[M+H]^+$.

Step a) *tert-Butyl 4-(3-bromo-4-(trifluoromethyl)phenoxy)piperidine-1-carboxylate*

To a solution of 3-bromo-4-(trifluoromethyl)phenol (500.0 mg, 2.54 mmol, CAS RN1214385-56-4) and 1-BOC-4-hydroxypiperidine (512 mg, 2.54 mmol, CAS RN 106-52-5) in THF (8.5 mL) was added PPh₃ (1000.9 mg, 3.82 mmol) and diethyl azodicarboxylate (664.53 mg, 3.82 mmol) and the mixture was stirred at 25 °C for 12 h. The mixture was purified by silica gel chromatography using PE : EA = 5 : 1 as eluant to provide the desired product (503 mg, 46.6% yield) as light yellow oil. MS (ESI): $m/z = 369.2$ $[M-56+H]^+$.

Step b) *tert-Butyl 4-(3-morpholino-4-(trifluoromethyl)phenoxy)piperidine-1-carboxylate*

A mixture of *tert*-butyl 4-[3-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (500.0 mg, 1.18 mmol), morpholine (154 mg, 1.77 mmol, CAS RN 110-91-8), (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (146.77 mg, 0.24 mmol, CAS RN 76189-55-4), cesium carbonate (1.15 g, 3.54 mmol) and tris(dibenzylideneacetone)dipalladium(0) (172.47 mg, 0.240 mmol, CAS RN 76971-72-7) in DMF (10 mL) was stirred at 110 °C for 12 h. The mixture was poured into H₂O and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum and the residue was purified by column

- 231 -

chromatography (gradient of EtOAc in PE 5% to 33%) to give the desired product (480 mg, 94.6%) as light yellow solid. MS (ESI): $m/z = 431.1$ $[M+H]^+$.

BB156**4-(4-Chloro-3-(1,2,4-triazol-1-yl)phenoxy)piperidine trifluoroacetate**

5 To a solution of tert-butyl 4-[4-chloro-3-(1,2,4-triazol-1-yl)phenoxy]piperidine-1-carboxylate (196.0 mg, 0.520 mmol) in DCM (5 mL) was added TFA (1.01 mL, 13.13 mmol) at 0 °C and the mixture was stirred at 20 °C for 1 h. The mixture was concentrated to give the title compound (178 mg, 87.6%) as brown oil. MS (ESI): $m/z = 279.1$ $[M+H]^+$.

Step a) *tert-Butyl 4-[4-chloro-3-(1,2,4-triazol-1-yl)phenoxy]piperidine-1-carboxylate*

10 A mixture of tert-butyl 4-(3-bromo-4-chloro-phenoxy)piperidine-1-carboxylate (500.0 mg, 1.28 mmol, BB102, intermediate a), 1,2,4-triazole (176.8 mg, 2.56 mmol), CuI (24.3 mg, 0.130 mmol) and cesium carbonate (1250.9 mg, 3.84 mmol) and dimethyl glycine (1.0 mL, 1.28 mmol) in DMF (10 mL) was stirred at 120 °C for 12 h. The mixture was concentrated to remove the DMF, diluted with H₂O (50 mL) and extracted three times with EtOAc (20 mL each). The combined organic layers were evaporated and the residue purified by reverse phase flash
15 chromatography (ACN and water containing 0.1% v/v FA) to give the title compound (196 mg, 37.1%) as colorless oil. MS (ESI): $m/z = 323.0$ $[M-56+H]^+$.

BB157**4-[3-Cyclopropyl-4-(trifluoromethyl)phenoxy]piperidine trifluoroacetate**

To a mixture of tert-butyl 4-[3-cyclopropyl-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (360.0
20 mg, 0.930 mmol) in DCM (18 mL) was added TFA (1.8 mL). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under vacuum to provide the desired compound as light yellow gum (370 mg, 99.2%). MS (ESI): $m/z = 286.2$ $[M+H]^+$.

Step a) *tert-Butyl 4-[3-cyclopropyl-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate*

A mixture of tert-butyl 4-[3-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (500.0
25 mg, 1.18 mmol, BB103, intermediate b), cyclopropylboronic acid (151.86 mg, 1.77 mmol), Na₂CO₃ (374.74 mg, 3.54 mmol) and Pd(PPh₃)₄ (13.6 mg, 0.010 mmol) in 1,4-dioxane (10 mL) and H₂O (1 mL) was stirred at 95 °C for 12 h. The mixture was poured into H₂O (50 mL) and extracted three times with EtOAc (50 mL each). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum and purified by column chromatography (PE :
30 EtOAc = 20 : 1~5 : 1) to give the desired product (380 mg, 83.7%) as colorless gum. MS (ESI): $m/z = 330.1$ $[M-56+H]^+$.

- 232 -

BB158**4-[3-Pyrazol-1-yl-4-(trifluoromethyl)phenoxy]piperidine trifluoroacetate**

To a solution of tert-butyl 4-[3-pyrazol-1-yl-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (180.0 mg, 0.440 mmol) in DCM (5 mL) was added TFA (0.5 mL). The mixture was stirred at 25 °C for 12 h and then concentrated under vacuum to give the desired product (180 mg, 96.7%) as light yellow gum. MS (ESI): m/z = 312.1 $[M+H]^+$.

Step a) tert-Butyl 4-[3-pyrazol-1-yl-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

A mixture of tert-butyl 4-[3-bromo-4-(trifluoromethyl)phenoxy]piperidine-1-carboxylate (500.0 mg, 1.18 mmol, BB103, intermediate b), pyrazole (120.35 mg, 1.77 mmol), CuI (22.37 mg, 0.120 mmol), N,N'-dimethylethylenediamine (519.45 mg, 5.89 mmol) and Cs₂CO₃ (767.99 mg, 2.36 mmol) in DMF (10 mL) was stirred at 110 °C for 12 h. The mixture was poured into H₂O (30 mL) and extracted three times with EtOAc (50 mL each). The combined organic layers were washed with ammonia (20 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated and the crude product was purified by prep-TLC (PE : EA = 5 : 1) to give the desired product (190 mg, 39.2%) as colorless oil. MS (ESI): m/z = 356.1 $[M-56+H]^+$.

BB159**4-[[2,6-Difluoro-4-(trifluoromethyl)phenyl]methyl]piperidine trifluoroacetate**

To a solution of tert-butyl 4-[[2,6-difluoro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate (70.0 mg, 0.180 mmol) in DCM (1 mL) was added TFA (0.2 mL) and the mixture was stirred at 20 °C for 1 h. The mixture was concentrated to give the title compound (50 mg, 68.9%) as brown oil. MS (ESI): m/z = 280.1 $[M+H]^+$.

Step a) 2-(Diethoxyphosphorylmethyl)-1,3-difluoro-5-(trifluoromethyl)benzene

A solution of 2-(bromomethyl)-1,3-difluoro-5-(trifluoromethyl)benzene (1.29 mL, 3.27 mmol, CAS RN 493038-91-8) in triethyl phosphite (5.44 g, 32.73 mmol) was stirred at 160 °C for 5 h. The mixture was concentrated under vacuum to provide the title compound (600 mg, 55.2%; colorless oil) which was used in the next step without further purification.

Step b) tert-Butyl 4-[[2,6-difluoro-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate

A mixture of 2-(diethoxyphosphorylmethyl)-1,3-difluoro-5-(trifluoromethyl)benzene (400.0 mg, 1.2 mmol) in THF (4 mL) was added to sodium hydride (144.49 mg, 3.61 mmol) in THF (4 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then 1-BOC-4-piperidone (479.83 mg, 2.41 mmol, CAS RN

- 233 -

79099-07-3) was added to the above mixture. The mixture was stirred at 20 °C for 12 h. The mixture was poured into H₂O (50 mL) and extracted three times with EtOAc (20 mL each). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (PE : EA = 1 : 0 to 2 : 1) to give the title compound (100 mg, 22.0%) as colorless oil. MS (ESI): m/z = 322.0 [M-56+H]⁺.

Step c) *tert-Butyl 4-[[2,6-difluoro-4-(trifluoromethyl)phenyl]methyl]piperidine-1-carboxylate*

To a solution of tert-butyl 4-[[2,6-difluoro-4-(trifluoromethyl)phenyl]methylene]piperidine-1-carboxylate (100.0 mg, 0.270 mmol) in MeOH (8 mL) was added Pd/C (10.0 mg, wt.10%). The mixture was stirred at 20 °C for 1 h under H₂ atmosphere, then filtered and concentrated to give the title compound as colorless oil (70 mg, 69.6%). MS (ESI): m/z = 324.1 [M-56+H]⁺.

BB160

4-[4-Chloro-3-(4-chlorophenyl)-2-fluoro-phenoxy]piperidine trifluoroacetate

To a mixture of tert-butyl 4-[4-chloro-3-(4-chlorophenyl)-2-fluoro-phenoxy]piperidine-1-carboxylate (145.0 mg, 0.330 mmol) in DCM (10 mL) was added TFA (1.0 mL). The mixture was stirred at 20 °C for 5 h. The mixture was concentrated under vacuum to give the desired product (149 mg, 99.6%) as light brown gum. MS (ESI): m/z = 340.1 [M+H]⁺.

Step a) *1-Chloro-2-(4-chlorophenyl)-3-fluoro-4-methoxy-benzene*

A mixture of 4-bromochlorobenzene (1.41 g, 7.34 mmol, CAS RN 106-39-8), (6-chloro-2-fluoro-3-methoxy-phenyl) boronic acid (1.0 g, 4.89 mmol, CAS RN 867333-04-8) and K₂CO₃ (2.03 g, 14.68 mmol) in 1,4-dioxane (15 mL) and H₂O (1.5 mL) was stirred under N₂ atmosphere at 110 °C for 1 h in a microwave oven. The mixture was poured into H₂O (20 mL) and extracted three times with EtOAc (20 mL each). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum and the residue was purified by column chromatography using PE as eluant to give the desired product (110 mg, 8.3%) as colorless oil which was used in the next step without further purification.

Step b) *4-chloro-3-(4-chlorophenyl)-2-fluoro-phenol*

To a mixture of 1-chloro-2-(4-chlorophenyl)-3-fluoro-4-methoxy-benzene (215.0 mg, 0.790 mmol) in DCM (7 mL) was added a solution of BBr₃ (993.36 mg, 3.97 mmol) in DCM (7 mL) drop wise at -78 °C. The mixture was stirred at 20 °C for 12 h. The reaction was quenched by adding MeOH (1 mL) followed by water (10 mL), and the mixture was extracted three times with DCM (10 mL each). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and filtered. The filtrate

- 234 -

was concentrated under vacuum to give the desired product (120 mg, 57.5%) as light brown solid which was used in the next step without further purification.

Step c) *tert-Butyl 4-[4-chloro-3-(4-chlorophenyl)-2-fluoro-phenoxy]piperidine-1-carboxylate*

A mixture of 4-chloro-3-(4-chlorophenyl)-2-fluoro-phenol (120.0 mg, 0.470 mmol), 1-BOC-4-hydroxypiperidine (187.88 mg, 0.930 mmol, CAS RN 106-52-5), PPh₃ (244.85 mg, 0.930 mmol) and DIAD (0.18 mL, 0.930 mmol) in THF (12 mL) was stirred at 20 °C for 12 h. The mixture was poured into H₂O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated under vacuum and the residue purified by column chromatography (PE : EA = 1 : 0~20 : 1) to give the desired product as light yellow gum (150 mg, 73%). MS (ESI): m/z = 384.0 [M-56+H]⁺.

BB161

3-[2-Chloro-4-(Trifluoromethyl)phenoxy]azetidine trifluoroacetate

To a solution of tert-butyl 3-[2-chloro-4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate (400.0 mg, 1.14 mmol) in DCM (10 mL) was added TFA (2.0 mL) at 20 °C. After stirring for 2 h the mixture was concentrated to give the crude product (410 mg, 98.6%) as light yellow oil which was used in the next step without further purification.

Step a) *tert-Butyl 3-[2-chloro-4-(trifluoromethyl)phenoxy]azetidine-1-carboxylate*

To a solution of 2-chloro-4-(trifluoromethyl)phenol (1000.0 mg, 5.09 mmol, CAS RN 35852-58-5) and tert-butyl 3-hydroxyazetidine-1-carboxylate (1057.5 mg, 6.11 mmol, CAS RN 141699-55-0) in THF (20 mL) was added PPh₃ (1999.49 mg, 7.63 mmol) and diethyl azodicarboxylate (1329.05 mg, 7.63 mmol), the mixture was stirred at 25 °C for 12 h. The reaction mixture solution was evaporated in vacuum, the residue was purified by reverse-phase flash (0.1% v/v FA) to afford the desired product (800 mg, 2.27 mmol, 44.7% yield) as light yellow oil. MS (ESI): m/z = 296.0 [M-56+H]⁺.

BB162

3-((2-Fluoro-6-(trifluoromethyl)benzyl)oxy)azetidine trifluoroacetate

To a solution of tert-butyl 3-[[2-fluoro-6-(trifluoromethyl)phenyl]methoxy]azetidine-1-carboxylate (400.0 mg, 1.15 mmol) in dry DCM (10 mL) was added TFA (2.0 mL) at 25 °C and the mixture was stirred at 25 °C for 12 h. The solvent was stripped off and the residue was dried under vacuum to afford the desired compound as yellow oil (300 mg, 22%). MS (ESI): m/z = 250.0 [M+H]⁺.

Step a) *tert-Butyl 3-[[2-fluoro-6-(trifluoromethyl)phenyl]methoxy]azetidine-1-carboxylate*

- 235 -

To a solution of 2-fluoro-6-(trifluoromethyl)benzyl bromide (1000.0 mg, 3.89 mmol, CAS RN 239087-08-2) and tert-butyl 3-hydroxyazetidine-1-carboxylate (673.92 mg, 3.89 mmol, CAS RN 141699-55-0) in dry THF (10 mL) at 25 °C, was added t-BuOK (5.84 mL, 5.84 mmol; 1.0 M in dry THF) and the mixture was stirred at 25 °C for 12 h. The mixture was poured into H₂O (10 mL) and
5 extracted three times with EA (20 mL each). The combined organic layers were combined, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure, purified by flash chromatography on silica gel (gradient PE : EA = 10 : 1 to 2 : 8) to give the title compound as colorless oil (1100 mg, 80.9%). MS (ESI): m/z = 294.0 [M-56+H]⁺.

BB16310 **3-[2-(2-Fluoro-4-methyl-phenyl)ethyl]azetidine trifluoroacetate**

To a solution of tert-butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethyl]azetidine-1-carboxylate (350.0 mg, 1.19 mmol) in dry DCM (10 mL) at 25 °C, was added TFA (1.0 mL, 1.19 mmol) and the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated by reduced pressure and the residue was dried in vacuum to provide the desired compound as colorless oil (260 mg, 70.9%). MS (ESI): m/z =
15 194.0 [M+H]⁺.

Step a) tert-Butyl 3-(2-trimethylsilylethynyl)azetidine-1-carboxylate

To a solution of trimethylsilylacetylene (9.97 g, 101.55 mmol, CAS RN 1066-54-2) in dry THF (200 mL) at 25 °C, was added i-PrMgCl (48.57 mL, 97.14 mmol; 1.0 M in dry THF) and the mixture was stirred at 25 °C for 15 mins. Then a solution of 1-BOC-3-iodoazetidine (25.0 g, 88.3 mmol, CAS RN
20 254454-54-1) was added followed by FeCl₂ (0.34 g, 2.65 mmol) in dry DMF (606 mL) and the mixture was stirred at 25 °C for 12 hrs. The mixture was poured into saturated aq. NH₄Cl solution (200 mL) and extracted three times with EtOAc (150 mL each). The organic layers were combined, dried with anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE : EA = 20 : 1 to 10 : 1) to give the desired product as
25 black oil (18 g, 80.4%).

¹H NMR (400MHz, CHLOROFORM-d) δ = 4.11 (t, J=8.4 Hz, 2H), 3.92 (dd, J=6.5, 8.1 Hz, 2H), 3.51 - 3.17 (m, 1H), 1.44 (s, 10H), 0.16 (s, 9H).

Step b) tert-Butyl 3-ethynylazetidine-1-carboxylate

To a solution of tert-butyl 3-(2-trimethylsilylethynyl)azetidine-1-carboxylate (6243 mg, 24.64
30 mmol) in dry MeOH (40 mL) was added potassium carbonate (1700 mg, 12.32 mmol) at 25 °C and the reaction mixture was stirred at 25 °C for 2 h. The mixture was filtered, the filtrate was poured into saturated aq. NH₄Cl solution (100 mL) and extracted with EA (100 mL three times). The combined

- 236 -

organic layers were dried with anhydrous Na₂SO₄, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE : EA = 50 : 1 to 15 : 1) to afford the title compound as light yellow oil (4100 mg, 91.8%). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 4.16 - 4.11 (m, 2H), 3.93 (dd, J=6.5, 8.2 Hz, 2H), 3.37 - 3.20 (m, 1H), 2.28 (d, J=2.4 Hz, 1H), 1.43 (s, 9H).

Step c) *tert*-Butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethynyl]azetidine-1-carboxylate

To a solution of *tert*-butyl 3-ethynylazetidine-1-carboxylate (1000.0 mg, 5.52 mmol) and 4-bromo-3-fluorotoluene (1251.58 mg, 6.62 mmol, CAS RN 452-74-4) in dry THF (20 mL) were added Pd(PPh₃)₄ (530.63 mg, 0.460 mmol), CuI (87.83 mg, 0.460 mmol) and TEA (4644.2 mg, 46.0 mmol) at 25 °C. The mixture was purged with N₂ for 1 min and then stirred at 60 °C under N₂ atmosphere for 12 h. The mixture was poured into saturated aq. NH₄Cl solution (50 mL) and extracted three times with EtOAc (30 mL each). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE : EA = 20 : 1 to 10 : 1) to provide the desired compound as colorless oil (650 mg, 40.7%). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.33 - 7.28 (m, 1H), 6.94 - 6.85 (m, 2H), 4.26 - 4.19 (m, 2H), 4.05 (dd, J=6.4, 8.1 Hz, 2H), 3.66 - 3.49 (m, 1H), 2.36 (s, 3H), 1.46 (s, 9H).

Step d) *tert*-Butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethyl]azetidine-1-carboxylate

Batch a: To a solution of *tert*-butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethynyl]azetidine-1-carboxylate (50.0 mg, 0.170 mmol, 1 eq) in EtOAc (5 mL) was added Pd/C (50.0 mg, wt.10%) at 25 °C. The mixture was stirred at 40 °C under a balloon of hydrogen gas for 12 h. LCMS analysis found 79.8% of desired product.

Batch b: To a solution of *tert*-butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethynyl]azetidine-1-carboxylate (500.0 mg, 1.73 mmol) in EtOAc (10 mL) was added Pd/C (250.0 mg, wt.10%) at 25 °C and the mixture was stirred at 40 °C under a balloon of hydrogen gas for 6 h. LCMS found 80.4% of desired product. Batch a and b were combined, the reaction mixture was filtered through a pad of celite, the filtrate was concentrated under reduced pressure and the residue was dried in vacuum to give the compound as colorless oil (350 mg, 69.0%). MS (ESI): m/z = 238.1 [M-56+H]⁺.

BB164

3-[2-[4-Methoxy-2-(trifluoromethyl)phenyl]ethyl]azetidine trifluoroacetate

To a solution of *tert*-butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethyl]azetidine-1-carboxylate (180.0 mg, 0.5 mmol) in dry DCM (10 mL) was added TFA (1.0 mL, 1.19 mmol) at 25 °C and the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the residue

- 237 -

was dried in vacuum to give the title compound (150 mg, 80.2%) as colorless oil. MS (ESI): $m/z = 260.1$ $[M+H]^+$.

Step a) *tert-Butyl 3-[2-[4-methoxy-2-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carboxylate*

To a solution of *tert*-butyl 3-ethynylazetidine-1-carboxylate (800.0 mg, 4.41 mmol, BB111, intermediate b) and 3-trifluoromethyl-4-bromoanisole (1350.9 mg, 5.3 mmol, CAS RN 400-72-6) in dry THF (30 mL) at 25 °C, was added $Pd(PPh_3)_4$ (509.41 mg, 0.440 mmol), CuI (84.31 mg, 0.440 mmol) and TEA (4458.42 mg, 44.14 mmol). The mixture was purged with N_2 for 1 min and then stirred at 60 °C under N_2 atmosphere for 12 h. The mixture was poured into saturated aq. NH_4Cl solution (100 mL) and extracted three times with EtOAc (50 mL each). The organic layers were combined, dried with anhydrous Na_2SO_4 , filtered, the filtrate was concentrated with reduced pressure. The residue was purified by flash chromatography on silica gel (PE : EA = 20 : 1 to 10 : 1) to provide the product as colorless oil (160 mg, 8.2%). MS (ESI): $m/z = 300.1$ $[M-56+H]^+$.

Step b) *tert-Butyl 3-[2-[4-methoxy-2-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

To a solution of *tert*-butyl 3-[2-(2-fluoro-4-methyl-phenyl)ethynyl]azetidine-1-carboxylate (230.0 mg, 0.65 mmol) in EtOAc (10 mL) at 25 °C, was added Pd/C (150.0 mg, wt.10%), the mixture was stirred at 40 °C under a balloon of H_2 (about 15 psi) for 12 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The residue was dried under vacuum to furnish the desired compound as colorless oil (180 mg, 77.4%). MS (ESI): $m/z = 304.1$ $[M-56+H]^+$.

BB165

20 **3-[[4-Methyl-2-(trifluoromethyl)phenyl]methoxy]azetidine trifluoroacetate**

To a solution of *tert*-butyl 3-[[4-methyl-2-(trifluoromethyl)phenyl]methoxy]azetidine-1-carboxylate (130.0 mg, 0.380 mmol) in DCM (6.5 mL) was added TFA (1.3 mL, 16.87 mmol) and the reaction was stirred at 20 °C. After 12 h the mixture was evaporated to give the desired crude product as light brown oil (130 mg, 96.1%). MS (ESI): $m/z = 246.5$ $[M+H]^+$.

25 Step a) *4-Bromo-1-(Bromomethyl)-2-(trifluoromethyl)benzene*

The solution of 5-bromo-2-methylbenzotrifluoride (2000 mg, 8.37 mmol, CAS RN 86845-27-4), N-bromosuccinimide (1489 mg, 8.37 mmol, CAS RN 128-08-5) and benzoyl peroxide (101.34 mg, 0.420 mmol, CAS RN 2685-64-5) in carbon tetrachloride (30 mL) was stirred at 90 °C for 12 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (100% PE) to give the desired product as light brown oil (690 mg, 25.9%) which was used in the next step without further purification.

Step b) *tert-Butyl 3-[[4-bromo-2-(Trifluoromethyl)phenyl]methoxy]azetidine-1-carboxylate*

- 238 -

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (337.5 mg, 1.95 mmol, CAS RN 22214-30-8) in THF (9 mL) was added t-BuOK (1.95 mL, 1.95 mmol), then 4-bromo-1-(bromomethyl)-2-(trifluoromethyl) benzene (590.0 mg, 1.86 mmol) was added and the mixture was stirred at 20 °C for 12 h. The mixture was poured into aq. NH₄Cl solution (200 mL) and extracted three times with EtOAc (50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-HPLC (ACN and water containing 0.225% v/v FA) to give the desired product as light brown oil (300 mg, 39.4%). MS (ESI): m/z = 356.3 [M-56+H]⁺.

Step c) *tert-Butyl 3-[[4-Methyl-2-(trifluoromethyl)phenyl]methoxy]azetidine-1-carboxylate*

To a solution of tert-butyl 3-[[4-bromo-2-(trifluoromethyl)phenyl]methoxy]azetidine-1-carboxylate (250.0 mg, 0.610 mmol), trimethylboroxine (114.8 mg, 0.910 mmol), K₂CO₃ (168.5 mg, 1.22 mmol) in 1,4-dioxane (10 mL) and H₂O (2.5 mL) was added Pd(dppf)Cl₂ (89.18 mg, 0.120 mmol). The reaction was stirred at 100 °C for 12 h. The mixture was filtered, concentrated, and the residue was purified by reversed flash chromatography (ACN and water containing 0.1% v/v FA) to give the desired product as light brown oil (146 mg, 69.4%). MS (ESI): m/z = 290.4 [M-56+H]⁺.

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BB166**3-[2-[2-Methoxy-6-(trifluoromethyl)phenyl]ethyl]azetidine trifluoroacetate**

To a solution of tert-butyl 3-[2-[2-methoxy-6-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate (300.0 mg, 0.830 mmol) in DCM (5 mL), TFA (1.0 mL) was added and stirred at 25 °C for 1 h. The reaction mixture was evaporated under reduced pressure to give the desired product (300 mg, 96.3%) as colorless oil. MS (ESI): m/z = 260.1 [M+H]⁺.

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Step a) *tert-Butyl 3-[2-[2-methoxy-6-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carboxylate*

To a solution of tert-butyl 3-ethynylazetidine-1-carboxylate (710.6 mg, 3.92 mmol, B111, intermediate b) and 2-bromo-1-methoxy-3-(trifluoromethyl)benzene (500.0 mg, 1.96 mmol) in dry DMSO (17.5 mL) at 25 °C, was added Pd(PPh₃)₂Cl₂ (137.6 mg, 0.200 mmol) and Cs₂CO₃ (1278 mg, 3.92 mmol). The mixture was purged with N₂ for 1 min and then stirred at 110 °C under N₂ atmosphere for 12 h. The mixture was filtered, the filtrate was concentrated and the residue was purified by silica gel (PE : EtOAc = 20 : 1) to give the desired product as light yellow oil (600 mg, 86.1%) that was used in the next step without further purification.

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Step b) *tert-Butyl 3-[2-[2-methoxy-6-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carboxylate*

To a solution of tert-butyl 3-[2-[2-methoxy-6-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carboxylate (400.0 mg, 1.13 mmol) in EtOAc (20 mL), wet Pd/C (50 mg, 10 wt.%) was added. The mixture was purged with H₂ 3 times and then stirred at 40 °C under H₂ atmosphere (balloon) for 12 h.

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- 239 -

The mixture was filtered and the filtrate was concentrated to give the desired product as light yellow oil (300 mg, 74.2% yield) which was used in the next step without further purification.

BB167**3-[2-[4-Methyl-2-(trifluoromethyl)phenyl]ethyl]azetidine trifluoroacetate**

- 5 To a solution of tert-butyl 3-[2-[4-methyl-2-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate (100.0 mg, 0.290 mmol) in DCM (4 mL) was added TFA (0.5 mL) and the mixture was stirred at 20 °C for 12 h. The reaction mixture was evaporated under reduced pressure to give the desired product as yellow oil (98 mg, 94.2%). MS (ESI): $m/z = 244.1$ $[M+H]^+$.

Step a) tert-Butyl 3-[2-[4-methyl-2-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carboxylate

- 10 To a solution of tert-butyl 3-ethynylazetidine-1-carboxylate (606.6 mg, 3.35 mmol) and 2-bromo-5-methylbenzotrifluoride (400.0 mg, 1.67 mmol) in dry DMSO (14.9 mL) at 25°C, was added Pd(PPh₃)₂Cl₂ (117.46 mg, 0.170 mmol) and Cs₂CO₃ (1091 mg, 3.35 mmol). The mixture was purged with N₂ for 1 min and then stirred at 110 °C under N₂ atmosphere for 12 h. The reaction mixture was poured into H₂O and extracted with EtOAc. The organic layer was evaporated and the residue was purified by silica gel
15 column chromatography (PE : EtOAc = 20 : 1) to give the desired compound as a yellow oil (390 mg, 68.7% yield). MS (ESI): $m/z = 284.1$ $[M-56+H]^+$.

Step b) tert-Butyl 3-[2-[4-methyl-2-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate

- To a solution of tert-butyl 3-[2-[4-methyl-2-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carboxylate (390.0 mg, 1.15 mmol) in EtOAc (19.5 mL), wet Pd/C (150 mg, 10 wt.%) was added, the mixture was
20 purged 3 times with H₂ and stirred at 40 °C under H₂ atmosphere (balloon) for 12 h. The mixture was filtered and the filtrate was concentrated to give the desired product as light yellow oil (295 mg, 72.9% yield). MS (ESI): $m/z = 288.1$ $[M-56+H]^+$.

BB168**1-[2-[2-(Azetidin-3-yl)ethyl]-5-(trifluoromethyl)phenyl]ethanone trifluoroacetate**

- 25 To a solution of tert-butyl 3-[2-[2-acetyl-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate (50.0 mg, 0.130 mmol) in DCM (1 mL) was added TFA (0.2 mL) and the solution was stirred at 20 °C for 12 h. The mixture was concentrated to give the desired product as light brown oil (50 mg, 96.4% yield). MS (ESI): $m/z = 272.1$ $[M+H]^+$.

Step a) 2-Bromo-1-(bromomethyl)-4-(trifluoromethyl)benzene

- 30 To a solution of [2-bromo-4-(trifluoromethyl)phenyl]methanol (500.0 mg, 1.96 mmol, CAS RN 497959-33-8) and PPh₃ (770.5 mg, 2.94 mmol) in THF (10 mL) was added carbon tetrabromide (975.3

- 240 -

mg, 2.94 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction was concentrated in vacuum and the residue was purified by silica gel column chromatography (PE : EA = 0 : 1~20 : 1) to yield the desired product as colorless oil (600 mg, 96.3% yield). ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.78 (s, 1H), 7.55 - 7.46 (m, 2H), 4.53 (s, 2H).

5 Step b) *2-Bromo-1-(diethoxyphosphorylmethyl)-4-(trifluoromethyl)benzene*

A solution of 2-bromo-1-(bromomethyl)-4-(trifluoromethyl)benzene (600.0 mg, 1.89 mmol) in triethyl phosphite (3136 mg, 18.87 mmol) was stirred at 160 °C for 5 h. The mixture was concentrated at 100 °C under reduced pressure to remove most of the triethyl phosphite to give the crude product (700 mg) as light yellow oil. MS (ESI): m/z = 375.2 [M+H]⁺.

10 Step c) *tert-Butyl 3-[(E)-2-[2-bromo-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate*

A mixture of 2-bromo-1-(diethoxyphosphorylmethyl)-4-(trifluoromethyl)benzene (600.0 mg, 1.6 mmol) in THF (10 mL) was added to another suspension of NaH (191.9 mg, 4.8 mmol, 60% dispersion in mineral oil) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. Then tert-butyl 3-formylazetidine-1-carboxylate (296.3 mg, 1.6 mmol) was added and the mixture was stirred at 20 °C for 15 11 h. The reaction mixture was poured into aq. NH₄Cl solution (100 mL) and extracted three times with EtOAc (50 mL each). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc = 20 : 1) to give the desired product as light yellow oil (450 mg, 69.3%). MS (ESI): m/z = 352.0 [M56+H]⁺. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.74 (d, J = 0.8 Hz, 1H), 7.58 - 7.51 (m, 1H), 20 7.49 - 7.41 (m, 1H), 6.71 (d, J = 15.8 Hz, 1H), 6.36 (dd, J = 8.4, 15.8 Hz, 1H), 4.13 (t, J = 8.5 Hz, 2H), 3.78 (dd, J = 5.8, 8.6 Hz, 2H), 3.44 - 3.31 (m, 1H), 1.39 (s, 9H).

Step d) *tert-Butyl 3-[(E)-2-[2-acetyl-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate*

A solution of tributyl(1-ethoxyvinyl)tin (426.7 mg, 1.18 mmol), tert-butyl 3-[(E)-2-[2-bromo-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate (400.0 mg, 0.980 mmol) and Pd(Ph₃P)₂Cl₂ (138.2 25 mg, 0.200 mmol) in THF (16 mL) was stirred at 80 °C under N₂ atmosphere for 4 h. The mixture was cooled down to room temperature and aq. KF solution (10 mL) was added. The mixture was stirred for 10 mins, extracted three times with EtOAc (20 mL each) and the combined organic layers were concentrated. The residue was dissolved in THF (20 mL) and aq. HCl (0.6 N, 20 mL) was added. The mixture was stirred at 20 °C for 0.5 h, extracted three times with EtOAc (20 mL each) and the combined 30 organic layers were concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc = 20 : 1) to give the desired product (280 mg, 77% yield) as light yellow oil. MS (ESI): m/z = 314.1 [M-56+H]⁺.

Step e) *tert-Butyl 3-[2-[2-acetyl-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

- 241 -

To a solution of tert-butyl 3-[(E)-2-[2-acetyl-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate (50.0 mg, 0.140 mmol) in EtOAc (5 mL) was added wet Pd/C (20.0 mg, 10 wt.%) and the mixture was stirred at 20°C under H₂ (balloon) atmosphere for 12 h. The reaction was then warmed up to 50 °C and stirred for another 12 h. The mixture was filtered and the filtrate was concentrated to give the
5 desired product (50 mg, 99.5%) as light yellow oil. MS (ESI): m/z = 316.2 [M-56+H]⁺.

BB169**3-[2-[2-Bromo-4-(trifluoromethyl)phenyl]ethyl]azetidine trifluoroacetate**

To a solution of tert-butyl 3-[2-[2-bromo-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate (400.0 mg, 0.980 mmol) in DCM (10 mL) was added TFA (1.0 mL) and the mixture was stirred at 20 °C
10 for 12 h. The reaction mixture was evaporated under reduced pressure to give the desired product (413 mg, 99.8% yield) as yellow oil. MS (ESI): m/z = 308.1 [M+H]⁺.

Step a) *tert-Butyl 3-[2-[2-bromo-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

To a suspension of tert-butyl 3-[(E)-2-[2-bromo-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate (600.0 mg, 1.48 mmol, BB116, intermediate c) and MgO (118.1 mg, 2.95 mmol) in EtOAc
15 (20 mL) was added Pd/C (300.0 mg, 10wt.%), the mixture was stirred at 25 °C under H₂ atmosphere (balloon) for 1 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give the desired product (500 mg, 82.9%) as light yellow oil. MS (ESI): m/z = 352.0 [M-56+H]⁺.

BB174**2-(Azetidin-3-ylmethoxy)-5-(trifluoromethyl)pyridine 2,2,2-trifluoroacetate**

Synthesis of BB174 was performed in analogy to BB57, starting from tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate and 2-bromo-5-(trifluoromethyl)pyridine. MS (ESI):
m/z = 233.1 [M+H]⁺.

BB175**3-Methyl-5-[[rac-(3R,4R)-3-methyl-4-piperidyl]methoxy]-2-(trifluoromethyl)pyridine dihydrochloride**

tert-Butyl (rac-3R,4R)-3-methyl-4-(((5-methyl-6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carboxylate (198 mg, 510 μmol) was dissolved in DCM (2 mL) and
HCl 2M in ether (1.53 mL, 3.06 mmol) was added. The reaction mixture was stirred at RT for 8

- 242 -

h. The reaction mixture was concentrated in vacuo to yield 180 mg of desired product as white solid (98%) MS (ESI): $m/z = 289.3$ $[M+H]^+$.

a) tert-Butyl (rac-3R,4R)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate

To a stirred solution of cis-N-BOC-3-methylpiperidine-4-carboxylic acid methyl ester (2 g, 7.77 mmol) in THF (10 ml) was added lithium borohydride (5.83 mL, 11.7 mmol) at 2-5°C. The reaction mixture was then heated at reflux for 3 h and then cooled to 2-5°C. Water was added and the aqueous layer was extracted twice with EtOAc (30mL each). The organic layer was washed with water, NaHCO₃ and brine, the layers were separated, and the organics dried over Na₂SO₄ and concentrated in vacuum. Purification by flash chromatography (gradient of EtOAc in n-heptane, 0 to 65%) provided the product as a colorless oil (930 mg, 50%). MS (ESI): $m/z = 174.1$ $[M-56+H]^+$.

b) tert-Butyl (rac-3R,4R)-3-methyl-4-(((5-methyl-6-(trifluoromethyl)pyridin-3-yl)oxy)methyl)piperidine-1-carboxylate

tert-butyl (3R,4R)-4-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (239 mg, 1.04 mmol) was dissolved in DMF (4.17 mL) and NaH in mineral oil (60%, 45.8 mg, 1.15 mmol) was added at RT. The reaction was stirred for 20 min, then 5-bromo-3-methyl-2-(trifluoromethyl)pyridine (250 mg, 167 μ L, 1.04 mmol) was added and stirring continued for 12h at RT. The reaction was quenched with 10 mL sat. NH₄Cl solution and extracted three times with water/EtOAc. The organic phases were combined and dried over MgSO₄ and the solvent was removed *in vacuo*. Flash chromatography (gradient of EtOAc in n-heptane, 0 to 50%) yielded the product as white solid (148 mg, 49%). MS (ESI): $m/z = 333.2$ $[M-56+H]^+$.

BB176

3-((2-Fluoro-4-(trifluoromethyl)benzyl)oxy)-2-methylazetidine 2,2,2-trifluoroacetate

To a solution of tert-butyl 3-((2-fluoro-4-(trifluoromethyl)benzyl)oxy)-2-methylazetidine-1-carboxylate (0.265 g, 729 μ mol) in DCM (4 mL) was added TFA (832 mg, 562 μ L, 7.29 mmol). The resultant reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated to give the title compound as a colorless oil. The crude product was used without further purification. MS (ESI): $m/z = 264.2$ $[M+H]^+$.

Step a) *[2-Fluoro-4-(trifluoromethyl)phenyl]methyl methanesulfonate*

- 243 -

To an ice-cold solution of (2-fluoro-4-(trifluoromethyl)phenyl)methanol (840 mg, 4.33 mmol) and triethylamine (1.31 g, 1.81 mL, 13 mmol) in DCM (8 mL) was added dropwise methanesulfonyl chloride (496 mg, 337 μ L, 4.33 mmol) and the mixture was stirred at 0°C for 1 h. The reaction mixture was poured on saturated aqueous NaHCO₃ solution (10 mL) and DCM (20 mL) and the layers were separated. The aqueous layer was extracted once with DCM (20 mL). The organic layers were washed once with brine, dried over MgSO₄, filtered and evaporated to yield the desired compound as a yellow oil (1.13 g, 96%).

Step b) *tert*-Butyl 3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-methyl-azetidine-1-carboxylate

To an ice-cold solution of *tert*-butyl 3-hydroxy-2-methylazetidine-1-carboxylate (250 mg, 1.34 mmol) in DMF (3 mL) was added NaH (60% in mineral oil, 58.7 mg, 1.47 mmol) in portions and the mixture was stirred at ice-bath temperature for 5 min followed by stirring at RT for 40 min. A solution of 2-fluoro-4-(trifluoromethyl)benzyl methanesulfonate (436 mg, 1.6 mmol) in DMF (1 mL) was added dropwise to the mixture at RT. Stirring of the slurry was continued at RT for 16 h. The reaction mixture was poured on saturated aqueous NH₄Cl solution (10 mL) and EtOAc (20 mL) and the layers were separated. The aqueous layer was extracted once with EtOAc (50 mL). The organic layers were washed twice with water, dried over Na₂SO₄, filtered, and concentrated. The crude compound was purified by silica gel chromatography (gradient of n-heptane : EtOAc 100 : 0 to 0 : 100) to get *tert*-butyl 3-[[2-fluoro-4-(trifluoromethyl)phenyl]methoxy]-2-methyl-azetidine-1-carboxylate as a colorless oil (0.265 g, 54.6 % yield). MS (ESI): m/z = 308.2 [M-56+H]⁺.

BB 177

2-(Azetidin-3-ylmethoxy)-4,5-bis(trifluoromethyl)pyridine 2,2,2-trifluoroacetate

Synthesis of BB177 was performed in analogy to BB57, starting from *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate and 2-chloro-4,5-bis(trifluoromethyl)pyridine. MS (ESI): m/z = 301.2 [M+H]⁺.

BB179

3-((4-Chloro-2-phenoxybenzyl)oxy)azetidine 2,2,2-trifluoroacetate

- 244 -

Synthesis of BB179 was done in analogy to BB39, starting from tert-butyl 3-hydroxyazetidine-1-carboxylate and 1-(bromomethyl)-4-chloro-2-phenoxybenzene (synthesis described below).

MS (ESI): $m/z = 290.2$ $[M+H]^+$.

1-(Bromomethyl)-4-chloro-2-phenoxybenzene

- 5 i) In a 10 mL round-bottomed flask, methyl 4-chloro-2-phenoxybenzoate (547 mg, 2.08 mmol) was diluted in toluene (3.82 mL) and the reaction mixture was cooled in an ice bath. Sodium bis(2-methoxyethoxy)aluminum hydride 70% in toluene (649 mg, 637 μ L, 2.25 mmol) was added dropwise slowly at max. 15°C to give a light yellow solution. The reaction mixture was stirred at r.t. for 30 min. The crude reaction mixture, containing the product (4-chloro-2-phenoxyphenyl)methanol was used directly in the next step.
- 10 ii) In a 25 mL round-bottomed flask, hydrobromic acid 48% in H₂O (6.49 g, 4.35 mL, 38.5 mmol) was cooled in an ice bath. Then 4-chloro-2-phenoxyphenyl)methanol (crude, 488 mg, 2.08 mmol) was added dropwise slowly and the mixture was stirred at 50°C for 2 h. Hydrobromic acid 48% in H₂O (6.25 g, 2.18 mL, 19.25 mmol) was added and the mixture was stirred at 60°C for 1 h, then cooled to RT. The aqueous phase was separated, the organic phase was washed four times with H₂O and evaporated. The crude material was purified by flash column chromatography (gradient 0% to 25% EtOAc in hexanes) and was used in the next step without further purification. Yield: 85%.
- 15

BB 181

20 **3-((1-(2,4-Dichlorophenyl)cyclopropyl)methoxy)azetidine 2,2,2-trifluoroacetate**

- To a solution of tert-Butyl 3-((1-(2,4-dichlorophenyl)cyclopropyl)methoxy)azetidine-1-carboxylate (165 mg, 443 μ mol) in DCM (2 mL) was added TFA (202 mg, 137 μ L, 1.77 mmol) and the reaction stirred at RT for 8 h. The mixture was concentrated in vacuo (azeotrop with toluene, EtOAc and n-heptane) to provide the compound as a colorless oil (170 mg, 99%). MS
- 25 (ESI): $m/z = 272.2$ $[M+H]^+$.

Step a) *1-(2,4-Dichlorophenyl)cyclopropyl)methanol*

- In a 50 mL three-necked flask, 1-(2,4-dichlorophenyl)cyclopropane-1-carboxylic acid (1 g, 4.33 mmol) was combined with THF (20 mL) to give a colorless solution. At 0°C, borane tetrahydrofuran complex solution 1.0 M in THF (6.49 mL, 6.49 mmol) was added dropwise over
- 30 a period of 15 min. The reaction was stirred at RT for 2 h. MeOH (2 mL) was added dropwise

- 245 -

followed by 1M aq. HCl solution and stirred for 30 min. The reaction mixture was extracted twice with EtOAc (40 mL each) and the organic layers were washed with 10% aq Na₂CO₃ solution (40 mL) followed by brine (40 mL). The organic fractions were combined and dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (gradient EtOAc in n-heptane, 0% to 30%) to yield the compound as colorless oil (90%) MS (ESI): m/z = 201.0 [M-16+H]⁺.

Step b) *1-(2,4-Dichlorophenyl)cyclopropyl)methyl methanesulfonate*

To an ice-cold solution of (1-(2,4-dichlorophenyl)cyclopropyl)methanol (350 mg, 1.61 mmol) and TEA (326 mg, 449 µL, 3.22 mmol) in DCM (6 mL) was added dropwise methanesulfonyl chloride (185 mg, 126 µL, 1.61 mmol) and the mixture was stirred at 0°C for 1 h, then at RT overnight. The reaction mixture was poured on saturated aqueous NaHCO₃ solution (10 mL) and DCM (10 mL) and the layers were separated. The aqueous layer was extracted once with DCM (10 mL). The organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to furnish the desired intermediate mesylate compound as a yellow oil (435 mg, 91%). MS (ESI): m/z = 201.0 [M-mesyl+H]⁺.

Step c) *tert-Butyl 3-((1-(2,4-dichlorophenyl)cyclopropyl)methoxy)azetidine-1-carboxylate*

To an ice-cold solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (220 mg, 1.27 mmol) in DMF (4 mL) was added sodium hydride in mineral oil (60%, 61 mg, 1.52 mmol) in portions and the mixture was stirred at ice-bath temperature for 5 min followed by stirring at RT for 40 min. A solution of 1-(2,4-dichlorophenyl)cyclopropyl)methyl methanesulfonate (431 mg, 1.46 mmol) was dissolved in DMF (1 mL) and added dropwise to the mixture at RT. Stirring of the slurry was continued at RT for 16 h, then at 55°C for 2.5 h. The reaction mixture was poured on saturated aqueous NH₄Cl solution (10 mL) and EtOAc (20 mL) and the layers were separated. The aqueous layer was extracted once with EtOAc (50 mL). The organic layers were washed twice with water, dried over MgSO₄, filtered and evaporated. Flash Chromatography (gradient of EtOAc in n-heptane 0 to 40%) yielded the product as colorless oil (165 mg, 35%) MS (ESI): m/z = 316.2 [M-56+H]⁺.

BB182

2-((Azetidin-3-yloxy)methyl)-6-(4-fluorophenoxy)-4-(trifluoromethyl)pyridine 4-methylbenzenesulfonate

- 246 -

Tert-butyl 3-((6-(4-fluorophenoxy)-4-(trifluoromethyl)pyridin-2-yl)methoxy)azetidine-1-carboxylate (150mg, 339 μ mol) was dissolved under argon in EtOAc (2 mL), p-toluenesulfonic acid monohydrate (77.4 mg, 407 μ mol) was added and the mixture was stirred at RT for 5 min, then for 80°C 3 h at and at RT over night. The reaction mixture was evaporated to provide the compound as 180 mg of a yellow oil which was used in the next step without further purification. MS (ESI): m/z = 343.2 $[M+H]^+$.

Step a) *tert-Butyl 3-((6-bromo-4-(trifluoromethyl)pyridin-2-yl)methoxy)azetidine-1-carboxylate*

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (272 mg, 1.57 mmol) in dry THF (8 mL) was added potassium tert-butoxide 1M in THF (1.57 mL, 1.57 mmol) and the turbid reaction mixture was stirred at RT for 30 min. 2-Bromo-6-(bromomethyl)-4-(trifluoromethyl)pyridine (500 mg, 1.57 mmol) was added at 0 - 2°C and the reaction stirred at 0 - 2°C for 20 min. The reaction mixture was then stirred at RT for 16 h. The reaction mixture was diluted with EtOAc, extracted with water, the organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated down to dryness. The crude material was purified by flash column chromatography (gradient of EtOAc in n-heptane, 0% to 40%) to provide the product as light yellow oil (41%) MS (ESI): m/z = 355.1 $[M-56+H]^+$.

Step b) *tert-Butyl 3-[[6-(4-fluorophenoxy)-4-(trifluoromethyl)-2-pyridyl]methoxy]azetidine-1-carboxylate*

tert-Butyl 3-((6-bromo-4-(trifluoromethyl)pyridin-2-yl)methoxy)azetidine-1-carboxylate (260 mg, 632 μ mol) and 4-fluorophenol (70.9 mg, 632 μ mol) were dissolved in DMF (2 mL), then K_2CO_3 (131 mg, 948 μ mol) was added and the mixture was stirred at 80° for 30 h. The reaction mixture was evaporated under vacuum and the residue was dissolved in EtOAc and extracted with water and brine. The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography (gradient of EtOAc in n-heptane, 0 to 30%) to yield the product as a light yellow oil (93%). MS (ESI): m/z = 443.4 $[M+H]^+$.

BB183

6-((Azetidin-3-yloxy)methyl)-2-(4-fluorophenoxy)-3-(trifluoromethyl)pyridine 4-methylbenzenesulfonate

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- 247 -

tert-Butyl 3-((6-(4-fluorophenoxy)-5-(trifluoromethyl)pyridin-2-yl)methoxy)azetidine-1-carboxylate (170 mg, 384 μ mol) was dissolved under argon atmosphere in EtOAc (2.27 mL) and p-toluenesulfonic acid monohydrate (87.7 mg, 461 μ mol) was added. The reaction was stirred at RT for 5 min, then at 80°C for 3 h and stirred at RT over night. The reaction mixture was
5 evaporated under reduced pressure to dryness to provide the desired product as light yellow oil (89%) MS (ESI): $m/z = 343.2 [M+H]^+$.

Step a) *Methyl 6-(4-fluorophenoxy)-5-(trifluoromethyl)picolinate*

Methyl 6-chloro-5-(trifluoromethyl)picolinate (800 mg, 3.34 mmol), 4-fluorophenol (412 mg, 3.67 mmol) and K_2CO_3 (692 mg, 5.01 mmol) were dissolved in DMF (6 mL) and stirred at 80°C
10 for 6 h. The reaction mixture was cooled to RT and extracted three times with water (20 mL each), twice with EtOAc (30 mL each), brine (20mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude residue was purified by flash column chromatography (gradient of EtOAc in n-heptane, 0 to 50%) to provide the product as white solid (67%). MS (ESI): $m/z = 316.1 [M+H]^+$.

15 Step b) *(6-(4-Fluorophenoxy)-5-(trifluoromethyl)pyridin-2-yl)methanol*

To a stirred solution of methyl 6-(4-fluorophenoxy)-5-(trifluoromethyl)picolinate (705 mg, 2.24 mmol) in THF (8 mL) was added lithium borohydride 2M in THF (1.34 mL, 2.68 mmol) at 2-5°C. The reaction mixture was stirred at RT for 3 h and then cooled to 2-4°C and quenched with 10 mL water (slowly added). The aqueous layer was extracted twice with EtOAc (30 mL each)
20 and the combined organic layers were washed with water, 10 mL $NaHCO_3$ solution and 10 mL brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuum. Purification by flash column chromatography (gradient of EtOAc in n-heptane, 0 to 50%) yielded the product as a colorless solid (95%). MS (ESI): $m/z = 288.2 [M+H]^+$.

Step c) *6-(Bromomethyl)-2-(4-fluorophenoxy)-3-(trifluoromethyl)pyridine*

25 To a solution of (6-(4-fluorophenoxy)-5-(trifluoromethyl)pyridin-2-yl)methanol (330 mg, 1.15 mmol) in dry DCM (5 mL) was added tetrabromomethane (457 mg, 1.38 mmol). The mixture was cooled to 0-3°C and over 10 min triphenylphosphine (392 mg, 1.49 mmol) in 1 mL dry DCM was added. The mixture was stirred 1 hr at 2-4°C, then 20mL DCM and silica gel was added. The solvent was removed in vacuo and the residue subjected to column flash
30 chromatography (gradient of EtOAc in n-heptane, 0 to 40%) to yield the desired product as a colorless oil (94%). MS (ESI): $m/z = 350.0 [M+H]^+$.

- 248 -

Step d) *tert*-Butyl 3-((6-(4-fluorophenoxy)-5-(trifluoromethyl)pyridin-2-yl)methoxy)azetidine-1-carboxylate

To a solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (183 mg, 1.06 mmol) in dry THF (5 mL) was added potassium *tert*-butoxide 1M in THF (1.11 mL, 1.11 mmol) and the reaction mixture was stirred at RT for 15 min. Then, 6-(bromomethyl)-2-(4-fluorophenoxy)-3-(trifluoromethyl)pyridine (370 mg, 1.06 mmol) was added. The reaction mixture was stirred at RT for 1 h and then diluted with EtOAc and extracted with 1M aq. NaHCO₃ solution. The organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over sodium sulfate and evaporated down to dryness. The residue was purified by column flash chromatography (gradient of EtOAc in *n*-heptane, 0 to 30%) to furnish the product as a colorless oil (34%). MS (ESI): $m/z = 387.2$ [M-56+H]⁺.

BB184

2-((Azetidin-3-yloxy)methyl)-4-(4-fluorophenyl)thiazole 2,2,2-trifluoroacetate

To a solution of *tert*-butyl 3-((4-(4-fluorophenyl)thiazol-2-yl)methoxy)azetidine-1-carboxylate (150 mg, 412 μ mol) in dry DCM (1.5 mL) under argon atmosphere was added TFA (282 mg, 190 μ L, 2.47 mmol) and the solution was stirred at RT for 8 h. The reaction mixture was concentrated in vacuo (azeotrop with toluene, EtOAc and heptane) to yield the desired product as a yellow solid (98%). MS (ESI): $m/z = 265.2$ [M+H]⁺.

Step a) *(4-(4-Fluorophenyl)thiazol-2-yl)methanol*

To a stirred solution of ethyl 4-(4-fluorophenyl)thiazole-2-carboxylate (835 mg, 3.32 mmol) in dry THF (10 mL) was added lithium borohydride 2M in THF (1.99 mL, 3.99 mmol) at 2-5°C. The reaction mixture was stirred at RT for 3h, then cooled to 2-4°C and quenched with water (10 mL slowly added). The aqueous layer was extracted twice with EtOAc (30 mL each) and the organic layers were washed with water, 10 mL NaHCO₃ solution and 10 mL brine. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by column flash chromatography (gradient of EtOAc in *n*-heptane, 0 to 60%) to yield the desired product as a white solid (94%) MS (ESI): $m/z = 210.1$ [M+H]⁺.

Step b) *2-(Bromomethyl)-4-(4-fluorophenyl)thiazole*

To a solution of *(4-(4-fluorophenyl)thiazol-2-yl)methanol* (400 mg, 1.91 mmol) in dry DCM (7 mL) was added tetrabromomethane (761 mg, 2.29 mmol), the solution was cooled to 0-3°C and

- 249 -

triphenylphosphine (652 mg, 2.49 mmol) in 1 mL dry DCM was added over 10 min. The mixture was stirred at 2-4°C for 1 h, then 20 mL DCM were added. The reaction mixture was extracted with water, saturated NH₄Cl solution and brine. The organic phase was dried over MgSO₄, filtered and evaporated. The residue was purified by flash chromatography (gradient of EtOAc in n-heptane, 0 to 40%) to provide 480 mg of the title compound as a light yellow oil (83%). MS (ESI): m/z = 273.9 [M+H]⁺.

Step c) *tert-Butyl 3-((4-(4-fluorophenyl)thiazol-2-yl)methoxy)azetidine-1-carboxylate*

To a solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (293 mg, 1.69 mmol) in dry THF (6 mL) was added potassium *tert*-butoxide 1M in THF (1.77 mL, 1.77 mmol) and the reaction mixture was stirred at RT for 15 min. After cooling down to 2-4°C 2-(bromomethyl)-4-(4-fluorophenyl)thiazole (460 mg, 1.69 mmol) in 1 mL THF was added. The reaction mixture was stirred at RT for 1h, diluted with EtOAc and extracted with 1M aq. NaHCO₃ solution. The organic phase was collected and the aqueous phase was back-extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and evaporated down to dryness. The residue was purified by column flash chromatography (gradient of EtOAc in n-heptane, 0 to 40%) to furnish the desired product as a light yellow solid (89%). MS (ESI): m/z = 365.2 [M+H]⁺.

BB186

***rac*-(2R,3S)-3-(2-Bromo-5-(trifluoromethyl)phenoxy)-2-methylpyrrolidine 2,2,2-trifluoroacetate**

To a solution of *rac*-*tert*-butyl (2R,3S)-3-(2-bromo-5-(trifluoromethyl)phenoxy)-2-methylpyrrolidine-1-carboxylate (225mg, 530 μmol) in dry DCM (2 mL) under argon atmosphere was added TFA (242 mg, 163 μL, 2.12 mmol) and the solution was stirred at RT over night. The reaction mixture was concentrated in vacuo to dryness (azeotrop with n-heptane) to provide 233 mg of the title compound as a colorless oil (97%). MS (ESI): m/z = 324.1 [M+H]⁺.

Step a) *rac-tert-Butyl (2R,3S)-3-(2-bromo-5-(trifluoromethyl)phenoxy)-2-methylpyrrolidine-1-carboxylate*

To a solution of *rac*-*tert*-butyl (2R,3S)-3-hydroxy-2-methylpyrrolidine-1-carboxylate (CAS:1807941-04-3, 150 mg, 745 μmol) in dry THF (4 mL) under argon atmosphere was added potassium *tert*-butoxide 1M in THF (783 μL, 783 μmol). The mixture was stirred at RT for 15

- 250 -

min, then cooled down to 2-4°C and a solution of 1-bromo-2-fluoro-4-(trifluoromethyl)benzene (181 mg, 745 µmol) in 0.5mL dry THF was added slowly. The mixture was stirred at RT for 2 h and then extracted with EtOAc and aqueous 5% NaHCO₃ solution followed by water and brine. The organic phase was dried over MgSO₄, filtered off and evaporated to dryness. The residue
 5 was purified by column flash chromatography (gradient of EtOAc in n-heptane, 0 to 40%) to yield the product as light yellow oil (71%). MS (ESI): m/z = 368 [M-56+H]⁺.

The following intermediates were synthesized from 4-nitrophenyl (4aR,8aS)-3-oxohexahydro-2H-pyrido[4,3-b][1,4]oxazine-6(5H)-carboxylate (BB7a) and the suitable building blocks in analogy to the reaction methods described herein.

BB No.	Building block(s)	MS, m/z	Method
BB203	BB198	480.1 [M+H] ⁺	A10 without DMAP
BB204	BB201	445.1 [M+H] ⁺	A10 without DMAP

10

BB206**3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethyl]azetidine;4-methylbenzenesulfonic acid**

The compound was prepared in analogy to BB95 from tert-butyl 3-(2-fluoro-4-(trifluoromethyl)phenethyl)azetidine-1-carboxylate and 4-methylbenzenesulfonic acid
 15 monohydrate. Upon cooling a suspension formed which was filtered. The filter cake was washed with a small volume of EtOAc to provide the desired product as a colorless solid (71.6%). MS (ESI): m/z = 248.2 [M+H]⁺.

Step a) Diethyl (2-fluoro-4-(trifluoromethyl)benzyl)phosphonate

The compound was prepared in analogy to BB159, step a, from 1-(bromomethyl)-2-fluoro-4-(trifluoromethyl)benzene and triethyl phosphite. Colorless oil (83.4%). MS (ESI): m/z = 315.2
 20 [M+H]⁺.

Step b) tert-Butyl 3-[(E)-2-[2-fluoro-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate

The compound was prepared in analogy to BB95, step a, from diethyl (2-fluoro-4-(trifluoromethyl)benzyl)phosphonate and tert-butyl 3-formylazetidine-1-carboxylate to yield the
 25 compound as a colorless oil (69.9%). MS (ESI): m/z = 290.1 [M-56+H]⁺.

- 251 -

Step c) *tert-Butyl 3-[2-[2-fluoro-4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

The compound was prepared in analogy to BB95, step b, from *tert-butyl 3-[(E)-2-[2-fluoro-4-(trifluoromethyl)phenyl]vinyl]azetidine-1-carboxylate*. Colorless oil (92.0%). MS (ESI): $m/z = 292.2$ $[M-56+H]^+$.

5

BB208

3-[2,2-Difluoro-2-[4-(trifluoromethyl)phenyl]ethyl]azetidine; 4-methylbenzenesulfonic acid

The compound was prepared in analogy to BB95 from *tert-butyl 3-(2,2-difluoro-2-[4-(trifluoromethyl)phenyl]ethyl)azetidine-1-carboxylate* and 4-methylbenzenesulfonic acid monohydrate and using the material isolated from the filtrate after evaporation, which was used
10 without further purification (30%). MS (ESI): $m/z = 266.2$ $[M+H]^+$.

Step a) *tert-Butyl 3-[2-[methoxy(methyl)amino]-2-oxo-ethyl]azetidine-1-carboxylate*

To a suspension of 2-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)acetic acid (2 g, 9.29 mmol) and HATU (3.89 g, 10.2 mmol) in DCM (65 mL) was added DIPEA (2.64 g, 3.57 mL, 20.4 mmol) and the mixture was stirred at RT for 30 min before *N,O*-dimethylhydroxylamine hydrochloride
15 (906 mg, 9.29 mmol) was added. Stirring was continued at RT overnight. The reaction mixture was poured on saturated aqueous NH_4Cl solution and EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic layers were washed twice with water, dried over $MgSO_4$, filtered, treated with silica gel and evaporated. The compound was purified by silica gel chromatography on a 25 g column using an MPLC system eluting with a
20 gradient of *n*-heptane : EtOAc (100 : 0 to 0 : 100) to furnish the desired compound as a colorless oil (100%) which was used in the next step without further purification. MS (ESI): $m/z = 203.2$ $[M-56+H]^+$.

Step b) *tert-Butyl 3-[2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

To an ice-cold solution of *tert-butyl 3-(2-(methoxy(methyl)amino)-2-oxoethyl)azetidine-1-carboxylate* (0.8 g, 3.1 mmol) in THF (5 mL) in an argon-flushed and heat-dried 2-neck flask
25 was added dropwise a turbid solution of (4-(trifluoromethyl)phenyl)magnesium bromide 2.22 M in THF (1.95 mL, 4.34 mmol). The brown solution was stirred in an ice-bath for 2.5 h allowing the temperature to rise to RT. The reaction mixture was poured on saturated aqueous NH_4Cl solution and EtOAc and the layers were separated. The aqueous layer was extracted twice with
30 EtOAc. The organic layers were dried over $MgSO_4$, filtered, treated with silica gel and

- 252 -

evaporated. The compound was purified by silica gel chromatography on a 25 g column using an MPLC system eluting with a gradient of n-heptane : EtOAc (100 : 0 to 0 : 100) to provide the desired compound as a colorless solid (25.9%). MS (ESI): $m/z = 342.3$ [M-H]⁻.

Step c) *tert-Butyl 3-[2,2-difluoro-2-[4-(trifluoromethyl)phenyl]ethyl]azetidine-1-carboxylate*

- 5 To a solution of *tert-butyl 3-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)azetidine-1-carboxylate* (50 mg, 146 μmol) in toluene (0.3 mL) under argon was added bis(2-methoxyethyl)aminosulphur trifluoride (50% solution in THF, 387 mg, 379 μL , 874 μmol) and the mixture was stirred at 80°C for 19 h. The dark mixture was allowed to cool down and another batch of bis(2-methoxyethyl)aminosulphur trifluoride (50% solution in THF, 387 mg,
10 379 μL , 874 μmol) was added. Heating was continued at 80°C for another 4 h. The reaction mixture was poured on saturated aqueous NaHCO₃ solution and EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic layers were dried over MgSO₄, filtered, treated with silica gel and evaporated. The compound was purified by silica gel chromatography on a 4 g column using an MPLC system eluting with a gradient of n-
15 heptane : EtOAc (100 : 0 to 50 : 50) to yield the desired compound as a light brown oil (45.1%). MS (ESI): $m/z = 266.1$ [M+H]⁺.

BB209

3-[2-Fluoro-5-(trifluoromethyl)phenoxy]pyrrolidine;4-methylbenzenesulfonic acid

- The compound was prepared in analogy to BB95 from *tert-butyl 3-[2-fluoro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carboxylate*. Colorless oil which was used in the next
20 step without further purification. MS (ESI): $m/z = 250.1$ [M+H]⁺.

Step a) *tert-Butyl 3-[2-fluoro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carboxylate*

- To a solution of 2-fluoro-5-(trifluoromethyl)phenol (321 mg, 1.78 mmol), *tert-butyl 3-hydroxypyrrolidine-1-carboxylate* (334 mg, 1.78 mmol; CAS RN: 103057-44-9) and
25 triphenylphosphine (467 mg, 1.78 mmol) in THF (5 mL) was added (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (450 mg, 1.78 mmol, CAS RN 10465-81-3) in portions and the mixture was stirred at RT for 40 h. Silica gel was added to the suspension and it was evaporated. The compound was purified by silica gel chromatography on a 24 g column using an MPLC (ISCO) system eluting with a gradient of n-heptane : EtOAc (100 : 0 to 75 : 25) to provide the

- 253 -

desired compound as a colorless oil (8.3%) which was used in the next step without further purification. MS (ESI): $m/z = 294.1$ $[M-56+H]^+$.

BB210**3-[2-Chloro-5-(trifluoromethyl)phenoxy]pyrrolidine;4-methylbenzenesulfonic acid**

- 5 The compound was prepared in analogy to BB95 from tert-butyl 3-[2-chloro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carboxylate. Colorless oil. MS (ESI): $m/z = 266.1$ $[M+H]^+$.

Step a) *tert-Butyl 3-[2-chloro-5-(trifluoromethyl)phenoxy]pyrrolidine-1-carboxylate*

- The compound was prepared in analogy to BB209, step a, from 2-chloro-5-(trifluoromethyl)phenol and tert-butyl 3-hydroxypyrrolidine-1-carboxylate. Colorless solid
10 which was used after chromatography without further purification. MS (ESI): $m/z = 310.1$ $[M-56+H]^+$.

BB211**3-[(E)-2-(2-fluoro-4-methyl-phenyl)vinyl]azetidine;4-methylbenzenesulfonic acid**

- 15 The compound was prepared in analogy to BB95 from tert-butyl 3-[(E)-2-(2-fluoro-4-methyl-phenyl)vinyl]azetidine-1-carboxylate and 4-methylbenzenesulfonic acid monohydrate. Colorless solid (87%). MS (ESI): $m/z = 192.2$ $[M+H]^+$.

Step a) *1-(Diethoxyphosphorylmethyl)-2-fluoro-4-methyl-benzene*

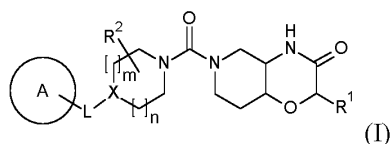
- The compound was prepared in analogy to BB206, step a, from 1-(bromomethyl)-2-fluoro-4-methylbenzene and triethyl phosphite followed by silica gel chromatography on a 40 g column
20 using an MPLC (ISCO) system eluting with a gradient of n-heptane : EtOAc (100 : 0 to 0 : 100). Colorless liquid (85%). MS (ESI): $m/z = 261.1$ $[M+H]^+$.

Step b) *tert-Butyl 3-[(E)-2-(2-fluoro-4-methyl-phenyl)vinyl]azetidine-1-carboxylate*

- The compound was prepared in analogy to example BB206, step b, from tert-butyl 3-formylazetidine-1-carboxylate and 1-(diethoxyphosphorylmethyl)-2-fluoro-4-methyl-benzene.
25 Colorless oil (7%). MS (ESI): $m/z = 236.2$ $[M-56+H]^+$.

CLAIMS

1. A compound of formula (I)



or a pharmaceutically acceptable salt thereof,

5 wherein:

X is $C-R^3$; m is 0 or 1; n is selected from 0, 1 and 2; and L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-NR^5-CH_2-CHR^4-$, $-NR^5-CHR^4-CH_2-$, $-CH_2-NR^5-CHR^4-$, $-(CR^6R^7)_p-C(O)-NR^8-$, $-C(O)-NR^8-(CR^6R^7)_p-$, $-(CR^6R^7)_p-NR^8-C(O)-$, $-NR^8-C(O)-(CR^6R^7)_p-$, $-(CH_2)_qNR^9-$, $-NR^9-(CH_2)_q-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SCH_2-$, $-CH_2S-$, $-S(O)CH_2-$, $-CH_2S(O)-$, $-SO_2CH_2-$, and $-CH_2SO_2-$; or

10

X is N; m is 1; n is 1 or 2; and L is selected from $-NR^5-CH_2-CHR^4-$, $-NR^5-CHR^4-CH_2-$, and $-NR^8-C(O)-(CR^6R^7)_p-$;

p and q are each independently selected from 0, 1 and 2;

A is selected from:

15

- (i) C_6-C_{14} -aryl substituted with R^{10} , R^{11} and R^{12} ;
- (ii) 5- to 14-membered heteroaryl substituted with R^{13} , R^{14} and R^{15} ; and
- (iii) 3- to 14-membered heterocycloalkyl substituted with R^{16} , R^{17} and R^{18} ;
- (iv) C_3-C_{10} -cycloalkyl substituted with R^{22} , R^{23} , and R^{24} ;

R^1 is hydrogen or C_{1-6} -alkyl;

20

R^2 is selected from hydrogen, C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl;

R^3 is selected from hydrogen, halogen, hydroxy, C_{1-6} -alkoxy, C_{1-6} -alkyl and halo- C_{1-6} -alkyl;

R^4 is selected from hydrogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl;

R^5 is selected from hydrogen, C_{1-6} -alkyl and halo- C_{1-6} -alkyl- CH_2- ;

25

each of R^6 and R^7 is independently hydrogen or C_{1-6} -alkyl; or

R^6 and R^7 , taken together with the carbon atom to which they are attached, form a 3- to 14-membered heterocycloalkyl or a C_{3-10} -cycloalkyl;

R^8 is selected from hydrogen, C_{1-6} -alkyl, and hydroxy- C_{1-6} -alkyl;

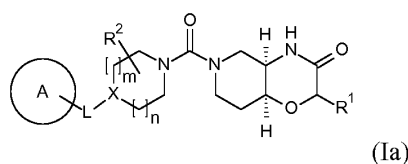
R^9 is selected from hydrogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl- CH_2- , $(C_{1-6}$ -alkyl)(halo- C_{1-6} -alkyl)CH- and hydroxy- C_{1-6} -alkyl- CH_2- ;

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- 255 -

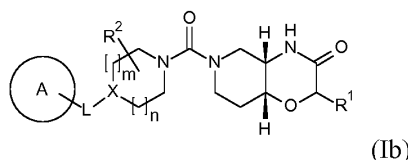
each of R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} is independently selected from hydrogen, halogen, cyano, hydroxy, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, halo- C_{1-6} -alkyl-CH(OH)-, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, SF_5 , C_{1-6} -alkylsulfonyl, C_{3-10} -cycloalkyl, C_{3-10} -cycloalkyl substituted with R^{19} , 3- to 14-membered heterocycloalkyl, 3- to 14-membered heterocycloalkyl substituted with R^{20} , 5- to 14-membered heteroaryl, C_6 - C_{14} -aryl and halo- C_6 - C_{14} -aryl; and each of R^{19} and R^{20} is independently selected from C_{1-6} -alkyl, cyano, and hydroxy.

2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (Ia):



wherein A, L, X, m, n, R^1 and R^2 are as defined in claim 1.

3. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (Ib):



wherein A, L, X, m, n, R^1 and R^2 are as defined in claim 1.

4. The compound of formula I according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein:

X is $C-R^3$;

m and n are each independently 0 or 1; and

L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-CH_2-NR^5-CHR^4-$, $-(CR^6R^7)_p-C(O)-NR^8-$, $-(CR^6R^7)_p-NR^8-C(O)-$, $-(CH_2)_qNR^9-$, $-S-$, $-S(O)-$, $-SO_2-$, $-SCH_2-$, $-CH_2S-$, $-S(O)CH_2-$, $-CH_2S(O)-$, $-SO_2CH_2-$, and $-CH_2SO_2-$.

5. The compound of formula I according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

X is $C-R^3$;

- 256 -

m and n are both 0; or

m and n are both 1; and

L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-(CH_2)_qNR^9-$, $-SCH_2-$, and $-CH_2S-$

.

- 5 6. The compound of formula I according to any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein p is 0 or 1.
7. The compound of formula I according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein q is 0.
8. The compound of formula I according to any one of claims 1-7, or a
10 pharmaceutically acceptable salt thereof, wherein A is selected from:
- (i) C_6-C_{14} -aryl substituted with R^{10} , R^{11} and R^{12} ;
 - (ii) 5- to 14-membered heteroaryl substituted with R^{13} , R^{14} and R^{15} ; and
 - (iii) C_3-C_{10} -cycloalkyl substituted with R^{22} , R^{23} , and R^{24} .
9. The compound of formula I according to any one of claims 1-7, or a
15 pharmaceutically acceptable salt thereof, wherein A is C_6-C_{14} -aryl substituted with R^{10} , R^{11} and R^{12} .
10. The compound of formula I according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein A is phenyl substituted with R^{10} , R^{11} and R^{12} .
- 20 11. The compound of formula I according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.
12. The compound of formula I according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.
13. The compound of formula I according to any one of claims 1-12, or a
25 pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, hydroxy, or C_{1-6} -alkyl.
14. The compound of formula I according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

- 257 -

15. The compound of formula I according to any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R⁴ is halo-C₁₋₆-alkyl.
16. The compound of formula I according to any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R⁴ is CF₃.
- 5 17. The compound of formula I according to any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen.
18. The compound of formula I according to any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R⁶ and R⁷ are both hydrogen; or R⁶ and R⁷, together with the carbon atom to which they are attached, form a C₃₋₁₀-
10 cycloalkyl.
19. The compound of formula I according to any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R⁹ is C₁₋₆-alkyl.
20. The compound of formula I according to any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R⁹ is methyl.
- 15 21. The compound of formula I according to any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkylsulfonyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-cycloalkyl substituted with R¹⁹, cyano, or halogen.
22. The compound of formula I according to any one of claims 1-20, or a
20 pharmaceutically acceptable salt thereof, wherein R¹⁰ is C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₃₋₁₀-cycloalkyl, or halogen.
23. The compound of formula I according to any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is methyl, difluoromethyl, CF₃, OCF₃, cyclopropyl, fluoro, or chloro.
- 25 24. The compound of formula I according to any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R¹¹ is hydrogen, C₁₋₆-alkyl, or halogen.

- 258 -

25. The compound of formula I according to any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R¹¹ is hydrogen, methyl, chloro, or fluoro.
26. The compound of formula I according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein R¹² is hydrogen or halogen.
27. The compound of formula I according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein R¹² is hydrogen or fluoro.
28. The compound of formula I according to any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein R¹³ is halogen.
29. The compound of formula I according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R¹⁴ is hydrogen.
30. The compound of formula I according to any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein R¹⁵ is hydrogen.
31. The compound of formula I according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof, wherein R¹⁹ is hydroxy or cyano.
32. The compound of formula I according to any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R²² is hydrogen or hydroxy.
33. The compound of formula I according to any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R²³ is hydrogen.
34. The compound of formula I according to any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein R²⁴ is hydrogen.
35. The compound of formula I according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein:

X is C-R³;

L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -CH₂-NR⁵-CHR⁴-, -(CR⁶R⁷)_p-C(O)-NR⁸-, -(CR⁶R⁷)_p-NR⁸-C(O)-, -(CH₂)_qNR⁹-, -S-, -S(O)-, -SO₂-, -SCH₂-, -CH₂S-, -S(O)CH₂-, -CH₂S(O)-, and -SO₂CH₂-;

m, n and p are each independently 0 or 1;

q is 0;

- 259 -

A is selected from:

- (i) C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;
- (ii) 5- to 14-heteroaryl substituted with R¹³, R¹⁴ and R¹⁵; and
- (iii) C₃-C₁₀-cycloalkyl substituted with R²², R²³, and R²⁴;

5 R¹ and R² are both hydrogen;

R³ is selected from hydrogen, hydroxy, and C₁₋₆-alkyl;

R⁴ is halo-C₁₋₆-alkyl;

R⁵ is hydrogen or C₁₋₆-alkyl;

R⁶ and R⁷ are both hydrogen; or

10 R⁶ and R⁷, together with the carbon atom to which they are attached, form a C₃₋₁₀-cycloalkyl;

R⁸ is selected from hydrogen, C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;

R⁹ is C₁₋₆-alkyl;

15 R¹⁰ is selected from hydrogen, C₁₋₆-alkyl, C₁₋₆-alkylsulfonyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₃₋₁₀-cycloalkyl, C₃₋₁₀-cycloalkyl substituted with R¹⁹, cyano, and halogen;

R¹¹ is selected from hydrogen, C₁₋₆-alkyl, and halogen;

R¹² is hydrogen or halogen;

R¹³ is halogen;

20 R¹⁴ and R¹⁵ are both hydrogen;

R¹⁹ is hydroxy or cyano;

R²² is hydrogen or hydroxy; and

R²³ and R²⁴ are both hydrogen.

36. The compound of formula I according to any one of claims 1-3, wherein:

25 X is C-R³;

L is selected from -C≡C-, -CHR⁴-NR⁵-CH₂-, -(CH₂)_qNR⁹-, -SCH₂-, and -CH₂S-

;

m and n are both 0; or

m and n are both 1;

30 q is 0;

A is C₆-C₁₄-aryl substituted with R¹⁰, R¹¹ and R¹²;

R¹, R² and R³ are all hydrogen;

R⁴ is halo-C₁₋₆-alkyl;

- 260 -

- R^5 is hydrogen;
 R^9 is C_{1-6} -alkyl;
 R^{10} is selected from C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, C_{3-10} -cycloalkyl,
 and halogen;
 5 R^{11} is selected from hydrogen, C_{1-6} -alkyl, and halogen; and
 R^{12} is hydrogen or halogen.
37. The compound of formula I according to any one of claims 1-3, wherein:
 X is $C-R^3$;
 L is selected from $-C\equiv C-$, $-CHR^4-NR^5-CH_2-$, $-(CH_2)_qNR^9-$, $-SCH_2-$, and $-CH_2S-$
 10 ;
 m and n are both 0; or
 m and n are both 1;
 q is 0;
 A is phenyl substituted with R^{10} , R^{11} and R^{12} ;
 15 R^1 , R^2 and R^3 are all hydrogen;
 R^4 is CF_3 ;
 R^5 is hydrogen;
 R^9 is methyl;
 R^{10} is selected from methyl, difluoromethyl, CF_3 , OCF_3 , cyclopropyl, chloro, and
 20 fluoro;
 R^{11} is selected from hydrogen, methyl, chloro, and fluoro; and
 R^{12} is hydrogen or fluoro.
38. A compound of formula (I) according to any one of claims 1 to 37, selected from the
 compounds disclosed in Table 1.
- 25 39. A compound of formula (I) according to any one of claims 1 to 37, selected from:
 (+)- or (-)-(4aR,8aS)-6-[3-[[[2,2,2-Trifluoro-1-[4-
 (trifluoromethyl)phenyl]ethyl]amino]methyl]azetidine-1-carbonyl]hexahydro-
 2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
 (4aR,8aS)-6-[4-[2-(2-Chlorophenyl)ethynyl]piperidine-1-carbonyl]-4,4a,5,7,8,8a-
 30 hexahydropyrido[4,3-b][1,4]oxazin-3-one;
 (+)- or (-)-(4aR,8aS)-6-[4-[2-(2-Chloro-4-fluorophenyl)ethynyl]piperidine-1-
 carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;

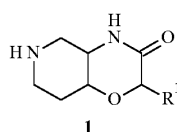
- (4aR,8aS)-6-[3-[2-(2-Chlorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-(2-Chloro-4-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 5 (4aR,8aS)-6-[4-[N-methyl-4-(trifluoromethyl)anilino]piperidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-(3-(((2-Chloro-4-(trifluoromethyl)phenyl)thio)methyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2-Fluoro-4-(trifluoromethyl)benzyl)thio)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- 10 (4aR,8aS)-6-(3-((2,6-Dichlorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-[2-Fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 15 (4aR,8aS)-6-(3-((2-Chloro-6-fluorophenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-(3-((2-Chloro-4-cyclopropylphenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-[4-Trifluoromethoxy]phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 20 (4aR,8aS)-6-[3-[2-(2,6-Dimethylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Trifluoromethoxy)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 25 (4aR,8aS)-6-(3-(o-Tolyethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one;
- (4aR,8aS)-6-[3-[2-(4-Chloro-2-fluorophenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-(Difluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- 30 (4aR,8aS)-6-[3-[2-(2-Chloro-6-methylphenyl)ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one;
- (4aR,8aS)-6-[3-[2-[2-Chloro-6-fluoro-4-(trifluoromethyl)phenyl]ethynyl]azetidine-1-carbonyl]-4,4a,5,7,8,8a-hexahydropyrido[4,3-b][1,4]oxazin-3-one; and

- 262 -

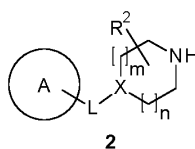
(4aR,8aS)-6-(3-((2-Chloro-4-(trifluoromethyl)phenyl)ethynyl)azetidine-1-carbonyl)hexahydro-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one.

40. A process of manufacturing the compounds of formula (I) according to any one of claims 1 to 39, comprising:

5 reacting a first amine of formula **1**, wherein R^1 is as described in any one of claims 1 to 39,



with a second amine **2**, wherein A, L, m, n, X and R^2 are as described in any one of claims 1 to 39



10

in the presence of a base and a urea forming reagent,
to form said compound of formula (I).

41. A compound of formula (I) according to any one of claims 1 to 39, when manufactured according to the process of claim 40.
- 15 42. The compound of formula (I) according to any one of claims 1 to 39 and 41, wherein said compound of formula (I) has an IC_{50} for monoacylglycerol lipase below 10 μM , preferably below 5 μM .
43. A compound of formula (I) according to any one of claims 1 to 39, 41 and 42 for use as therapeutically active substance.
- 20 44. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 39, 41 and 42 and a therapeutically inert carrier.
45. The use of a compound of formula (I) according to any one of claims 1 to 39, 41 and 42 or of a pharmaceutical composition according to claim 44 for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or
- 25 mental disorders in a mammal.

- 263 -

46. The use of a compound of formula (I) according to any one of claims 1 to 39, 41 and 42 or of a pharmaceutical composition according to claim 44 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.
47. A compound of formula (I) according to any one of claims 1 to 39, 41 and 42 or of a pharmaceutical composition according to claim 44 for use in the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.
48. A compound of formula (I) according to any one of claims 1 to 39, 41 and 42 or of a pharmaceutical composition according to claim 44 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.
49. The use of a compound of formula (I) according to any one of claims 1 to 39, 41 and 42 for the preparation of a medicament for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal.
50. The use of a compound of formula (I) according to any one of claims 1 to 39, 41 and 42 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.
51. A method for the treatment or prophylaxis of neuroinflammation, neurodegenerative diseases, pain, cancer and/or mental disorders in a mammal, which method

- 264 -

comprises administering an effective amount of a compound of formula (I) according to any one of claims 1 to 39, 41 and 42 or of a pharmaceutical composition according to claim 44 to the mammal.

52. A method for the treatment or prophylaxis of multiple sclerosis, Alzheimer's disease,
5 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
10 compound of formula (I) according to any one of claims 1 to 39, 41 and 42 or of a pharmaceutical composition according to claim 44 to the mammal.
53. A method for determining the MAGL inhibitory activity of a test compound, e.g. of a compound according to any one of claims 1 to 39, 41 and 42, comprising measuring the ratio of arachidonic acid / d8-arachidonic acid in a solution.
- 15 54. The invention as described hereinbefore.