

TITLE

POSITIVE ALLOSTERIC MODULATORS OF NICOTINIC ACETYLCHOLINE RECEPTOR

FIELD OF THE INVENTION

5 The present invention relates to compounds useful in therapy, to compositions comprising said compounds, and to methods of treating diseases comprising administration of said compounds. The compounds referred to are positive allosteric modulators (PAMs) of the nicotinic acetylcholine $\alpha 7$ receptor.

10 BACKGROUND OF THE INVENTION

Nicotinic acetylcholine receptors (nAChRs) belong to the super family of ligand gated ionic channels, and gate the flow of cations including calcium. The nAChRs are endogenously activated by acetylcholine (ACh) and can be divided into nicotinic receptors of the neuromuscular junction and neuronal nicotinic receptors (NNRs). The NNRs are widely expressed
15 throughout the central nervous system (CNS) and the peripheral nervous system (PNS). The NNRs have been suggested to play an important role in CNS function by modulating the release of many neurotransmitters, for example, ACh, norepinephrine, dopamine, serotonin, and GABA, among others, resulting in a wide range of physiological effects.

Seventeen subunits of nAChRs have been reported to date, which are identified as
20 $\alpha 2$ - $\alpha 10$, $\beta 1$ - $\beta 4$, γ , δ and ϵ . From these subunits, nine subunits, $\alpha 2$ through $\alpha 7$ and $\beta 2$ through $\beta 4$, prominently exist in the mammalian brain. Many functionally distinct nAChR complexes exist, for example five $\alpha 7$ subunits can form a receptor as a homomeric functional pentamer or combinations of different subunits can form heteromeric receptors such as $\alpha 4\beta 2$ and $\alpha 3\beta 4$ receptors (Gotti, C. et al., *Prog. Neurobiol.*, 2004, 74: 363-396;
25 Gotti, C. et al., *Biochemical Pharmacology*, 2009, 78: 703-711)

The homomeric $\alpha 7$ receptor is one of the most abundant NNRs, along with $\alpha 4\beta 2$ receptors, in the brain, wherein it is heavily expressed in the hippocampus, cortex, thalamic nuclei, ventral tegmental area and substantia nigra (Broad, L. M. et al., *Drugs of the Future*, 2007, 32(2): 161-170, Poorthuis RB, *Biochem Pharmacol.* 2009, 1;78(7):668-76).

30 The role of $\alpha 7$ NNR in neuronal signalling has been actively investigated. The $\alpha 7$ NNRs have been demonstrated to regulate interneuron excitability and modulate the release of excitatory as well as inhibitory neurotransmitters. In addition, $\alpha 7$ NNRs have been reported to be involved in neuroprotective effects in experimental models of cellular damage (Shimohama, S., *Biol Pharm Bull.* 2009, 32(3):332-6).

Studies have shown that $\alpha 7$ subunits, when expressed recombinant in-vitro, activate and desensitize rapidly, and exhibit relatively higher calcium permeability compared to other NNR combinations (Papke, R.L. et al., *J Pharmacol Exp Ther.* 2009, 329(2):791-807).

The NNRs, in general, are involved in various cognitive functions, such as learning, memory and attention, and therefore in CNS disorders, i.e., Alzheimer's disease (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, schizophrenia, bipolar disorder, pain and tobacco dependence (Keller, J. J. et al., *Behav. Brain Res.* 2005, 162: 143-52; Haydar, S.N. et al., *Curr Top Med Chem.* 2010;10(2):144-52).

The $\alpha 7$ NNRs in particular, have also been linked to cognitive disorders including, for example, ADHD, autism spectrum disorders, AD, mild cognitive impairment (MCI), age associated memory impairment (AAMI) senile dementia, frontotemporal lobar degeneration, HIV associated dementia (HAD), HIV associated cognitive impairment (HIV-CI), Pick's disease, dementia associated with Lewy bodies, cognitive impairment associated with Multiple Sclerosis, Vascular Dementia, cognitive impairment in Epilepsy, cognitive impairment associated with fragile X, cognitive impairment associated with Friedreich's Ataxia, and dementia associated with Down's syndrome, as well as cognitive impairment associated with schizophrenia. In addition, $\alpha 7$ -NNRs have been shown to be involved in the neuroprotective effects of nicotine both in vitro (Jonnala, R. B. et al., *J. Neurosci. Res.*, 2001, 66: 565- 572) and in vivo (Shimohama, S., *Brain Res.*, 1998, 779: 359-363) as well as in pain signalling. More particularly, neurodegeneration underlies several progressive CNS disorders, including, but not limited to, AD, PD, amyotrophic lateral sclerosis, Huntington's disease, dementia with Lewy bodies, as well as diminished CNS function resulting from traumatic brain injury. For example, the impaired function of $\alpha 7$ NNRs by beta-amyloid peptides linked to AD has been implicated as a key factor in development of the cognitive deficits associated with the disease (Liu, Q.-S., et al., *PNAS*, 2001,98: 4734-4739). Thus, modulating the activity of $\alpha 7$ NNRs demonstrates promising potential to prevent or treat a variety of diseases indicated above, such as AD, other dementias, other neurodegenerative diseases, schizophrenia and neurodegeneration, with an underlying pathology that involves cognitive function including, for example, aspects of learning, memory, and attention (Thomsen, M.S. et al., *Curr Pharm Des.* 2010 Jan;16(3):323-43; Olincy, A. et al., *Arch Gen Psychiatry.* 2006, 63(6):630-8; Deutsch, S.I., *Clin Neuropharmacol.* 2010, 33(3):114-20; Feuerbach, D., *Neuropharmacology.* 2009, 56(1): 254-63)

The NNR ligands, including $\alpha 7$ ligands, have also been implicated in weight control, diabetes inflammation, obsessive-compulsive disorder (OCD), angiogenesis and as potential analgesics (Marrero, M.B. et al., *J. Pharmacol. Exp. Ther.* 2010, 332(1):173-80; Vincler, M.,

Exp. Opin. Invest. Drugs, 2005, 14 (10): 1191-1 198; Rosas-Ballina, M., *J. Intern Med.* 2009 265(6):663-79; Arias, H.R., *Int. J. Biochem. Cell Biol.* 2009, 41(7):1441-51; Tizabi, Y., *Biol Psychiatry*. 2002, 51(2):164-71).

Nicotine is known to enhance attention and cognitive performance, reduced anxiety, enhanced sensory gating, and analgesia and neuroprotective effects when administered. Such effects are mediated by the non-selective effect of nicotine at multiple nicotinic receptor subtypes. However, nicotine also exerts adverse events, such as cardiovascular and gastrointestinal problems (Karaconji, I.B. et al., *Arh Hig Rada Toksikol.* 2005, 56(4):363-71). Consequently, there is a need to identify subtype-selective compounds that retain the beneficial effects of nicotine, or an NNR ligand, while eliminating or decreasing adverse effects.

Examples of reported NNR ligands are $\alpha 7$ NNR agonists, such as DMXB-A, SSR180711 and ABT-107, which have shown some beneficial effects on cognitive processing both in rodents and humans (H312: 1213-22; Olincy, A. et al., *Arch Gen Psychiatry*. 2006 63(6):630-8; Pichat, P., et al., *Neuropsychopharmacology*. 2007 32(1):17-34; Bitner, R.S., *J Pharmacol Exp Ther.* 2010 1;334(3):875-86). In addition, modulation of $\alpha 7$ NNRs have been reported to improve negative symptoms in patients with schizophrenia (Freedman, R. et al., *Am J Psychiatry*. 2008 165(8):1040-7).

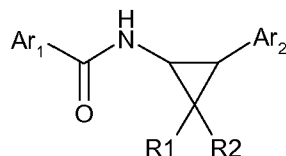
Despite the beneficial effects of NNR ligands, it remains uncertain whether chronic treatment with agonists affecting NNRs may provide suboptimal benefit due to sustained activation and desensitization of the NNRs, in particular the $\alpha 7$ NNR subtype. In contrast to agonists, administering a positive allosteric modulator (PAM) can reinforce endogenous cholinergic transmission without directly stimulating the target receptor. Nicotinic PAMs can selectively modulate the activity of ACh at NNRs, preserving the activation and deactivation kinetics of the receptor. Accordingly, $\alpha 7$ NNR-selective PAMs have emerged (Faghih, R., *Recent Pat CNS Drug Discov.* 2007, 2(2):99-106).

Consequently, it would be beneficial to increase $\alpha 7$ NNR function by enhancing the effect of the endogenous neurotransmitter acetylcholine via PAMs. This could reinforce the endogenous cholinergic neurotransmission without directly activating $\alpha 7$ NNRs, like agonists. Indeed, PAMs for enhancing channel activity have been proven clinically successful for GABA_A receptors where benzodiazepines and barbiturates, behave as PAMs acting at distinct sites (Hevers, W. et al., *Mol. Neurobiol.*, 1998, 18: 35-86).

To date, only a few NNR PAMs are known, such as 5-hydroxyindole (5-HI), ivermectin, galantamine, and SLURP-1, a peptide derived from acetylcholinesterase (AChE). Genistein, a kinase inhibitor was also reported to increase $\alpha 7$ responses. PNU-120596, a urea derivative, was reported to increase the potency of ACh as well as improve auditory gating deficits induced by amphetamine in rats. Also, NS1738, JNJ-1930942 and compound 6 have

been reported to potentiate the response of ACh and exert beneficial effect in experimental models of sensory and cognitive processing in rodents. Other NNR PAMs include derivatives of quinuclidine, indole, benzopyrazole, thiazole, and benzoisothiazoles (Hurst, R. S. et al., *J. Neurosci.* 2005, 25: 4396-4405; Faghieh, R., *Recent Pat CNS Drug Discov.* 2007, 2(2):99-106; Timmermann, D.B., *J. Pharmacol. Exp. Ther.* 2007, 323(1):294-307; Ng, H.J. et al., *Proc. Natl. Acad. Sci. U S A.* 2007, 8;104(19):8059-64; Dinklo, T., *J. Pharmacol. Exp. Ther.* 2011, 336(2):560-74.).

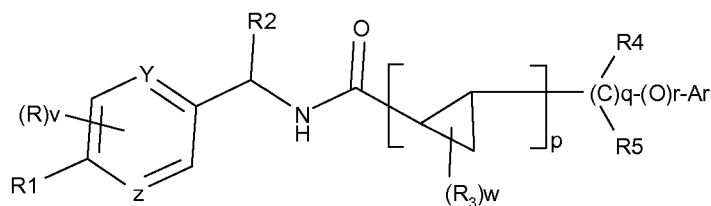
WO 2009/043784 recites compounds of the overall structure



which compounds are said to be PAMs of the $\alpha 7$ NNR.

The $\alpha 7$ NNR PAMs presently known generally demonstrate weak activity, have a range of non-specific effects, or can only achieve limited access to the central nervous system where $\alpha 7$ NNRs are abundantly expressed. Accordingly, it would be beneficial to identify and provide new PAM compounds of $\alpha 7$ NNRs and compositions for treating diseases and disorders wherein $\alpha 7$ NNRs are involved. It would further be particularly beneficial if such compounds can provide improved efficacy of treatment while reducing adverse effects associated with compounds targeting neuronal nicotinic receptors by selectively modulating $\alpha 7$ NNRs.

WO 2010/137351 recites compounds of the overall structure



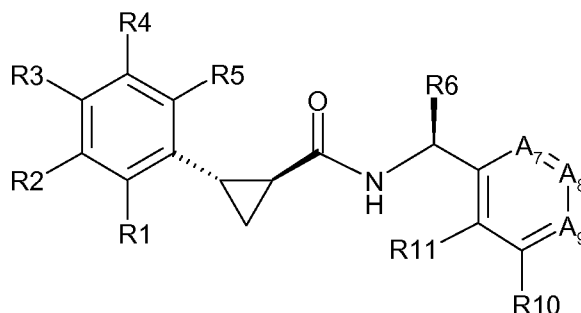
as calcium or sodium channel blockers. Compound examples disclosed in WO 2010/137351 are not intended to be included in the present invention.

Particularly the compounds (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide, (1S,2S)-2-(2-Chloro-4-fluoro-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide and (1S,2S)-2-(2-Fluoro-4-methoxy-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide are disclosed in WO 2010/137351 are disclaimed from the present invention

SUMMARY OF THE INVENTION

The objective of the present invention is to provide compounds that are positive allosteric modulators (PAMs) of the nicotinic acetylcholine receptor subtype $\alpha 7$.

5 The compounds of the present invention are defined by formula [I] below:



[I]

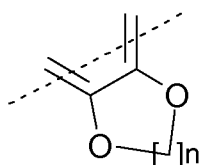
wherein R1, R2, R3, R4 and R5 are selected independently of each other from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano and halogen, wherein said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl is optionally substituted with one or more substituents independently selected from chlorine and fluorine;

R6 is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆alkoxy, wherein said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl is optionally substituted with one or more substituents independently selected from hydroxy, C₁₋₆alkoxy and fluorine;

A7 is C-R7 or N, A8 is C-R8 or N and A9 is C-R9 or N, provided that at least one of A7, A8 or A9 is N and no more than two of A7, A8 and A9 is N;

R7, R8, R9, R10 and R11 are selected independently of each other from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano, NR₁₂R₁₃, C₁₋₆alkylsulfonyl, halogen and OR₁₄, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₆alkoxy is optionally substituted with one or more substituents selected from chlorine, fluorine, C₁₋₆alkoxy, cyano and NR₁₂R₁₃; R12 and R13 independently represent hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl; R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C;

25 or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1, 2 or 3;

and pharmaceutically acceptable salts thereof;

with the proviso that the compound of formula [I] is other than

(1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide;

5 (1S,2S)-2-(2-Chloro-4-fluoro-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide;

(1S,2S)-2-(2-Fluoro-4-methoxy-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide.

10 In one embodiment, the invention relates to a compound according to formula [I], and pharmaceutically acceptable salts thereof, for use as a medicament.

In one embodiment, the invention relates to a compound according to formula [I], and pharmaceutically acceptable salts thereof, for use in therapy.

15 In one embodiment, the invention relates to a compound according to formula [I], and pharmaceutically acceptable salts thereof, for use in the treatment of a disease or disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease; Parkinson's

20 disease (PD); obsessive-compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with depression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain.

25 In one embodiment, the invention relates to a pharmaceutical composition comprising a compound according to formula [I] and pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carrier or excipient.

30 In one embodiment, the invention relates to a kit comprising a compound according to formula [I], and pharmaceutically acceptable salts thereof, together with a compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate receptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 antagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers.

35 In one embodiment, the invention relates to a method for the treatment of a disease or disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated

memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease; Parkinson's disease (PD); obsessive-compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with depression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain, which method comprises the administration of a therapeutically effective amount of a compound according to formula [I], and pharmaceutically acceptable salts thereof.

In one embodiment, the invention relates to the use of a compound according to formula [I], and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the treatment of a disease or disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease; Parkinson's disease (PD); obsessive-compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with depression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain.

Definitions

In the present context, "optionally substituted" means that the indicated moiety may or may not be substituted, and when substituted is mono-, di-, or tri-substituted, such as with 1, 2 or 3 substituents. In some instances, the substituent is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, phenyl, C₁₋₆alkoxy, hydroxy and halogen. It is understood that where no substituents are indicated for an "optionally substituted" moiety, then the position is held by a hydrogen atom.

In the present context, "alkyl" is intended to indicate a straight, branched and/or cyclic saturated hydrocarbon. In particular "C₁₋₆alkyl" is intended to indicate such hydrocarbon having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of C₁₋₆alkyl include methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclopropyl, 2-methylpropyl and tert-butyl. Examples of substituted C₁₋₆alkyl include e.g. fluoromethyl and hydroxymethyl.

In the present context, "alkenyl" is intended to indicate a non-aromatic, straight, branched and/or cyclic hydrocarbon comprising at least one carbon-carbon double bond. In

particular "C₂₋₆alkenyl" is intended to indicate such hydrocarbon having 2, 3, 4, 5 or 6 carbon atoms. Examples of C₂₋₆alkenyl include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl and cyclohexenyl.

In the present context, "alkynyl" is intended to indicate a non-aromatic, straight, branched and/or cyclic hydrocarbon comprising at least one carbon-carbon triple bond and optionally also one or more carbon-carbon double bonds. In particular "C₂₋₆alkynyl" is intended to indicate such hydrocarbon having 2, 3, 4, 5 or 6 carbon atoms. Examples of C₂₋₆alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl and 5-but-1-en-3-ynyl.

In the present context, "hydroxy" is intended to indicate -OH.

In the present context, "alkoxy" is intended to indicate a moiety of the formula -OR', wherein R' indicates alkyl as defined above. In particular "C₁₋₆alkoxy" is intended to indicate such moiety wherein the alkyl part has 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of "C₁₋₆alkoxy" include methoxy, ethoxy, n-butoxy and tert-butoxy.

In the present context, "alkylsulfonyl" is intended to indicate -S(O)₂alkyl. In particular C₁₋₆alkylsulfonyl is intended to indicate such a moiety wherein the alkyl part has 1, 2, 3, 4, 5 or 6 carbon atoms. Particular mention is made of methylsulfonyl.

In the present context, a "monocyclic moiety" is intended to cyclic moiety comprising only one ring, said cyclic moiety can be saturated or unsaturated.

In the present context, the terms "halo" and "halogen" are used interchangeably and refer to fluorine, chlorine, bromine or iodine.

In the present context, the term "cyano" indicates the group -C≡N, which consists of a carbon atom triple-bonded to a nitrogen atom.

In the present context, "ring atom" is intended to indicate the atoms constituting a ring, and ring atoms are selected from C, N, O and S. As an example, benzene and toluene both have 6 carbons as ring atoms whereas pyridine has 5 carbons and 1 nitrogen as ring atoms.

In the present context, "heteroatom" means a nitrogen, oxygen or sulfur atom.

In the present context, "deuterium" indicates the atomic isotope of hydrogen consisting of one proton and one neutron in its nucleus, and thus having an approximate weight of two (2). Deuterium is represented as D, d or ²H. An example of a substituent comprising deuterium is (2,2,2-d₃)-ethoxy wherein three of the hydrogens in ethoxy are the ²H isotopes.

In the present context, "enantiomeric excess" represents the % excess of a compound in a mixture of compound enantiomers. If for example an enantiomeric excess is 90% then the ratio of the compound to its enantiomer is 95:5 and if an enantiomeric excess is 95% then the ratio of the compound to its enantiomer is 97.5:2.5. Likewise, "diastereomeric excess" represents % excess of a compound in a mixture of compound diastereomers.

In the present context, pharmaceutically acceptable salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

5 Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like.

 Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halothephyllines, for example 8-bromothephylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in
10 Berge, S.M. et al., *J. Pharm. Sci.* 1977,66,2, which is incorporated herein by reference.

 Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

 Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.
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 In the present context, pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. Examples of solid carriers include lactose, terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers include, but are not
25 limited to, syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

 In the present context, the term "therapeutically effective amount" of a compound
30 means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications in a therapeutic intervention comprising the administration of said compound. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that
35 determining an appropriate dosage may be achieved using routine experimentation, by con-

structing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician.

In the present context, the term "treatment" and "treating" means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatments are two separate aspects of the present invention. The patient to be treated is preferably a mammal, in particular a human being.

In the present context, the term "cognitive disorders" is intended to indicate disorders characterized by abnormalities in aspects of perception, problem solving, language, learning, working memory, memory, social recognition, attention and pre-attentional processing, such as by not limited to Attention Deficit Hyperactivity Disorder (ADHD), autism spectrum disorders, Alzheimer's disease (AD), mild cognitive impairment (MCI), age associated memory impairment (AAMI), senile dementia, vascular dementia, frontotemporal lobe dementia, Pick's disease, dementia associated with Lewy bodies, and dementia associated with Down's syndrome, cognitive impairment associated with Multiple Sclerosis, cognitive impairment in epilepsy, cognitive impairment associated with fragile X, cognitive impairment associated with neurofibromatosis, cognitive impairment associated with Friedreich's Ataxia, progressive supranuclear palsy (PSP), HIV associated dementia (HAD), HIV associated cognitive impairment (HIV-CI), Huntington's Disease, Parkinson's disease (PD), obsessive-compulsive disorder (OCD), traumatic brain injury, epilepsy, post-traumatic stress, Wernicke-Korsakoff syndrome (WKS), post-traumatic amnesia, cognitive deficits associated with depression as well as cognitive impairment associated with schizophrenia.

The cognitive enhancing properties of a compound can be assessed e.g. by the attentional set-shifting paradigm which is an animal model allowing assessment of executive functioning via intra-dimensional (ID) versus extra-dimensional (ED) shift discrimination learning. The study can be performed by testing whether the compound is attenuating "attentional performance impairment" induced by subchronic PCP administration in rats as described by Rodefer, J.S. et al., *Eur. J. Neurosci.* 2005, 21:1070-1076.

In the present context, the term "autism spectrum disorders" is intended to indicate disorders characterized by widespread abnormalities of social interactions and verbal and non-verbal communication, as well as restricted interests, repetitive behavior and attention, such as by not limited to autism, Asperger syndrome, Pervasive Developmental Disorder Not
5 Otherwise Specified (PDD-NOS), Rett syndrome, Angelmann syndrome, fragile X, DiGeorge syndrome and Childhood Disintegrative Disorder.

In the present context, the term "inflammatory disorders" is intended to indicate disorders characterized by abnormalities in the immune system such as by not limited to, allergic reactions and myopathies resulting in abnormal inflammation as well as non-immune
10 diseases with etiological origins in inflammatory processes are thought to include but not be limited to cancer, atherosclerosis, osteoarthritis, rheumatoid arthritis and ischaemic heart disease.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have found that certain new compounds are positive allosteric modulators (PAMs) of NNRs, and as such may be used in the treatment of various disorders.
15

PAMs of NNRs may be dosed in combination with other drugs in order to achieve more efficacious treatment in certain patient populations. An $\alpha 7$ NNR PAM may act synergistically with another drug, this has been described in animals for the combination of compounds affecting nicotinic receptors, including $\alpha 7$ NNRs and D2 antagonism (Wiker, C., *Int. J. Neuropsychopharmacol.* 2008, 11(6):845-50).
20

Thus, compounds of the present invention may be useful treatment in the combination with another drug e.g. selected from acetylcholinesterase inhibitors, glutamate receptor antagonists, dopamine transport inhibitors, noradrenalin transport inhibitors, D2 antagonists, D2
25 partial agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT₆ antagonists and KCNQ antagonists, lithium, sodium channel blockers, GABA signalling enhancers.

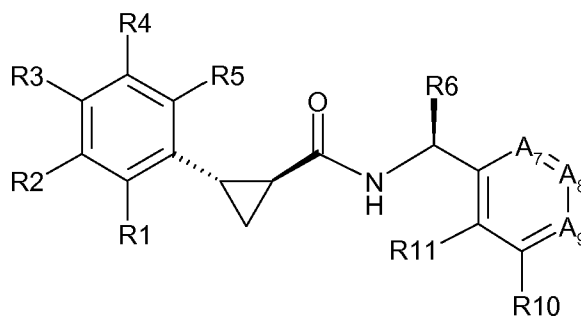
In one embodiment, compounds of the present invention are used for treatment of patients who are already in treatment with another drug selected from the list above. In one embodiment, compounds of the present invention are adapted for administration simultaneous
30 with said other drug. In one embodiment compounds of the present invention are adapted for administration sequentially with said other drug. In one embodiment, compounds of the present invention are used as the sole medicament in treatment of a patient. In one embodiment, compounds of the present invention are used for treatment of patients who are not already in treatment with another drug selected from the list above.

Embodiments according to the invention

In the following, embodiments of the invention are disclosed. The first embodiment is denoted E1, the second embodiment is denoted E2 and so forth.

E1. A compound according to formula [I]

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[I]

wherein R1, R2, R3, R4 and R5 are selected independently of each other from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano and halogen, wherein said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl is optionally substituted with one or more substituents independently selected from chlorine and fluorine;

R6 is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆alkoxy, wherein said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl is optionally substituted with one or more substituents independently selected from hydroxy, C₁₋₆alkoxy and fluorine;

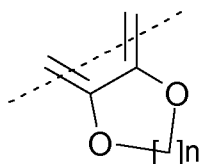
A7 is C-R7 or N, A8 is C-R8 or N and A9 is C-R9 or N, provided that at least one of A7, A8 or 9 is N and no more than two of A7, A8 and A9 is N;

R7, R8, R9, R10 and R11 are selected independently of each other from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano, NR₁₂R₁₃, C₁₋₆alkylsulfonyl, halogen and OR₁₄, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₆alkoxy is optionally substituted with one or more substituents selected from chlorine, fluorine, C₁₋₆alkoxy, cyano and NR₁₂R₁₃;

R12 and R13 independently represent hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl;

R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C;

or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1, 2 or 3;

and pharmaceutically acceptable salts thereof;

with the proviso that the compound of formula [I] is other than

(1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide;

(1S,2S)-2-(2-Chloro-4-fluoro-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide;

(1S,2S)-2-(2-Fluoro-4-methoxy-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide.

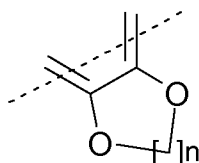
E2. The compound according to embodiment 1, wherein R1, R2, R3, R4 and R5 are selected independently of each other from H, methyl, fluorine and chlorine;

R6 is selected from methyl, hydroxymethyl, methoxymethyl and fluoromethyl;

R7, R8, R9, R10 and R11 are selected independently of each other from H, C₁₋₄alkyl, C₁₋₄alkoxy, cyano, -N(CH₃)₂, methylsulfonyl, fluorine, chlorine and OR14, wherein said C₁₋₄alkyl or C₁₋₄alkoxy is optionally substituted with one or more substituents selected from fluorine, C₁₋₄alkoxy and cyano;

R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C;

or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1 or 2.

E3. The compound according to any of embodiments 1-2, wherein R1, R2, R3, R4 and R5 are selected independently of each other from H, methyl, fluorine and chlorine.

E4. The compound according to any of embodiments 1-3, wherein four or more of R1, R2, R3, R4 and R5 are H.

E5. The compound according to embodiment 4, wherein all of R1, R2, R3, R4 and R5 are H.

E6. The compound according to any of embodiments 1-5, wherein R6 is selected from methyl, hydroxymethyl, methoxymethyl and fluoromethyl.

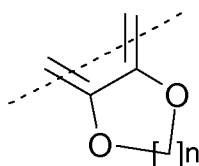
E7. The compound according to embodiment 6, wherein R6 is methyl.

E8. The compound according to embodiment 6, wherein R6 is hydroxymethyl.

5 E9. The compound according to embodiment 6, wherein R6 is methoxymethyl.

E10. The compound according to embodiment 6, wherein R6 is fluoromethyl.

E11. The compound according to any of embodiments 1-10, wherein R7, R8, R9, R10 and
 10 R11 are selected independently of each other from H, C₁₋₄alkyl, C₁₋₄alkoxy, cyano, -N(CH₃)₂,
 methylsulfonyl, fluorine, chlorine and OR₁₄, wherein said C₁₋₄alkyl or C₁₋₄alkoxy is optionally
 substituted with one or more substituents selected from fluorine, C₁₋₄alkoxy and cyano;
 R₁₄ represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said
 ring atoms is O and the others are C;
 15 or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1 or 2;

E12. The compound according to any of embodiments 1 and 3-11, wherein R7, R8, R9,
 20 R10 and R11 are selected independently from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy,
 cyano or halogen, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₆alkoxy is optionally
 substituted with one or more substituents selected from fluorine, C₁₋₆alkoxy and cyano.

E13. The compound according to any of embodiments 1-12, wherein R7, R8, R9, R10 and
 25 R11 are selected independently from H, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, cyano
 and halogen, wherein said C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl or C₁₋₄alkoxy is optionally substi-
 tuted with one or more substituents selected from fluorine and C₁₋₄alkoxy.

E14. The compound according to any of embodiments 1-13, wherein one or more of the
 30 hydrogen atoms are represented by deuterium.

E15. The compound according to embodiment 14, wherein one or more of the hydrogen
 atoms in R7, R8, R9, R10 and R11 are represented by deuterium.

E16. The compound according to any of embodiments 14-15, wherein at least about 85% of the compound has a deuterium atom at each position designated as deuterium, and any atom not designated as deuterium is present at about its natural isotopic abundance.

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E17. The compound according to embodiment 16, wherein at least about 90% of the compound has a deuterium atom at each position designated as deuterium, and any atom not designated as deuterium is present at about its natural isotopic abundance.

10 E18. The compound according to any of embodiments 1-17, wherein no more than one of A7, A8 or A9 is N.

E19. The compound according to any of embodiments 1-18, wherein A7 is N, A8 is C-R8 and A9 is C-R9.

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E20. The compound according to embodiment 19, wherein R8, R10 and R11 all represent H.

20 E21. The compound according to any of embodiments 1-18, wherein A8 is N, A7 is C-R7 and A9 is C-R9.

E22. The compound according to embodiment 21, wherein R7, R10 and R11 all represent H.

25 E23. The compound according to any of embodiments 19-22, wherein R9 is selected from methyl, C₁₋₄alkoxy or cyano, wherein said methyl is optionally substituted with C₁₋₄alkoxy or one or more fluorine.

30 E24. The compound according to embodiment 23, wherein R9 represents C₁₋₄alkoxy and one or more of the hydrogen atoms in said C₁₋₄alkoxy are represented by deuterium.

E25. The compound according to any of embodiments 19-22, wherein R9 is OR14, wherein R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C.

35

E26. The compound according to any of embodiments 1-18, wherein A9 is N, A7 is C-R7 and A8 is C-R8.

E27. The compound according to embodiment 26, wherein R7, R8 and R11 all represent H.

5

E28. The compound according to any of embodiments 26-27, wherein R10 is selected from methyl, C₁₋₄alkoxy or cyano, wherein said methyl is optionally substituted with C₁₋₄alkoxy or one or more fluorine.

10 E29. The compound according to embodiment 28, wherein R10 represents C₁₋₄alkoxy and one or more of the hydrogen atoms in said C₁₋₄alkoxy are represented by deuterium.

E30. The compound according to any of embodiments 1-17, wherein two of A7, A8 or A9 are N.

15

E31. The compound according to any of embodiments 1-30 having a diastereomeric excess of at least 80% such as at least 85%, such as at least 90%, such as at least 95%.

E32. The compound according to embodiment 1 selected from

- 20 **1:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide;
- 2:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(5-methyl-pyridin-2-yl)-ethyl]-amide;
- 3:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methoxy-pyridin-3-yl)-ethyl]-amide;
- 4:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methyl-pyridin-3-yl)-ethyl]-amide;
- 25 **5:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-cyano-pyridin-3-yl)-ethyl]-amide;
- 6:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide;
- 7:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethoxy-pyridin-3-yl)-ethyl]-amide;
- 8:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethyl-pyridin-3-yl)-ethyl]-amide;
- 30 **9:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methoxymethyl-pyridin-3-yl)-ethyl]-amide;
- 10:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-ethyl}-amide;
- 11:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-ethyl}-amide;
- 35 **12:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2-ethoxy-pyridin-4-yl)-ethyl]-amide;

- 13:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((S)-1-{6-[(S)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide;
- 14:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((S)-1-{6-[(R)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide;
- 5 **15:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((S)-1-[1,3]dioxolo[4,5-b]pyridin-6-yl-ethyl)-amide;
- 16:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-ethyl]-amide;
- 17:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2-ethoxy-pyrimidin-5-yl)-ethyl]-amide;
- 10 **18:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-chloro-pyridin-3-yl)-ethyl]-amide;
- 19:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(oxetan-3-yloxy)-pyridin-3-yl]-ethyl}-amide;
- 20:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-cyanomethoxy-pyridin-3-yl)-ethyl]-amide;
- 15 **21:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide;
- 22:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide;
- 20 **23:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(5-cyano-pyridin-2-yl)-2-hydroxy-ethyl]-amide;
- 24:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-methoxy-pyridin-3-yl)-ethyl]-amide;
- 25:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-methyl-pyridin-3-yl)-ethyl]-amide;
- 25 **26:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide;
- 27:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 30 **28:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 29:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide;
- 30:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide;
- 35

- 31:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 32:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 5 **33:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 34:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1,2,2,2-d₅)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 35:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 10 **36:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 37:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 15 **38:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(1,1,2,2,2-d₅)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 39:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 40:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 20 **41:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 42:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;
- 25 **43:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((R)-2-hydroxy-1-{6-[(R)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide;
- 44:** (1S,2S)-N-[(1R)-2-hydroxy-1-[6-[(3S)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide;
- 45:** (1S,2S)-2-((Z)-1-Methylene-penta-2,4-dienyl)-cyclopropanecarboxylic acid {(R)-2-hydroxy-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethyl}-amide;
- 30 **46:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-methoxy-ethyl]-amide;
- 47:** (1S,2S)-N-[(1R)-2-methoxy-1-[6-[(3R)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide;
- 35 **48:** (1S,2S)-N-[(1R)-2-methoxy-1-[6-[(3S)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide;

49: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(R)-2-methoxy-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethyl}-amide;

50: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(oxetan-3-yloxy)-pyridin-3-yl]-ethyl}-amide;

5 **51:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethanesulfonyl-pyridin-3-yl)-ethyl]-amide;

52: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(5-ethoxy-pyridin-2-yl)-2-hydroxy-ethyl]-amide;

and pharmaceutically acceptable salts of any of these compounds.

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E33. A compound according to any of embodiments 1-32, for use as a medicament.

E34. A compound according to any of embodiments 1-32, for use in therapy.

15 E35. A compound according to any of embodiments 1-32, for use in the treatment of a disease or disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease; Parkinson's disease (PD); obsessive-compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with depression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain.

25

E36. The compound according to embodiment 35, wherein said a disease or disorder is selected from schizophrenia; AD; ADHD; autism spectrum disorders; PD; amyotrophic lateral sclerosis; Huntington's disease; dementia associated with Lewy bodies and pain.

30 E37. The compound according to embodiment 36, wherein said disease or disorder is selected from schizophrenia; AD; ADHD and autism spectrum disorders.

E38. The compound according to embodiment 37, wherein said disease or disorder is selected from negative and/or cognitive symptoms of schizophrenia.

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E39. The compound according to any of embodiments 1-32, for use concomitantly or sequentially with a therapeutically effective amount of a compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate receptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 antagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers in the treatment of a disease or disorder according to any of embodiments 35-38.

E40. A pharmaceutical composition comprising a compound according to any of embodiments 1-32, and one or more pharmaceutically acceptable carrier or excipient.

E41. The composition according to embodiment 40, which composition additionally comprises a second compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate receptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 antagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers.

E42. The composition according to embodiment 41, wherein said second compound is an acetylcholinesterase inhibitor.

E43. A kit comprising a compound according to any of embodiments 1-32, together with a second compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate receptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 antagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers.

E44. The kit according to embodiment 43, wherein said second compound is an acetylcholinesterase inhibitor.

E45. A method for the treatment of a disease or disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease; Parkinson's disease (PD); obsessive-

compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with depression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain, which method comprises the administration of a therapeutically effective amount of a compound according to any of embodiments 1-32 to a patient in need thereof.

E46. The method according to embodiment 45, wherein said disease or disorder is selected from schizophrenia; AD; ADHD; autism spectrum disorders; PD; amyotrophic lateral sclerosis; Huntington's disease; dementia associated with Lewy bodies and pain.

E47. The method according to embodiment 46, wherein said disease or disorder is selected from schizophrenia; AD; ADHD and autism spectrum disorders.

E48. The method according to embodiment 47, wherein said treatment comprises the treatment of negative and/or cognitive symptoms of schizophrenia.

E49. The method according to any of embodiments 45-48, wherein said treatment further comprises the administration of a therapeutically effective amount of a second compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate receptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 antagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers.

E50. The method according to embodiment 49, wherein said second compound is an acetylcholinesterase inhibitor.

E51. Use of a compound according to any of embodiments 1-32, for the manufacture of a medicament for the treatment of a disease or disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease; Parkinson's disease (PD); obsessive-compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with de-

pression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain.

E52. The use according to embodiment 51, wherein said disease or disorder is selected from schizophrenia; AD; ADHD; autism spectrum disorders; PD; amyotrophic lateral sclerosis; Huntington's disease; dementia associated with Lewy bodies and pain.

E53. The use according to embodiment 52, wherein said disease or disorder is selected from schizophrenia; AD; ADHD and autism spectrum disorders.

E54. The use according to embodiment 53, wherein said disease is the positive, negative and/or cognitive symptoms of schizophrenia.

E55. The use according to any of embodiments 51-54, wherein said manufacture further comprises the use of a second compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate receptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 antagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers.

E56. The use according to embodiment 55, wherein said second compound is an acetylcholinesterase inhibitor.

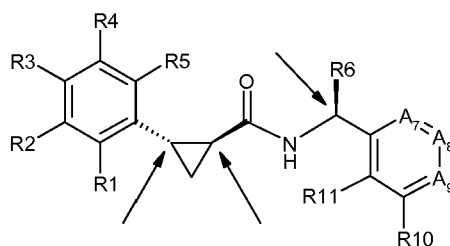
The compounds of the invention may exist in unsolvated as well as in solvated forms in which the solvent molecules are selected from pharmaceutically acceptable solvents such as water, ethanol and the like. In general, such solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Included in this invention are also isotopically labeled compounds, which are identical to those claimed in formula [I], wherein one or more atoms are represented by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (e.g., ^2H , ^3H , ^{11}C , ^{13}C , ^{15}N , ^{18}F and the like). Particular mention is made of ^2H substituted compounds i.e. compounds wherein one or more H atoms are represented by deuterium. In one embodiment of the invention one or more of the hydrogen atoms of the compound of formula [I] are represented by deuterium. It is recognized that elements are present in natural isotopic abundances in most synthetic compounds, and result in inherent incorporation of deuterium. However, the natural isotopic abundance of hydrogen

isotopes such as deuterium is immaterial (about 0.015%) relative to the degree of stable isotopic substitution of compounds indicated herein. Thus, as used herein, designation of an atom as deuterium at a position indicates that the abundance of deuterium is significantly greater than the natural abundance of deuterium. Any atom not designated as a particular isotope is intended to represent any stable isotope of that atom, as will be apparent to the ordinarily skilled artisan.

In one embodiment, designation of a position as "D" in a compound has a minimum deuterium incorporation of greater than about 60% at that position such as greater than about 70% at that position such as greater than about 80% at that position such as greater than about 85% at that position. In a further embodiment, designation of a position as "D" in a compound has a minimum deuterium incorporation of greater than about 90% at that position such as greater than about 95% at that position such as greater than about 97% at that position such as greater than about 99% at that position.

The compounds of the present invention have three asymmetric centers with fixed stereochemistry indicated by the arrows below.



The compounds of the present invention can be manufactured from two chiral intermediates with one and two asymmetric centers, respectively, as illustrated by the examples below.

In this context is understood that when specifying the enantiomeric form of the intermediate, then the intermediate is in enantiomeric excess, e.g. essentially in a pure, mono-enantiomeric form. Accordingly, the resulting compounds of the invention are having a diastereomeric excess of at least 80%. One embodiment of the invention relates to a compound of the invention having a diastereomeric excess of at least 80% such as at least 85%, such as at least 90%, preferably at least 95% or at least 97% with reference to the three asymmetric centers indicated above.

Dependent on the individually substituents R1-R14, the compounds of the present invention may furthermore have one or more additional asymmetric centers. It is intended that any optical isomers (i.e. enantiomers or diastereomers), in the form of separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures, i.e. a mixture of stereoisomers, which have emerged because of asymmetric centers in any of substituents R1-R14, are included within the scope of the invention.

Racemic forms can be resolved into the optical antipodes by known methods, for example by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography of an optically active matrix. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives. Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981). Optically active compounds can also be prepared from optically active starting materials.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The compounds of the present invention may be administered alone as a pure compound or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile
5 powders to be reconstituted in sterile injectable solutions or dispersions prior to use.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants, etc.

In one embodiment, the compound of the present invention is administered in an amount from about 0.001 mg/kg body weight to about 100 mg/kg body weight per day. In particular, daily dosages may be in the range of 0.01 mg/kg body weight to about 50 mg/kg body
10 weight per day. The exact dosages will depend upon the frequency and mode of administration, the sex, the age the weight, and the general condition of the subject to be treated, the nature and the severity of the condition to be treated, any concomitant diseases to be treated, the desired effect of the treatment and other factors known to those skilled in the art.

A typical oral dosage for adults will be in the range of 0.1-1000 mg/day of a compound of the present invention, such as 1-500 mg/day, such as 1-100 mg/day or 1-50 mg/day. Conveniently, the compounds of the invention are administered in a unit dosage form containing said compounds in an amount of about 0.1 to 500 mg, such as 10 mg, 50 mg 100 mg, 150
15 mg, 200 mg or 250 mg of a compound of the present invention.

For parenteral administration, solutions of the compound of the invention in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration.
20 The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and
30 lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. The pharmaceutical compositions formed by combining the compound of the invention and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined
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amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tablet, e.g.

5 placed in a hard gelatine capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

10 Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents followed by the compression of the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used
15 provided that they are compatible with the active ingredients.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set
20 forth in its entirety herein (to the maximum extent permitted by law), regardless of any separately provided incorporation of particular documents made elsewhere herein.

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. For example, the phrase "the
25 compound" is to be understood as referring to various "compounds" of the invention or particular described aspect, unless otherwise indicated.

The description herein of any aspect or aspect of the invention using terms such as "comprising", "having", "including", or "containing" with reference to an element or elements is intended to provide support for a similar aspect or aspect of the invention that "consists of",
30 "consists essentially of", or "substantially comprises" that particular element or elements, unless otherwise stated or clearly contradicted by context (e.g., a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

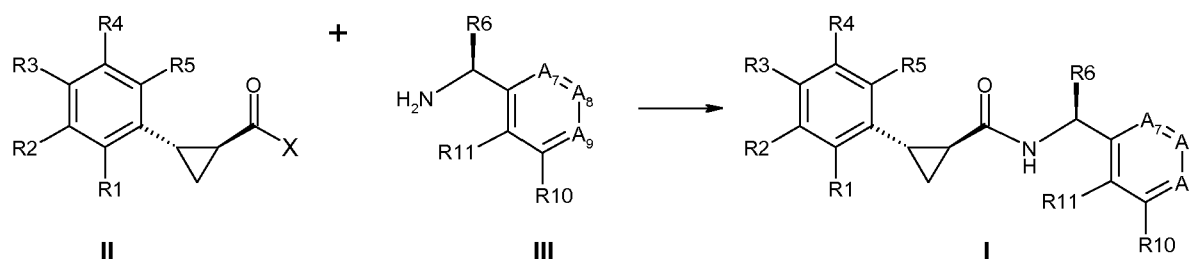
It should be understood that the various aspects, embodiments, implementations and
35 features of the invention mentioned herein may be claimed separately, or in any combination.

The compounds of formula I may be prepared by methods described below, together with synthetic methods known in the art of organic chemistry, or modifications that are familiar to those of ordinary skill in the art. The starting materials used herein are available commercially or may be prepared by routine methods known in the art, such as those method described in standard reference books such as "Compendium of Organic Synthetic Methods, Vol. I-XII" (published with Wiley-Interscience). Preferred methods include, but are not limited to, those described below.

The schemes are representative of methods useful in synthesizing the compounds of the present invention. They are not to constrain the scope of the invention in any way.

Methods of Preparation of the Compounds of the Invention.

The compounds of the invention with formula I can be prepared from intermediate III and II as described in Scheme 1.



Scheme 1

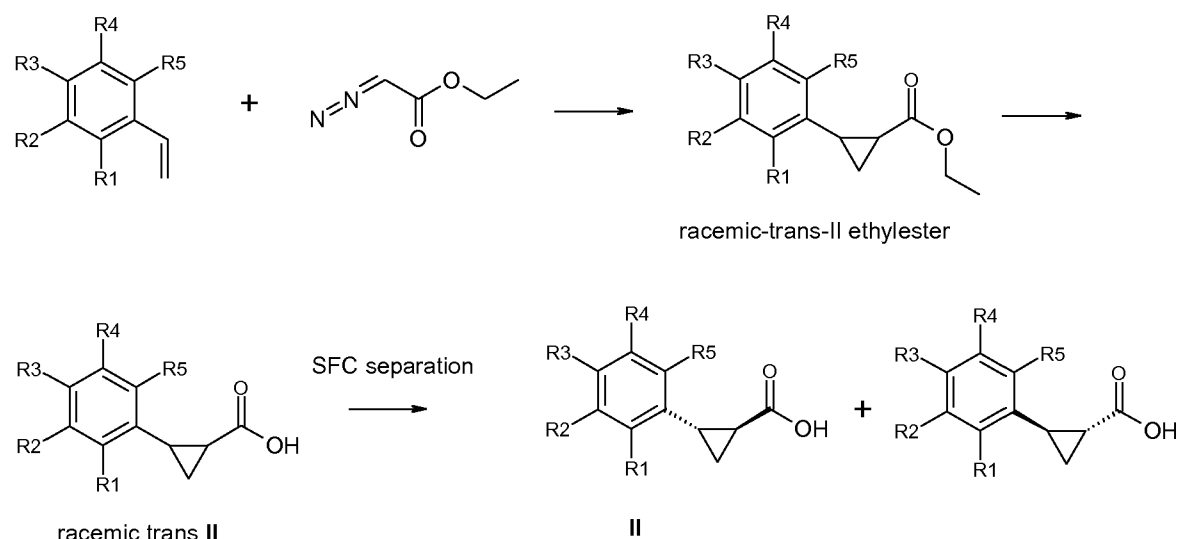
If X is a hydroxyl, the carboxylic acid II and the amine III can be condensed to form the amide I using standard peptide coupling chemistry, e.g. as described in the textbook *Synthetic Peptides A user's Guide* (Edited by Gregory A. Grant, W. H. Freeman and company (1992) ISBN 0-7167-7009-1) or as described in the textbook *Houben-Weyl Volume E22a Synthesis of peptides* (George Thiemes Verlag Stuttgart (2003) 4th ed.). One example of this amide formation is the use of the coupling reagent HATU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate). Typically, one eq. of II is reacted with one eq. of HATU in the presence of two eq. of a tertiary amine e.g. triethylamine in a suitable solvent e.g. DMF. After a short period of time (e.g. five minutes) this mixture is reacted with one eq. of III to form I. Another example of this amide formation uses 1-hydroxybenzotriazole together with the water soluble carbodiimide EDC (CAS 25952-53-8) and triethyl amine in a suitable solvent e.g. THF. These reactions are usually performed at room temperature or between 0 °C and 50 °C.

If X is a chloride (e.g. prepared from the carboxylic acid II, X = OH, using thionyl chloride) III can be reacted with II to form I in the presence of a tertiary amine in a suitable solvent. Alternatively, the carboxylic acid chloride (II, X = Cl) can be reacted with N-hydroxy succinimide to produce the HOSU ester which can be isolated and then reacted with III to produce I.

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Methods of Preparation of the Intermediates of the Invention.

The Intermediates of the invention with formula II are either commercially available or can be prepared as described in Scheme 2.



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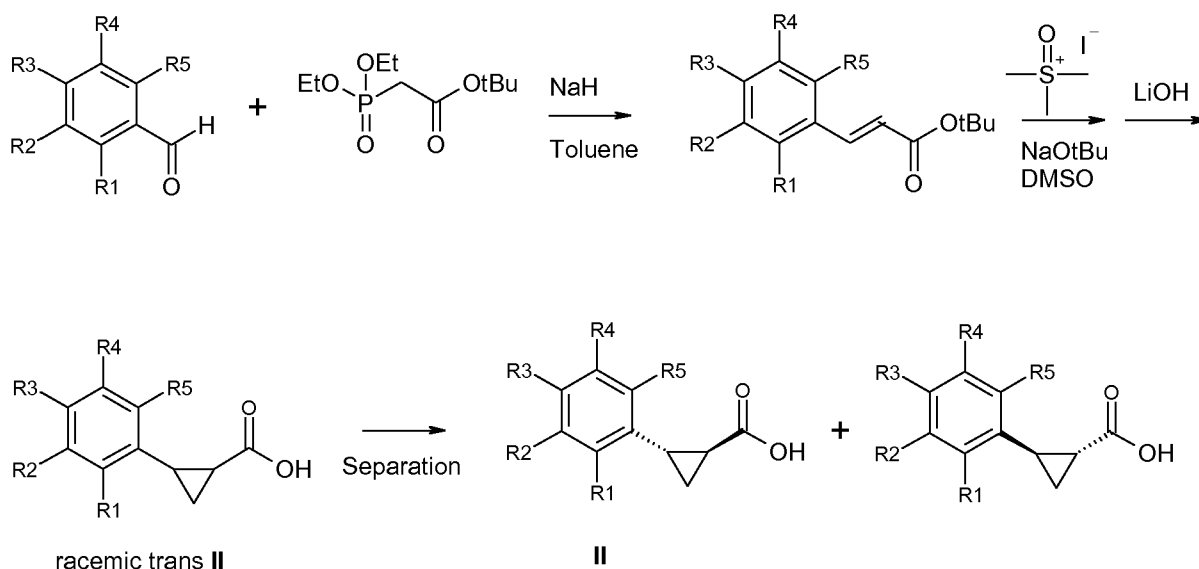
Scheme 2. Preparation of the (1S, 2S) enantiomer of formula II.

Ethyl diazoacetate can be reacted with the styrene in Scheme II to produce the racemic-trans II ethyl ester. This ester can then be hydrolyzed to racemic trans II which can then be separated into the two enantiomers using SFC. Alternatively, racemic trans II can be resolved into the two enantiomers by known methods as described in the textbook "Enantiomers, Racemates and Resolutions" (J. Jaques, et al., John Wiley and sons, New York (1981)).

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Another preparation of the compounds with formula II is described in Scheme 3. This method has been described in detail in WO2012/037258

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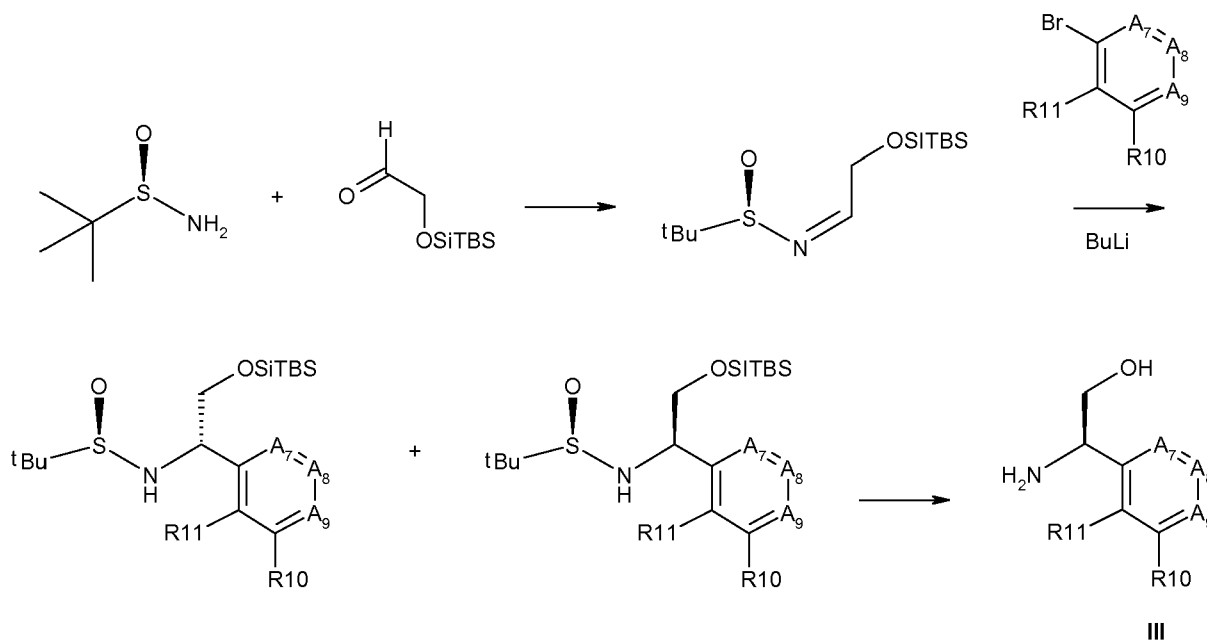


Scheme 3. Preparation of the (1*S*, 2*S*) enantiomer of formula II.

The benzaldehyde shown in **Scheme 3** can be reacted with the anion of (Diethoxyphosphoryl)-acetic acid tert-butyl ester to produce the unsaturated ester shown. Cylopropanation followed by hydrolysis then produces Racemic trans II, which can be separated as described above.

The Intermediates of the invention with formula III are either commercially available or can be prepared as described in Scheme 4 in which R₆ is CH₂OH.

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Scheme 4. Preparation of the chiral amines of formula III, with $R_6 = CH_2OH$. The method is described in: Barrow, J. C. et al. *Tetrahedron Letters* (2001) 2051.

(R)-(+)-2-methyl-2-propanesulfinamide can be reacted with (*tert*-butyldimethylsilyloxy)acetaldehyde as described in the literature (Barrow, J. C. et al. Tetrahe-
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The invention will be illustrated by the following non-limiting examples.

Abbreviations

- AcOH = acetic acid. α_D = specific optical rotation. Aq = Aqueous. BBr₃ = boron tribromide
 5 (used as DCM solution; Aldrich 17,893-4). Boc₂O = Boc anhydride / di-*t*-butyl dicarbonate
 (e.g. Aldrich 19,913-3). Brine = saturated aqueous solution of sodium chloride. CDCl₃ deuter-
 ated chloroform (e.g. Aldrich 225789). Celite = filter-aid. CH₃I = methyl iodide / iodomethane
 (e.g. Aldrich 28,956-6). Cs₂CO₃ = cesium carbonate (Aldrich 441902). DCM = dichloro-
 methane. DMF = dimethyl formamide. DMSO = dimethyl sulfoxide. *d*₆-DMSO = deuterated
 10 dimethyl sulfoxide (e.g. Aldrich 296147). ELSD = evaporative light scattering detection. Et₃N =
 triethyl amine. EtOAc = ethyl acetate. 99% EtOH = absolute ethanol. Et₂O = diethyl ether. h =
 hours. HATU = O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophos-
 phate. HBTU = 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. *i* =
iso. K₂CO₃ = potassium carbonate (e.g. Aldrich 20,961-9). LDA = lithium di-*i*-propylamide
 15 (used as a THF/heptane/ethylbenzene solution; Fluka 62491). LC/MS = high-performance
 liquid chromatography / mass spectrometer. LAH = lithium aluminium hydride (used as a 1M
 THF solution; Aldrich 21,277-6). MeOH = methanol. min = minutes. NaCNBH₃ = sodium
 cyanoborohydride (Aldrich 15,615-9). NaH = sodium hydride (used as a 60% dispersion;
 Aldrich 45,291-2). NaOH = aqueous solution of sodium hydroxide. Pd/C = palladium-on-
 20 charcoal (e.g. Aldrich 20,569-9). PTSA = *para*-toluene sulfonic acid hydrate (e.g. Aldrich
 40,288-5). rt = room temperature. RT = retention time. sat. NaHCO₃ = saturated aqueous so-
 lution of sodium hydrogen carbonate. sat. NH₄Cl = saturated aqueous solution of ammonium
 chloride. SFC = supercritical flash chromatography. TFA = trifluoroacetic acid. THF = tetrahy-
 drofuran (dried over 4Å molecular sieves). TLC = thin layer chromatography.
- 25 Chemical names were obtained using the software MDL ISIS/DRAW 2.5 from MDL informa-
 tion systems

Spectroscopic methods.

Method A:

- 30 LC-MS were run on a Sciex API150EX equipped with APPI-source operating in positive ion
 mode. The HPLC consisted of Shimadzu LC10-ADvp LC pumps, SPD-M20A PDA detector
 (operating at 254 nm) and SCL-10A system controller. Autosampler was Gilson 215, Column
 oven was a Jones Chromatography 7990R and ELS detector was a Sedere Sedex 85.

LC-conditions: The column was a Waters Symmetry C-18, 4.6x30 mm, 3.5 μ m operating at 60°C with 3.0 mL/min of a binary gradient consisting of water + 0.05% TFA (A) and methanol + 0.05% TFA (B).

5 Gradient:

0.01 min 17% B

0.27 min 28% B

0.53 min 39% B

0.80 min 50% B

10 1.07 min 59% B

1.34 min 68% B

1.60 min 78% B

1.87 min 86% B

2.14 min 93% B

15 2.38 min 100% B

2.40 min 17% B

2.80 min 17% B

Total run time: 2.8 min.

The retention times (t_R) are expressed in minutes based on UV-trace at 254 nm.

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Method B:

LC-MS were run on Waters Acquity UPLC-MS consisting of Waters Acquity including column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nm), ELS detector, and SQD-MS equipped with APPI-source operating in positive ion mode.

25 LC-conditions: The column was Acquity UPLC BEH C18 1.7 μ m ; 2.1x50mm operating at 60°C with 1.2 mL/min of a binary gradient consisting of water + 0.05 % trifluoroacetic acid (A) and acetonitrile + 5% water + 0.035 % trifluoroacetic acid.(B)

Gradient:

0.00 min 10% B

30 1.00 min 100% B

1.01 min 10% B

1.15 min 10% B

Total run time: 1.2 min.

The retention times (t_R) are expressed in minutes based on UV-trace at 254 nm.

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Method C:

Preparative supercritical fluid chromatography (SFC) was performed on a Berger Multigram II operating at 50 mL/min at 35°C and 100 bar backpressure using stacked injections. The column was a ChiralpakAD 5 u, 250x21 mm. The eluent was CO₂ (70%) and ethanol (30%).

Method D:

Preparative supercritical fluid chromatography (SFC) was performed on a Thar SFC-80 operating at 60 g/min at 35°C and 140 bar backpressure using stacked injections. The column was a ChiralPakAD-H (250x30 mm). The eluent was CO₂ (88%) and Ethanol (12%).

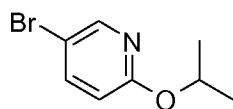
Method E:

Preparative supercritical fluid chromatography (SFC) was performed on a Thar SFC-200 operating at 100 g/min at 35°C and 140 bar backpressure using stacked injections. The column was a ChiralPakAD-H (250x30 mm). The eluent was CO₂ (90%) and Ethanol (10%).

Method F:

Enantiomeric excess (ee) was determined on an Aurora Fusion A5 SFC system operating at 3 ml/min at 40 °C and 100 bar backpressure. The column was a Chiralpak AD (150x4.6 mm). The eluent was CO₂ (70%) and ethanol + 0.1% diethyl amine (30%).

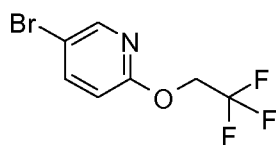
¹H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX-500 instrument at T=303.3 K or at 600 MHz on a Bruker Avance AV-III-600 instrument. Chemical shift values are expressed in ppm-values relative to tetramethylsilane unless noted otherwise. The following abbreviations or their combinations are used for multiplicity of NMR signals: s = singlet, d = doublet, m = multiplet and br = broad.

Preparation of intermediatesPreparation of bromopyridines.**IM1:** 5-Bromo-2-isopropoxy-pyridine

60% NaH in oil (1.5:1, Sodium hydride:Mineral Oil, 5.20 g) was added in two portions to isopropyl alcohol (150 mL) at room temperature under N₂. The mixture was stirred at 60°C for 30 min. 5-bromo-2-chloropyridine (10.00 g, 51.96 mmol) was added in two portions and the mixture was stirred at reflux 4h and then at 80°C overnight. The solution was concentrated in

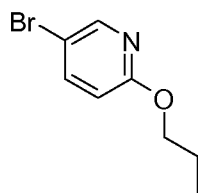
vacuo. Water (50 mL) and EtOAc (50 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was removed in vacuo. The crude product was subjected to flash chromatography (silica, 0-50% EtOAc in heptanes) to give the title compound as a clear oil (8.74 g, 78%). ^1H NMR (600 MHz, DMSO) δ 8.17 (s, 1H), 7.61 (dd, 1H), 6.59 (d, 1H), 5.23 (m, 1H), 1.33 (s, 6H).

IM2: 5-Bromo-2-(2,2,2-trifluoro-ethoxy)-pyridine



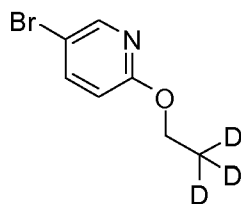
Prepared analogously to **IM1** to give the title compound as a colorless liquid (2.78 g, 54%) sufficiently pure for the next step.

IM3: 5-Bromo-2-propoxy-pyridine



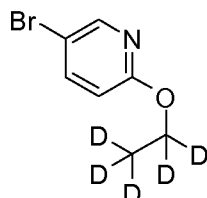
Potassium *tert*-butoxide (1.85 g, 16.5 mmol) was added to a mixture of 5-bromo-2-chloropyridine (2.89 g, 15.0 mmol) and 1-propanol (1.230 mL, 16.5 mmol) in THF (15 mL). The reaction mixture was heated at 120°C for 30 minutes in a microwave reactor. The mixture was poured into a mixture of water (50 mL) and EtOAc (100 mL). The organic layer was washed with brine, dried over MgSO_4 and evaporated to dryness. Flash chromatography (silica, 0-20% EtOAc in heptanes) gave the title compound as a yellow oil (3.13 g, 97%) sufficiently pure for the next step.

IM4: 5-Bromo-2-(2,2,2- d_3)-ethoxy-pyridine



Prepared analogously to **IM3** using commercially available 2,2,2-d₃-ethanol (Sigma-Aldrich, catalog no 329347) to give the title compound as a colorless oil (2.53 g, 82%) sufficiently pure for the next step.

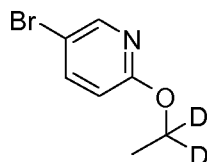
5 **IM5: 5-Bromo-2-(1,1,2,2,2-d₅)-ethoxy-pyridine**



Prepared analogously to **IM3** using commercially available 1,1,2,2,2-d₅-ethanol (Sigma-Aldrich, catalog no 489336) to give the title compound as a colorless oil (1.16 g, 87%) sufficiently pure for the next step.

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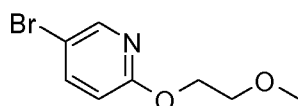
IM6: 5-Bromo-2-(1,1-d₂)-ethoxy-pyridine



Prepared analogously to **IM3** using commercially available 1,1-d₂-ethanol (Sigma-Aldrich, catalog no 347434) to give the title compound as a colorless oil (2.61 g, 85%) sufficiently pure for the next step.

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IM7: 5-Bromo-2-(2-methoxy-ethoxy)-pyridine

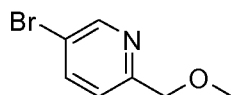


2-Methoxyethanol (5.12 mL, 65.0 mmol) was dissolved in 1,4-dioxane (125 mL). Potassium *tert*-butoxide (7.00 g, 62.4 mmol) was added under N₂. The mixture was stirred for 10 minutes. 5-Bromo-2-chloropyridine (10.0 g, 52.0 mmol) was added and the resulting mixture was refluxed for 2 hours. The mixture was poured into brine and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and evaporated to dryness. Purification by flash chromatography (silica, heptanes/EtOAc 4:1) gave the title compound as a colorless oil (8.74 g, 73%) sufficiently pure for the next step.

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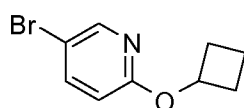
IM8: 5-Bromo-2-methoxymethyl-pyridine



To a solution of 5-bromopyridine-2-carbaldehyde (5.00 g, 26.9 mmol) dissolved in a mixture of ethanol (75 mL) and THF (25 mL) was added sodium borohydride (0.407 g, 10.8 mmol) in small portions. After 45 minutes 0.5 mL water was added and the mixture was evaporated to dryness. The oily residue was subjected to flash chromatography (silica, EtOAc/EtOH/Et3N 90:5:5) to give (5-bromo-pyridin-2-yl)-methanol (4.81 g, 86%) as pale-yellow oil.

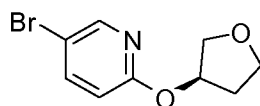
A solution of this (5-bromo-pyridin-2-yl)-methanol (4.80 g, 23.0 mmol) in DMF (25 mL) was added drop wise over 5 minutes to a slurry of sodium hydride (1.10 g, 27.6 mmol) in DMF (50 mL) at 0 °C under N₂. The mixture was stirred for 15 minutes before the drop wise addition of a solution of methyl iodide (1.57 mL, 25.3 mmol) in DMF (25 mL). The mixture was allowed to reach room temperature and was then stirred overnight. The mixture was poured into brine and extracted with EtOAc. The combined organic layers were thoroughly washed with brine, dried over MgSO₄ and evaporated to dryness to give the title compound as a yellow oil (4.77 g, 98%) sufficiently pure for the next step.

IM9: 5-Bromo-2-cyclobutoxy-pyridine

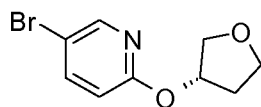


Prepared analogously to **IM3** using commercially available cyclobutanol to give the title compound as a clear oil (2.72 g, 80%) sufficiently pure for the next step.

IM10: 5-Bromo-2-[(R)-(tetrahydro-furan-3-yl)oxy]-pyridine

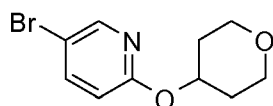


To a solution of 5-bromo-2-chloropyridine (10 g, 52.1 mmol) in 100 mL of DMF was added commercially available (R)-(-)-3-hydroxytetrahydrofuran (6.87 g, 78.1 mmol) and Cs₂CO₃ (33.85 g, 0.104 mol), the resulting mixture was heated 90 °C for 36 hours. The solvent was concentrated and the residue was extracted with EtOAc (500ml), washed with water (200ml). The organic layer was dried over Na₂SO₄, concentrated and purified by chromatography on silica gel (eluting with Petrol ether: EtOAc = 100:1) to afford 5-Bromo-2-[(R)-(tetrahydro-furan-3-yl)oxy]-pyridine (5.9 g, yield: 47%) as a solid. ¹HNMR (CDCl₃ 400MHz): δ 8.15 (d, J = 2.4 Hz, 1 H), 7.61-7.64 (m, 1 H), 6.64 (d, J = 8.8 Hz, 1 H), 5.47-5.50 (m, 1 H), 3.85-4.02 (m, 4 H), 2.07-2.28 (m, 2 H). [α]_D²⁰ = +18.5 (C=0.189, CHCl₃).

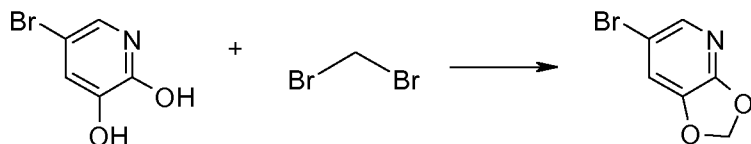
IM11: 5-Bromo-2-[(S)-(tetrahydro-furan-3-yl)oxy]-pyridine

Prepared analogously to **IM10** using commercially available (S)-(+)-3-hydroxytetrahydrofuran
5 to afford 5-Bromo-2-[(S)-(tetrahydro-furan-3-yl)oxy]-pyridine

(9.62 g, yield: 51%) as a solid. ¹H NMR (CDCl₃ 400 MHz): δ 8.16 (d, *J* = 2.4 Hz, 1 H), 7.62-7.65 (m, 1 H), 6.64-6.66 (m, 1 H), 5.48-5.52 (m, 1 H), 3.99-4.03 (m, 2 H), 3.86-3.97 (m, 2 H), 2.20-2.29 (m, 1 H), 2.08-2.15 (m, 1 H). [α]_D²⁰ = -20.7 (C=0.21, CHCl₃).

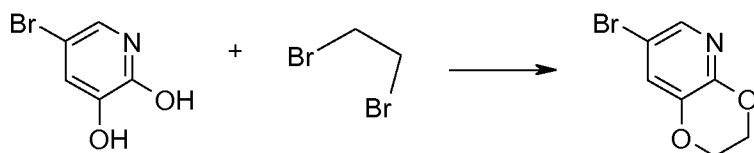
10 **IM12:** 5-Bromo-2-(tetrahydro-pyran-4-yloxy)-pyridine

Prepared analogously to **IM3** using commercially available tetrahydro-4-pyranol to give the title compound sufficiently pure for the next step.

15 **IM13:** 6-Bromo-[1,3]dioxolo[4,5-b]pyridine

To a suspension of 5-Bromo-pyridine-2,3-diol (10.0 g, 52.63 mmol, commercially available, CAS 34206-49-0) in NMP (100 mL) was added K₂CO₃ (21.97 g, 158 mmol) and dibromo methane (10.97 g, 63.16 mmol). The reaction mixture was heated to 90 °C for 16 h. EtOAc
20 was added and the salts were filtered off. Water was added, the phases were separated and the aq layer was extracted with more ethyl acetate. The combined organic layers was dried over anhydrous Na₂SO₄ and concentrated under vacuo to get the crude compound. The crude compound was purified by silica gel chromatography (eluent 5 % ethyl acetate in petrol ether). Yield of 6-Bromo-[1,3]dioxolo[4,5-b]pyridine 2.2 g (21%) pure by ¹H NMR (400 MHz,
25 DMSO) δ 7.71 (d, 1H, *J* = 2 Hz), 7.55 (d, 1H, *J* = 2 Hz), 6.20 (s, 2H). Mp 69-71 °C.

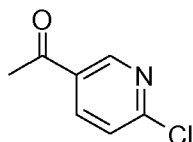
IM14: 7-Bromo-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine



To a suspension of 5-Bromo-pyridine-2,3-diol (10.0 g, 52.63 mmol, commercially available, CAS 34206-49-0) in DMF (150 mL) was added K_2CO_3 (21.78 g, 158 mmol) and 1,2-dibromoethane (11.87 g, 63.2 mmol). The reaction mixture was heated to 100 °C for 5 h. The reaction mixture was cooled to rt and poured into ice cold water EtOAc was added and the phases were separated and the aq layer was extracted with more ethyl acetate. The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated under vacuo to get the crude compound. The crude compound was purified by silica gel chromatography (eluent 10 % ethyl acetate in petrol ether). Yield of 6-Bromo-[1,3]dioxolo[4,5-b]pyridine 2.2 g (18 %) pure by 1H NMR (400 MHz, DMSO) δ 7.85 (d, 1H, J = 2 Hz), 7.59 (d, 1H, J = 2 Hz), 4.41 (m, 2H), 4.27 (m, 2H).

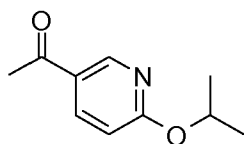
Acetylation of pyridines.

IM15: 1-(6-Chloro-pyridin-3-yl)-ethanone



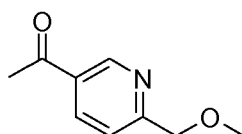
A round bottomed flask was charged with 5-bromo-2-chloropyridine (5.30 g, 27.6 mmol) in THF under N_2 and cooled at 0 °C. A solution of 1 M *iso*-propylmagnesiumchloride - lithium chloride complex in THF (40 mL) was added drop wise over 15 min. After 70 min *N*-methoxy-*N*-methylacetamide (4.1 mL, 38 mmol) was added drop wise. After stirring for 5 min at 0 °C the cooling bath was removed. The mixture was left stirring overnight and was then quenched by the addition of 100 mL saturated aqueous NH_4Cl solution. The mixture was extracted with 3x100 mL EtOAc. The combined organic layers were washed with water followed by brine and dried over $MgSO_4$. Evaporation of the volatiles at 80 °C, 10 mbar for 1h gave the title compound (3.596 g, 84) sufficiently pure for the next step.

IM16: 1-(6-Iso-propoxy-pyridin-3-yl)-ethanone



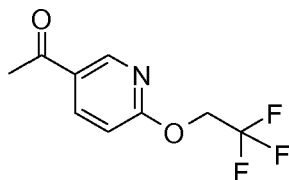
A round-bottomed flask was charged with 5-bromo-2-*iso*-propoxypyridine (**IM1**) (5.00 g, 23.1 mmol) in THF (100) under N₂ and cooled in an acetone/dry-ice bath to -66 °C (internal temperature). A solution of 2.5 M *n*-butyllithium in hexane (10.1 mL, 25.3 mmol) was added drop wise over 10 minutes at keeping the internal temperature below -55 °C. The mixture was stirred at -65 °C for 15 minutes. *N*-methoxy-*N*-methylacetamide (3.07 mL, 28.9 mmol) dissolved in THF (10 mL) was then added drop wise over 10 minutes while keeping the internal temperature below -65 °C. After stirring for 1 h the mixture was allowed to reach room temperature. The mixture was poured into saturated aqueous NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and evaporated to dryness. Flash chromatography (silica, heptanes/EtOAc 4:1) gave the title compound as a colorless oil (3.20 g, 77%) sufficiently pure for the next step.

IM17: 1-(6-Methoxymethyl-pyridin-3-yl)-ethanone



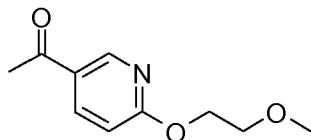
Prepared analogously to **IM16** from **IM8** to give the title compound as a colorless liquid (0.379 g, 17%) sufficiently pure for the next step.

IM18: 1-[6-(2,2,2-Trifluoro-ethoxy)-pyridin-3-yl]-ethanone



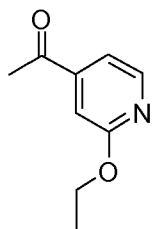
Prepared analogously to **IM16** from **IM2** to give the title compound as a colorless liquid (1.234 g, 48%) sufficiently pure for the next step.

IM19: 1-[6-(2-Methoxy-ethoxy)-pyridin-3-yl]-ethanone



Prepared analogously to **IM16** from **IM7** to give the title compound as a colorless liquid (2.13 g, 57%) sufficiently pure for the next step.

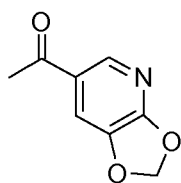
IM20: 1-(2-Ethoxy-pyridin-4-yl)-ethanone



Prepared analogously to **IM16** from commercially available 4-bromo-2-ethoxy-pyridine, Synchem OHG catalog no CT091 to give the title compound as a colorless liquid (1.20 g, 49%) sufficiently pure for the next step.

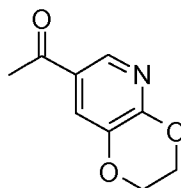
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IM21: 1-[1,3]Dioxolo[4,5-b]pyridin-6-yl-ethanone



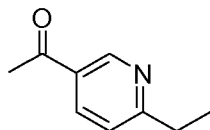
A round-bottomed flask was charged with 6-Bromo-[1,3]dioxolo[4,5-b]pyridine **IM13** (1.74 g, 8.61 mmol) in DMF (25 ml) under N₂ and tributyl(1-ethoxyvinyl)tin (3.65 ml, 10.8 mmol) was added. Tetrakis(triphenylphosphine)palladium(0) (0.50 g, 0.43 mmol) was added and the solution was stirred at 65 °C overnight. The mixture was added to water and EtOAc and the phases were separated. The org phase was washed with brine, dried (MgSO₄) filtered and was rotovaped. The residue was dissolved in THF (100 ml), and a mixture of water (15 ml) and conc. HCl (2.5 ml) was added and the solution was stirred at rt 5 min. The solution was added to brine and sat NaHCO₃ solution was added until the solution was slightly alkaline. The org Phase was extracted with EtOAc and the phases were separated. The org phase was washed with brine, dried (MgSO₄) filtered and was rotovaped. The residue was redissolved in THF (10 ml) EtOAc (20 ml) and heptanes (20 ml). The mixture was concentrated until 25 ml remained and cooled in ice. A solid precipitated and was collected by filtration. Yield: 0.942 g (66%) of **IM21**. ¹H-NMR (500 MHz, DMSO) δ 8.47 (s, 1H), 8.54 (s, 1H), 6.27 (s, 2H), 2.53 (s, 3H).

IM22: 1-(2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-ethanone



Prepared analogously to **IM21** from with 7-Bromo-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine (3.00 g, 13.9 mmol) to give the title compound as a white powder (1.84 g, 74%). ¹H-NMR (500 MHz, DMSO) δ 8.47 (s, 1H), 8.54 (s, 1H), 6.27 (s, 2H), 2.53 (s, 3H).

5 **IM23: 1-(6-Ethyl-pyridin-3-yl)-ethanone**

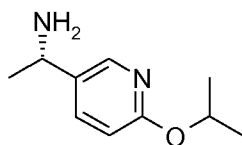


A dry round bottomed flask was charged with 1-(6-chloro-3-pyridinyl)-1-ethanone (**IM15**) (3.596 g, 23.11 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (1.694 g, 2.315 mmol) in THF (100 mL) under N₂. A 1 M solution of diethyl zinc in hexane (35 mL, 35 mmol) was added drop wise to this mixture followed by *N,N*-dimethylaminoethanol (0.50 mL, 5.0 mmol). The mixture was heated to reflux for 30 minutes. The mixture was cooled to room temperature and then quenched by the addition of saturated aqueous NH₄Cl solution (100 mL). The mixture was filtered through a plug of celite. The aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were washed with water, brine and then dried over Mg₂SO₄. Flash Chromatography (120 g silica, 0-40% EtOAc in heptanes) gave the title compound as a yellow oil (0.699 g, 20%) sufficiently pure for the next step.

Preparation of chiral amines.

Chiral amines were made, if not commercially available, according to well-described procedure for either 1,2-stereoselective reduction of sulfinyl imines or 1,2-stereoselective addition of organometallic reagents to sulfinyl imines. These methods have been described by Chelucci, G., Baldino, S., Chessa, S., Pinna, G., Soccolini, S., *Tetrahedron Asymmetry* 2006, 17, 3163-3169, Evans, J., Ellman, J., *J. Org. Chem.* 2003, 68, 9948-9957 and Robak, M., Herbage, M., Ellman, J., *Chem. Rev.* 2010, 110, 3600-3740 and references cited herein.

IM24: (S)-1-(6-Isopropoxy-pyridin-3-yl)-ethylamine



Step 1: Formation of sulfinyl imine:

1-(6-Isopropoxy-pyridin-3-yl)-ethanone **IM16** (3.20 g, 17.8 mmol) was dissolved in THF (55 mL) under N₂. *R*(+)-2-methyl-2-propanesulfinamide (2.21 g, 18.2 mmol) and tita-

nium(IV)ethoxide (7.40 mL, 35.7 mmol) was added. The mixture was refluxed for 24 hours. The mixture was allowed to reach room temperature. The mixture was diluted with EtOAc (200 mL) and poured into ice/brine. The resulting slurry was filtered through Celite. The organic layer was washed with brine, dried over MgSO_4 and evaporated to dryness. Flash chromatography (silica, heptanes/EtOAc 2:1) gave (*R*)-2-methyl-propane-2-sulfinic acid [1-(6-isopropoxy-pyridin-3-yl)-ethylidene]-amide (4.04 g, 80%) as a yellow oil sufficiently pure for the next step.

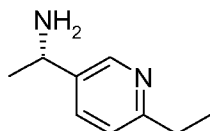
Step 2: Reduction of the imine:

A round-bottomed flask was charged with (*R*)-2-methyl-propane-2-sulfinic acid [1-(6-isopropoxy-pyridin-3-yl)-ethylidene]-amide (4.00 g, 14.2 mmol) in THF (50 mL) under N_2 and cooled to -66°C (internal temperature). A 1.00 M solution of *L*-Selectride in THF (29.0 mL, 29.0 mmol) was added drop wise over 15 minutes. The mixture was stirred at -70°C for 1 hour. The cold mixture was poured into saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 and evaporated to dryness. Flash chromatography (silica, EtOAc) gave (*R*)-2-methyl-propane-2-sulfinic acid [(*S*)-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amid (2.91 g, 72%) as a colorless powder. Diastereomeric excess $>95\%$ based on ^1H NMR.

Step 3: Removal of chiral auxiliary:

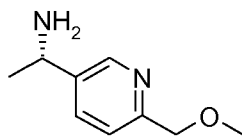
(*R*)-2-Methyl-propane-2-sulfinic acid [(*S*)-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide (2.90 g, 10.2 mmol) was dissolved in methanol (48 mL). A mixture of 12.0 M HCl in water (4.25 mL) and water (4.25 mL) was added drop wise over 3 minutes. The mixture was stirred at room temperature overnight. The mixture was evaporated to dryness. The oily residue was subjected to flash chromatography (silica, EtOAc/EtOH/triethylamine 90:5:5) on a short column to give (*S*)-1-(6-isopropoxy-pyridin-3-yl)-ethylamine **IM24** (1.71 g, 93%) as a pale-yellow oil sufficiently pure for the next step. The overall yield from 1-(6-isopropoxy-pyridin-3-yl)-ethanone **IM16** was 54%.

IM25: (*S*)-1-(6-Ethyl-pyridin-3-yl)-ethylamine



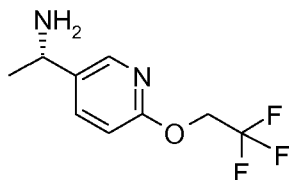
Prepared analogously to **IM24** from **IM23** to give the title compound sufficiently pure for the next step.

IM26: (*S*)-1-(6-Methoxymethyl-pyridin-3-yl)-ethylamine



Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

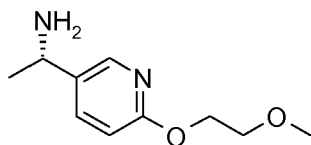
IM27: (S)-1-[6-(2,2,2-Trifluoro-ethoxy)-pyridin-3-yl]-ethylamine



5

Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

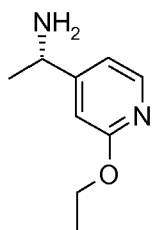
IM28: (S)-1-[6-(2-Methoxy-ethoxy)-pyridin-3-yl]-ethylamine



10

Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

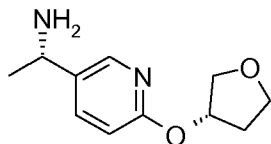
IM29: (S)-1-(2-Ethoxy-pyridin-4-yl)-ethylamine



Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

15

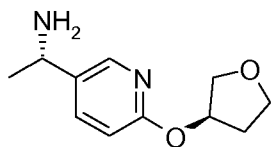
IM30: (S)-1-{6-[(S)-(Tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethylamine



Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

20

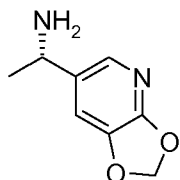
IM31: (S)-1-{6-[(R)-(Tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethylamine



Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

IM32: *(S)*-1-[1,3]Dioxolo[4,5-*b*]pyridin-6-yl-ethylamine

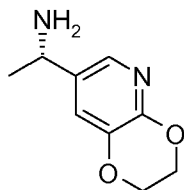
5



Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

IM33: *(S)*-1-(2,3-Dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)-ethylamine

10



Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

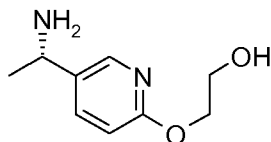
IM34: *(S)*-1-(2-Ethoxy-pyrimidin-5-yl)-ethylamine



15

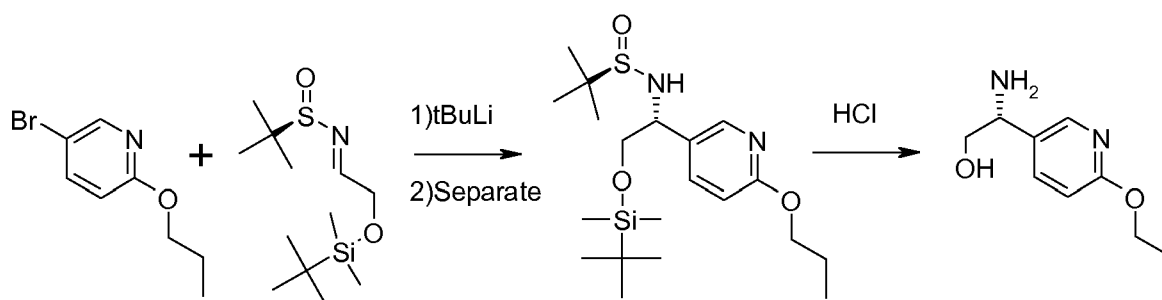
Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

IM35: 2-[5-((*S*)-1-Amino-ethyl)-pyridin-2-yloxy]-ethanol



20

Prepared analogously to **IM24** to give the title compound sufficiently pure for the next step.

IM36: (*R*)-2-Amino-2-(6-propoxy-pyridin-3-yl)-ethanolStep 1:

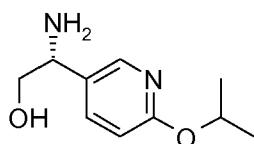
A 1.7 M solution of *tert*-butyllithium in pentane (15.2 mL, 25.8 mmol) was added drop wise to a stirring solution of 5-bromo-2-propoxypyridine **IM3** (2.54 g, 11.8 mmol) dissolved in dry THF (29.4 mL) at -78°C under Ar. The solution was subsequently stirred at this temperature for 30 min. A solution of (*R*)-2-methyl-propane-2-sulfinic acid [2-(*tert*-butyl-dimethyl-silanyloxy)-ethylidene]-amide **IM49** (3.26 g, 11.8 mmol) in dry THF (15 mL) was then added drop wise at -78°C and the solution was stirred at this temperature for 30 min. The cooling bath was removed and the mixture was allowed to reach room temperature overnight. The mixture was quenched with saturated aqueous NH₄Cl solution (75 mL) and EtOAc (150 mL). The phases were separated and the organic layer was washed with brine and then dried over MgSO₄. Flash chromatography (silica, 10-100% EtOAc in heptanes) gave (*R*)-2-Methyl-propane-2-sulfinic acid [(*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide, the fastest eluding isomer, as a clear oil (2.33 g, 48%) sufficiently pure for the next step. Diastereomeric excess >95% based on ¹H NMR.

Step 2:

A 2.00 M solution of hydrogen chloride in diethyl ether (28 mL, 56 mmol) was added to a stirred solution of [(*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide (2.33 g, 5.62 mmol) dissolved in MeOH (11 mL) at 0°C under Ar. After the addition was completed the cooling bath was removed and the solution was stirred at room temperature overnight. The mixture was then evaporated to dryness and the residue was suspended in methylene chloride and transferred to a short silica gel column. After eluting with EtOAc:EtOH:Et₃N (90:5:5) (*R*)-2-Amino-2-(6-propoxy-pyridin-3-yl)-ethanol, **IM36**, was obtained as an oil (0.813 g, 74%). The overall yield from 5-bromo-2-propoxypyridine **IM3** was 36%.

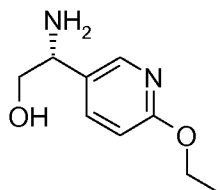
¹H NMR (600 MHz, CDCl₃) δ 8.61 (s, 1H), 8.60 (dd, 1H), 7.71 (d, 1H), 4.22 (t, 2H), 4.06 (m, 1H), 3.72 (m, 1H), 3.60 (m, 1H), 1.78 (m, 2H), 1.24 (m, 1H), 1.02 (m, 4H).

IM37: (*R*)-2-Amino-2-(6-isopropoxy-pyridin-3-yl)-ethanol



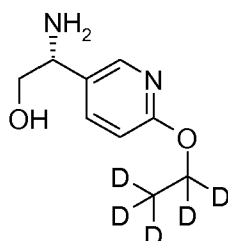
Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step (1.07 g, 36% overall yield from **IM1**).

5 **IM38:** *(R)*-2-Amino-2-(6-ethoxy-pyridin-3-yl)-ethanol



Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step (0.360 g, 35% overall yield from commercially available 5-bromo-2-ethoxy-pyridine, Apollo catalog no OR13065).

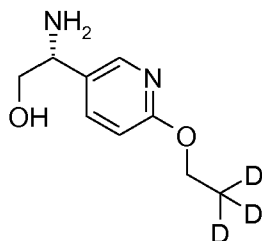
10 **IM39:** *(R)*-2-Amino-2-(6-(1,1,2,2,2- d_5)-ethoxy-pyridin-3-yl)-ethanol



Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step (0.500 g, 22% overall yield from **IM5**).

15

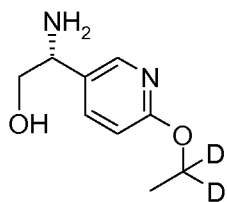
IM40: *(R)*-2-Amino-2-(6-(2,2,2- d_3)-ethoxy-pyridin-3-yl)-ethanol



Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step (0.647 g, 30% overall yield from **IM4**).

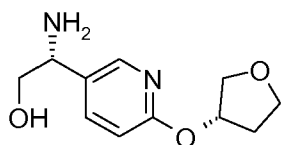
20

IM41: *(R)*-2-Amino-2-(6-(1,1- d_2)-ethoxy-pyridin-3-yl)-ethanol



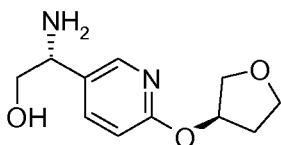
Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step (0.380 g, 18% overall yield from **IM6**).

- 5 **IM42:** *(R)*-2-Amino-2-{6-[(*S*)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethanol



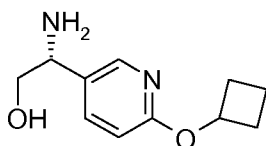
Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step.

- IM43:** *(R)*-2-Amino-2-{6-[(*R*)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethanol



- 10 Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step.

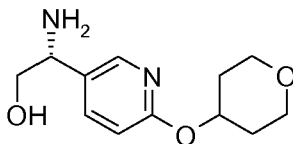
- IM44:** *(R)*-2-Amino-2-(6-cyclobutoxy-pyridin-3-yl)-ethanol



Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step.

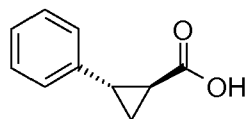
15

- IM45:** *(R)*-2-Amino-2-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethanol

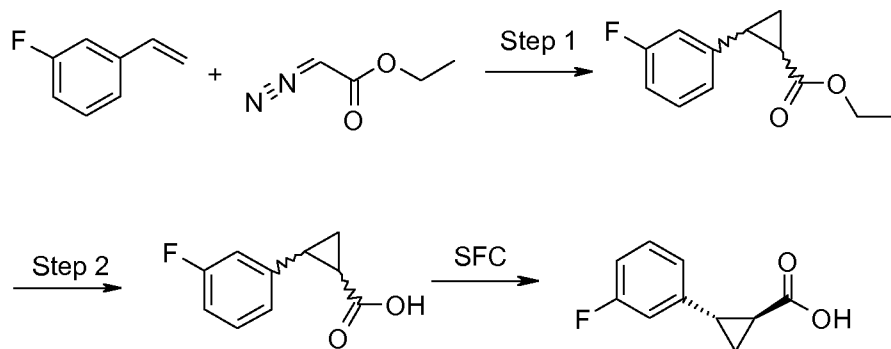
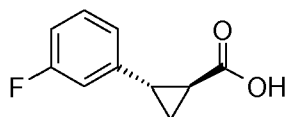


Prepared analogously to **IM36** to give the title compound sufficiently pure for the next step.

- 20 Preparation of carboxylic acids.

IM46: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid

Commercially available, racemic *trans* 2-phenyl-cyclopropanecarboxylic acid (Sigma-Aldrich, catalog no P22354) was subjected to chiral SFC separation, method C to give **IM46** as an oil that slowly solidified upon standing. Enantiomeric purity 95% ee (Method F). Specific optical rotation +300.9° [α]_D²⁰ (C = 1% EtOH). (Lit: +389° [α]_D²⁰ (C = 0.61, CHCl₃) Kozikowski et al., *J. Med. Chem.* **2009**, 52, 1885-1902), (Lit: +311.7° [α]_D²⁰ (C = 1.776, EtOH) Walborsky et al., *Tetrahedron* **1964**, 20, 1695-1699.)

10 **IM47:** (1*S*,2*S*)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acidStep 1:

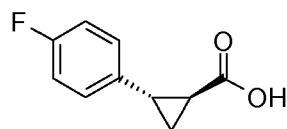
A round-bottomed flask was charged with 3-fluorostyrene (13.0 g, 0.107 mol) in anhydrous methylene chloride (130 mL). To this mixture was added rhodium acetate dimer (1.30 g, cat amount). A solution of ethyldiazoacetate (33.28 g, 0.291 mol) in anhydrous methylene chloride (130 mL) was added to the reaction via a syringe pump over 5 h and stirred at room temperature for 1h in darkness. The reaction mixture was filtered through a plug of celite, which was washed with water followed by brine. The organic layer was dried over Na₂SO₄ and evaporated to dryness. Flash chromatography (silica, EtOAc/petroleum ether 1:9) gave rac-*trans* 2-(3-fluoro-phenyl)-cyclopropanecarboxylic acid ethyl ester (13.0 g, 59%) as a colorless liquid sufficiently pure for the next step.

Step 2:

To a solution of rac-*trans* 2-(3-fluoro-phenyl)-cyclopropanecarboxylic acid ethyl ester (13.0 g, 0.062 mol) in MeOH (310 mL) was added a solution of KOH (35.0 g, 0.625 mol) in MeOH

(150 mL) at 0°C. After addition of the base the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with methylene chloride (2x50 mL). The aqueous layer was acidified with 10% HCl. The resulting mixture was extracted with methylene chloride (2x150 mL). The combined organic layers were dried over Na₂SO₄ and evaporated to dryness to give rac-trans-2-(3-fluoro-phenyl)-cyclopropanecarboxylic acid as colorless crystals (9.5 g, 85%). Separation of the isomers by chiral SFC (Method D) gave the title compound (1S,2S)-2-(3-fluoro-phenyl)-cyclopropanecarboxylic acid **IM47** as colorless crystals (3.27 g, 17% overall yield from 3-fluorostyrene) sufficiently pure for the next step. Specific optical rotation +263.4° [α]_D²⁰ (C = 1% MeOH)

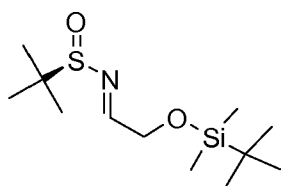
IM48: (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid



Prepared analogously to **IM48** using SFC method E to give the title compound sufficiently pure for the next step (3.1 g, 13% overall yield from 4-fluorostyrene). Specific optical rotation +263.2° [α]_D²⁰ (C = 1% MeOH)

Other intermediates.

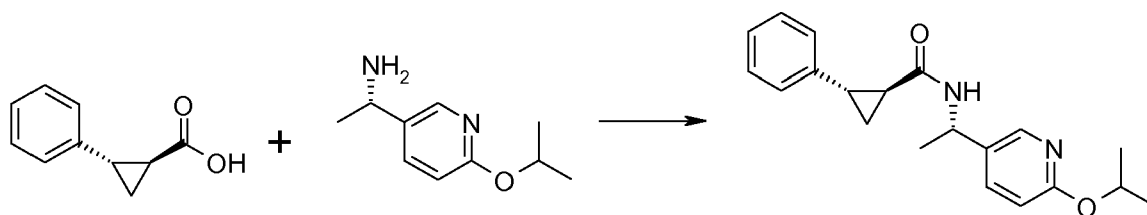
IM49: (R)-2-Methyl-propane-2-sulfinic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethylidene]-amide



(R)-(+)-2-methyl-2-propanesulfinamide (8.70 g, 71.8 mmol), pyridinium *p*-toluenesulfonate (0.902 g, 3.59 mmol) and MgSO₄ (43.2 g, 359 mmol) was suspended in methylene chloride (25 mL). A solution of (*tert*-butyldimethylsilyloxy)acetaldehyde (25.0 g, 144 mmol) dissolved in methylene chloride (10 mL) was added drop wise at room temperature. The reaction was stirred at room temperature overnight. The mixture was evaporated to dryness. Flash chromatography (silica, EtOAc/heptanes 1:4) gave the title compound as an oil that slowly solidified upon standing (18.3 g, 92%) sufficiently pure for the next step.

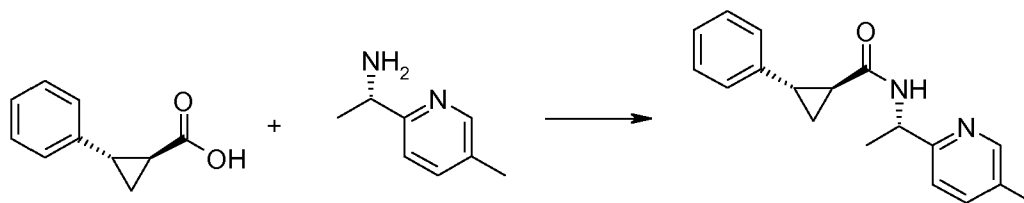
Example 1: Preparation of example compounds of the invention:

Compound 1: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide



- 5 *Trans*-2-phenyl-1-cyclopropanecarboxylic acid **IM46** (0.590 g, 3.64 mmol) was dissolved in DMF (15.0 mL). *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.38 g, 3.63 mmol) was added. Triethylamine (1.10 mL, 7.89 mmol) was then added and the mixture was stirred for 15 minutes at room temperature. This mixture was added drop wise to a solution of (*S*)-1-(6-isopropoxy-pyridin-3-yl)-ethylamine **IM24** (0.655 g, 3.63 mmol)
- 10 dissolved in DMF (15.0 mL) over 2 minutes. The mixture was stirred at room temperature over night. The mixture was evaporated to dryness. The residue was transferred to a silica gel column and eluted with EtOAc/heptanes 1:1 to give **Compound 1** as a solid. This solid was dissolved in EtOAc (50 mL) and to this solution was slowly added heptanes (50 mL). The mixture was concentrated to approx. 25 mL in vacuo and this solution was cooled in an
- 15 ice/water bath. A white precipitate formed. The solids was collected by filtration and dried in vacuo to give the title compound as colorless crystals (0.794 g, 67%). LC-MS (*m/z*) 325.4 (*MH*⁺), *t_R* = 1.51 min (method A). ¹H NMR (500 MHz, DMSO) δ 8.57 – 8.50 (m, 1H), 8.06 (br s, 1H), 7.65 – 7.57 (m, 1H), 7.30 – 7.24 (m, 2H), 7.20 – 7.14 (m, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 1H), 5.25 – 5.16 (m, 1H), 4.98 – 4.88 (m, 1H), 2.24 – 2.15 (m, 1H), 1.94 –
- 20 1.88 (m, 1H), 1.41 – 1.32 (m, 4H), 1.26 (d, *J* = 6.2 Hz, 6H), 1.20 (ddd, *J* = 8.5, 6.1, 4.1 Hz, 1H). Diastereomeric excess >95% based on ¹H NMR.

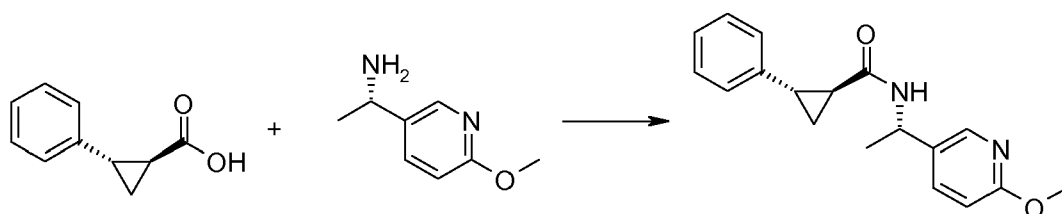
Compound 2: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(5-methyl-pyridin-2-yl)-ethyl]-amide



- 25 *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.709 g, 3.70 mmol) and 1-hydroxybenzotriazole (0.667 g, 4.93 mmol) were added to a stirred mixture of **IM46** (0.60 g, 3.70 mmol) and commercially available (*S*)-1-(5-methyl-pyridin-2-yl)-ethylamine hydrochloride

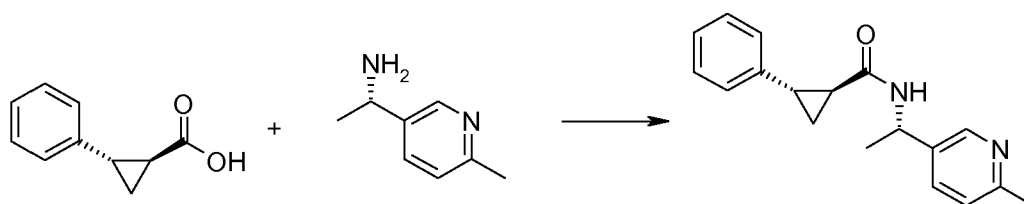
(Supplier Netchem Inc., Catalog No 528193) (0.426 g, 2.47 mmol) and N,N-diisopropylethylamine (0.859 ml, 4.93 mmol) in THF (25 ml). The solution was stirred at rt overnight. Water was added and the mixture was extracted with EtOAc (3x80 ml). The combined organic phases were washed with brine, dried over MgSO₄, filtered and the solvent was evaporated of in vac. The crude product was purified by silica gel chromatography (EtOAc in heptanes 1:1). Yield of **Compound 2**: 110 mg (16%). LC-MS (m/z) 281.1 (MH⁺), t_R = 0.91 min (method A).

Compound 3: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methoxy-pyridin-3-yl)-ethyl]-amide



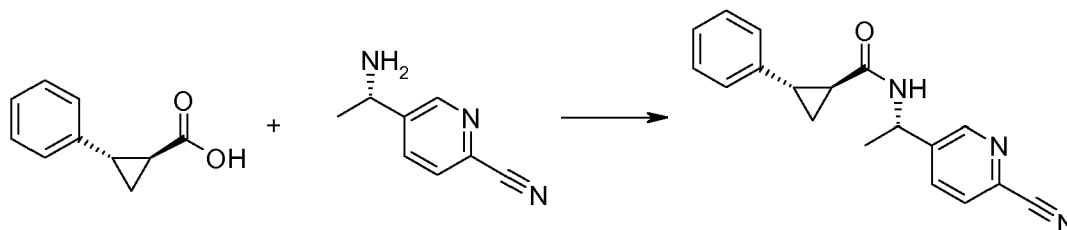
Prepared analogously to **Compound 1** using **IM46** and commercially available (S)-1-(6-methoxy-pyridin-3-yl)-ethylamine (Supplier Netchem Inc., Catalog No 517706). Yield = 0.88 g (66%). ¹H NMR (500 MHz, DMSO) δ 8.55 (d, 1H), 8.10 (s, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.17 (m, 1H), 7.10 (d, 2H), 6.78 (d, 1H), 4.93 (m, 1H), 3.72 (s, 3H), 2.21 (m, 1H), 1.90 (m, 1H), 1.37 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 297.4 (MH⁺), t_R = 1.36 min (method A).

Compound 4: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methyl-pyridin-3-yl)-ethyl]-amide



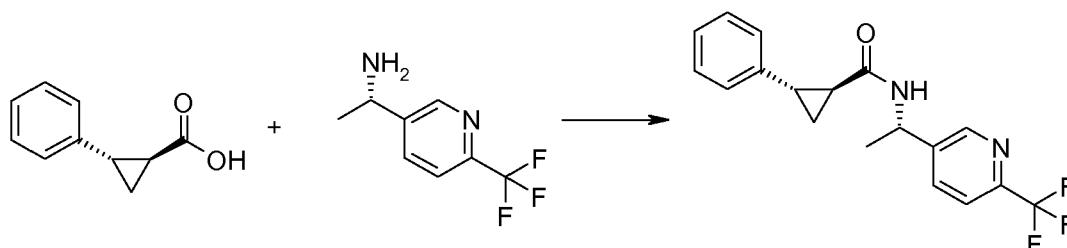
Prepared analogously to **Compound 1** using **IM46** and commercially available (S)-1-(6-methyl-pyridin-3-yl)-ethylamine (Supplier Netchem Inc., Catalog No 519526). Yield = 0.27 g (21%). ¹H NMR (600 MHz, DMSO) δ 8.61 (d, 1H), 8.37 (s, 1H), 7.57 (d, 1H), 7.26 (m, 2H), 7.16 (m, 2H), 7.09 (d, 2H), 4.92 (m, 1H), 2.41 (s, 3H), 2.19 (m, 1H), 1.91 (m, 1H), 1.36 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 281.2 (MH⁺), t_R = 0.86 min (method A).

Compound 5: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-cyano-pyridin-3-yl)-ethyl]-amide



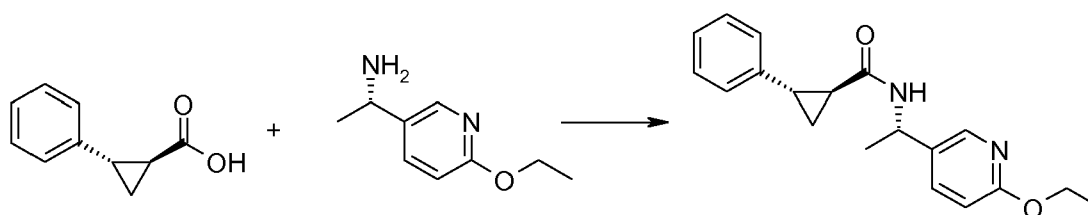
Prepared analogously to **Compound 2** using **IM46** and commercially available 5-((*S*)-1-amino-ethyl)-pyridine-2-carbonitrile hydrochloride (Supplier Netchem Inc., Catalog No 549493). Yield = 0.104 g (20%). ¹H NMR (600 MHz, DMSO) δ 8.76 (d, 1H), 8.71 (s, 1H), 8.02 (d, 1H), 7.94 (d, 1H), 7.29 (m, 2H), 7.19 (m, 1H), 7.12 (d, 2H), 5.03 (m, 1H), 2.21 (m, 1H), 1.92 (m, 1H), 1.40 (d, 3H), 1.37 (m, 1H), 1.23 (m, 1H). LC-MS (*m/z*) 292.0 (MH⁺), *t_R* = 1.31 min (method A).

Compound 6: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide



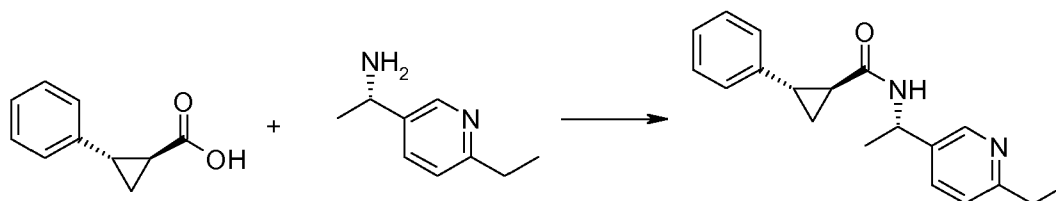
Prepared analogously to **Compound 2** using **IM46** and commercially available (*S*)-1-(6-trifluoromethyl-pyridin-3-yl)-ethylamine hydrochloride. (Supplier Netchem Inc., Catalog No 517662). Yield = 0.33 g (55%). ¹H NMR (500 MHz, DMSO) δ 8.77 (d, 1H), 8.72 (s, 1H), 7.99 (d, 1H), 7.88 (d, 1H), 7.27 (m, 2H), 7.17 (m, 1H), 7.13 (d, 2H), 5.05 (m, 1H), 2.20 (m, 1H), 1.93 (m, 1H), 1.41 (d, 3H), 1.37 (m, 1H), 1.23 (m, 1H). LC-MS (*m/z*) 335.2 (MH⁺), *t_R* = 1.59 min (method A).

Compound 7: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-ethoxy-pyridin-3-yl)-ethyl]-amide



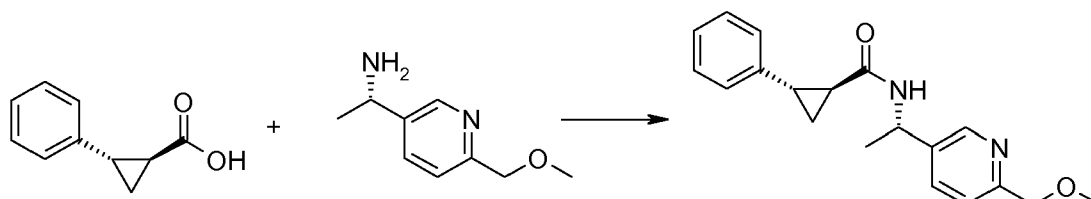
Prepared analogously to **Compound 2** using **IM46** and commercially available (S)-1-(6-ethoxy-pyridin-3-yl)-ethylamine hydrochloride (Supplier Sial GmbH, Catalog No 528261-HCl, Lot no LNA098). Yield = 0.30 g (39%). ¹H NMR (500 MHz, DMSO) δ 8.54 (d, 1H), 8.08 (s, 1H), 7.62 (d, 1H), 7.27 (m, 2H), 7.16 (m, 1H), 7.12 (d, 2H), 6.73 (d, 1H), 4.92 (m, 1H), 4.25 (q, 2H), 2.20 (m, 1H), 1.91 (m, 1H), 1.35 (m, 4H), 1.30 (t, 3H), 1.19 (m, 1H). LC-MS (m/z) 311.4 (MH⁺), t_R = 1.45 min (method A).

Compound 8: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethyl-pyridin-3-yl)-ethyl]-amide



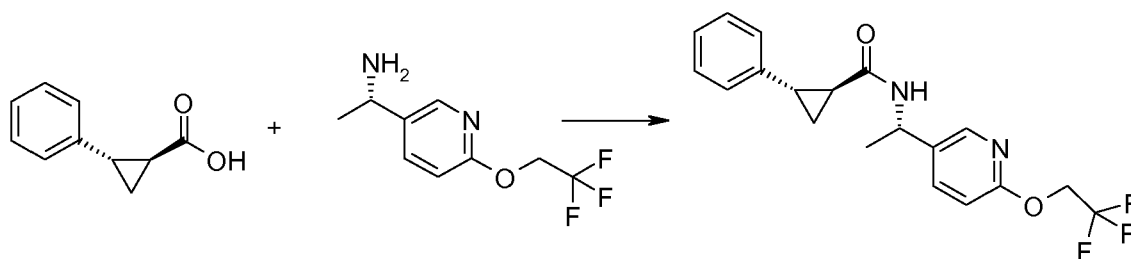
Prepared analogously to **Compound 1** using **IM46** and **IM25**. Yield = 0.44 g (65%). ¹H NMR (500 MHz, DMSO) δ 8.51 (d, 1H), 8.41 (s, 1H), 7.27-7.14 (m, 4H), 7.10 (d, 2H), 4.96 (m, 1H), 2.72 (q, 2H), 2.20 (m, 1H), 1.92 (m, 1H), 1.38 (m, 4H), 1.21 (m, 4H). LC-MS (m/z) 295.1 (MH⁺), t_R = 0.90 min (method A).

Compound 9: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methoxymethyl-pyridin-3-yl)-ethyl]-amide



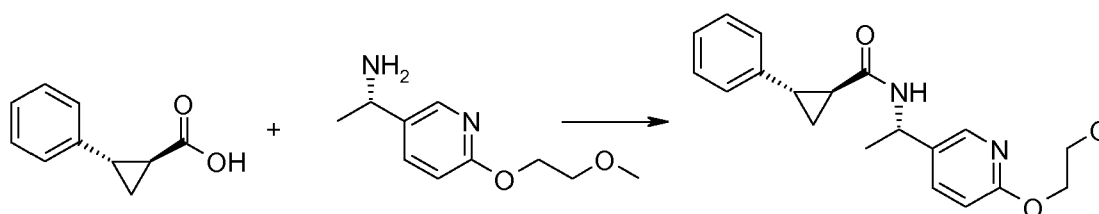
Prepared analogously to **Compound 1** using **IM46** and **IM26**. Yield = 0.18 g (40%). ¹H NMR (500 MHz, DMSO) δ 8.63 (d, 1H), 8.10 (s, 1H), 7.71 (d, 1H), 7.37 (d, 1H), 7.27 (m, 2H), 7.17 (m, 1H), 7.10 (d, 2H), 4.97 (m, 1H), 3.37 (s, 3H), 2.21 (m, 1H), 1.93 (m, 1H), 1.39 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 311.3 (MH⁺), t_R = 0.98 min (method A).

Compound 10: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(2,2,2-trifluoroethoxy)-pyridin-3-yl]-ethyl}-amide



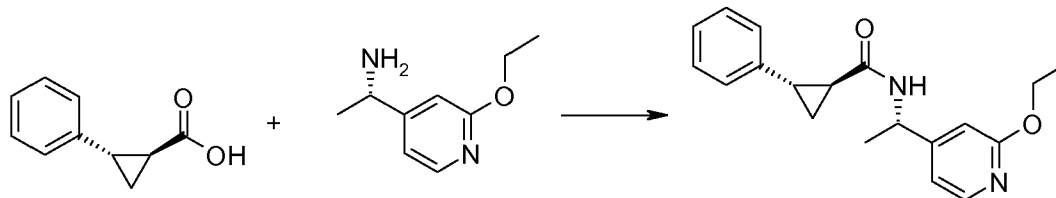
Prepared analogously to **Compound 1** using **IM46** and **IM27**. Yield = 0.695 g (50%). ¹H NMR (500 MHz, DMSO) δ 8.62 (d, 1H), 8.12 (s, 1H), 7.73 (d, 1H), 7.27 (m, 2H), 7.15 (m, 1H), 7.10 (d, 2H), 6.95 (d), 4.97 (m, 3H), 2.20 (m, 1H), 1.91 (m, 1H), 1.37 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 365.3 (MH⁺), t_R = 1.78 min (method A).

Compound 11: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-ethyl}-amide



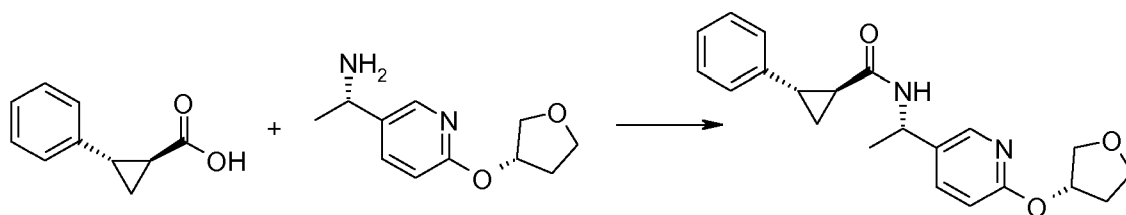
Prepared analogously to **Compound 1** using **IM46** and **IM28**. Yield = 0.758 g (30%). ¹H NMR (500 MHz, DMSO) δ 8.57 (d, 1H), 8.08 (s, 1H), 7.65 (d, 1H), 7.26 (m, 2H), 7.17 (m, 1H), 7.10 (d, 2H), 6.78 (d, 1H), 4.92 (m, 2H), 4.32 (m, 2H), 3.62 (m, 2H), 3.27 (s, 3H), 2.20 (m, 1H), 1.89 (m, 1H), 1.37 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 341.0 (MH⁺), t_R = 1.33 min (method A).

Compound 12: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2-ethoxy-pyridin-4-yl)-ethyl]-amide



Prepared analogously to **Compound 1** using **IM46** and **IM29**. Yield = 0.11 g (48%). ¹H NMR (500 MHz, DMSO) δ 8.55 (d, 1H), 8.06 (s, 1H), 7.30 (m, 2H), 7.19 (m, 1H), 7.14 (m, 2H), 6.90 (d, 1H), 6.67 (d, 1H), 4.88 (m, 1H), 4.26 (m, 2H), 2.20 (m, 1H), 1.96 (m, 1H), 1.40-1.27 (m, 7H), 1.22 (m, 1H). LC-MS (m/z) 311.4 (MH⁺), t_R = 1.36 min (method A).

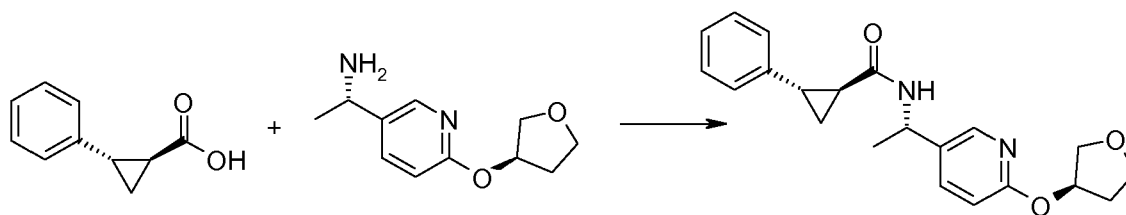
Compound 13: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid ((*S*)-1-{6-[(*S*)-(tetrahydrofuran-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide



- 5 Prepared analogously to **Compound 1** using **IM46** and **IM30**. Yield = 0.983 g (62%). ¹H-NMR (500 MHz, DMSO) δ 8.55 (d, 1H), 8.09 (s, 1H), 7.64 (d, 1H), 7.27 (m, 2H), 7.16 (m, 1H), 7.11 (d, 2H), 6.78 (d, 1H), 5.48 (m, 1H) 4.96 (m, 1H), 3.92 (m, 1H), 3.85 (m, 1H), 3.74 (m, 2H), 2.21 (m, 2H), 1.95 (m, 2H), 1.37 (m, 4H), 1.19 (m, 1H). LC-MS (m/z) 353.3 (MH⁺), t_R = 1.45 min (method A).

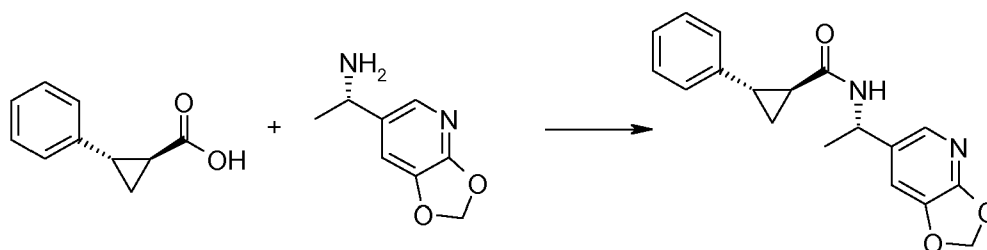
10

Compound 14: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid ((*S*)-1-{6-[(*R*)-(tetrahydrofuran-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide



- 15 Prepared analogously to **Compound 1** using **IM46** and **IM31**. Yield = 0.696 g (62%). ¹H-NMR (500 MHz, DMSO) δ 8.56 (d, 1H), 8.08 (s, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.15 (m, 1H), 7.10 (d, 2H), 6.78 (d, 1H), 5.47 (m, 1H) 4.92 (m, 1H), 3.91 (m, 1H), 3.84 (m, 1H), 3.73 (m, 2H), 2.20 (m, 2H), 1.95 (m, 2H), 1.37 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 353.3 (MH⁺), t_R = 1.45 min (method A).

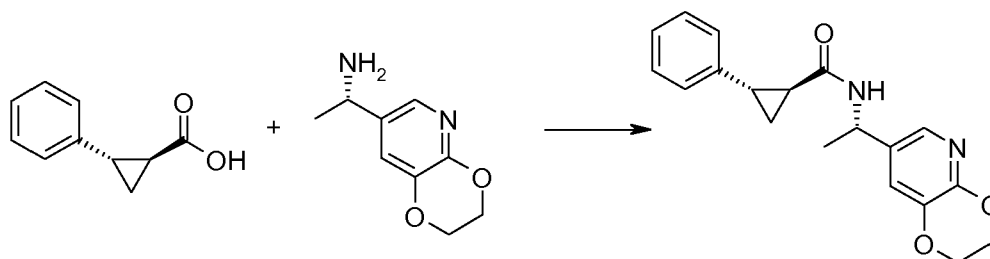
- 20 **Compound 15:** (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid ((*S*)-1-[1,3]dioxolo[4,5-*b*]pyridin-6-yl-ethyl)-amide



Prepared analogously to **Compound 1** using **IM46** and **IM32**. Yield = 0.572 g (42%). ¹H-NMR (500 MHz, DMSO) δ 8.54 (d, 1H), 7.52 (s, 1H), 7.27 (m, 2H), 7.20-7.15 (m, 2H), 7.10 (d, 2H),

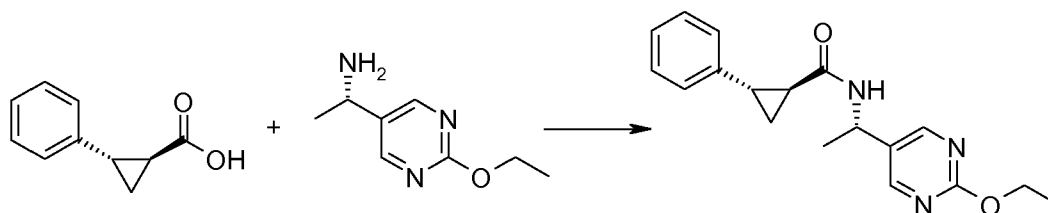
6.11 (s, 2H), 4.91 (m, 1H), 2.20 (m, 1H), 1.88 (m, 1H), 1.35 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 311.1 (MH⁺), t_R = 0.61 min (method B).

Compound 16: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl)-ethyl]-amide



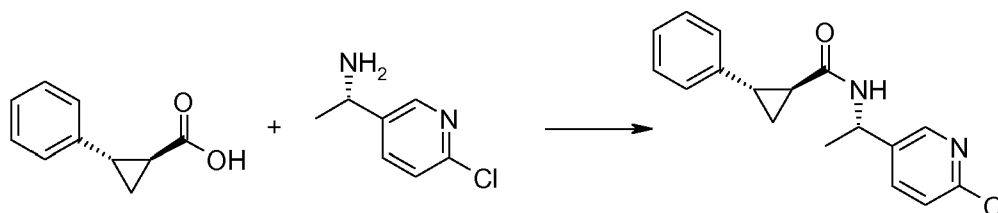
Prepared analogously to **Compound 1** using **IM46** and **IM33**. Yield = 0.877 g (39%). ¹H-NMR (500 MHz, DMSO) δ 8.52 (d, 1H), 7.68 (s, 1H), 7.27 (m, 2H), 7.22 (s, 1H), 7.18 (m, 1H), 7.10 (d, 2H), 4.92 (m, 1H), 4.37 (d, 2H), 4.22 (d, 2H), 2.20 (m, 1H), 1.90 (m, 1H), 1.35 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 325.5 (MH⁺), t_R = 1.28 min (method A).

Compound 17: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(2-ethoxy-pyrimidin-5-yl)-ethyl]-amide



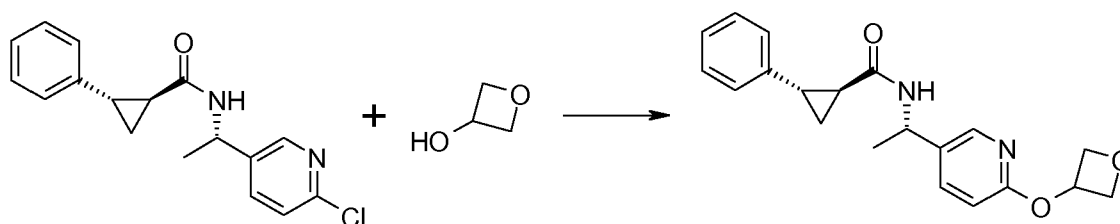
Prepared analogously to **Compound 1** using **IM46** and **IM34**. Yield = 0.195 g (32%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.52 (s, 2H), 7.26 (m, 2H), 7.16 (s, 1H), 7.10 (d, 2H), 4.92 (m, 1H), 4.32 (m, 2H), 2.20 (m, 1H), 1.88 (m, 1H), 1.40 (d, 3H), 1.35 (m, 1H), 1.31 (t, 3H), 1.20 (m, 1H). LC-MS (m/z) 312.2 (MH⁺), t_R = 0.62 min (method B).

Compound 18: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-chloro-pyridin-3-yl)-ethyl]-amide



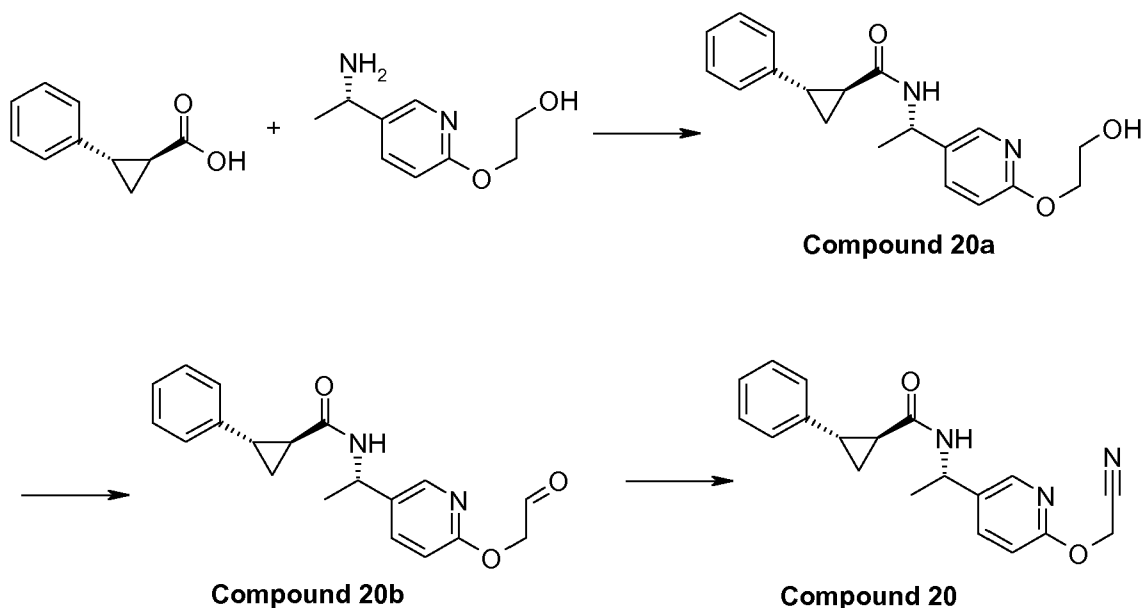
Prepared analogously to **Compound 1** using **IM46** and commercially available (S)-1-(6-Chloro-pyridin-3-yl)-ethylamine (Aurora building blocks catalogue nr A06.814.555). Yield = 1.40 g (71%). ¹H-NMR (500 MHz, DMSO) δ 8.68 (d, 1H), 8.36 (s, 1H), 7.78 (d, 1H), 7.48 (d, 1H), 7.28 (m, 2H), 7.18 (m, 1H), 7.11 (d, 2H), 4.99 (m, 1H), 2.20 (m, 1H), 1.92 (m, 1H), 1.37 (m, 4H), 1.20 (m, 1H). LC-MS (m/z) 301.2 and 303.1 (MH⁺), t_R = 0.67 min (method B).

Compound 19: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-[6-(oxetan-3-yloxy)-pyridin-3-yl]-ethyl]-amide



(1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-chloro-pyridin-3-yl)-ethyl]-amide (**Compound 18**) (2.00 g, 6.65 mmol) was dissolved in DMF (50 ml). Oxetan-3-ol (4.00 g, 54 mmol) and dicesium carbonate (16.2 g, 49.9 mmol) were added and the mixture was heated at 100 °C ON. The mixture was poured out into brine and extracted with EtOAc. The organic layer was washed with brine, dried (MgSO₄) and was filtered and then evaporated to dryness. The residue was transferred to a silica gel column and eluted with EtOAc/heptanes 1:1 to give **Compound 19** as a solid. This solid was dissolved in a mixture of THF (10 ml), EtOAc (20 mL) and heptanes (10 ml). The mixture was concentrated to approx. 15 mL in vacuo and this solution was cooled in an ice/water bath. A white precipitate formed. The solids were collected by filtration and dried in vacuo to give the title compound as colorless crystals (0.097 g, 4%). ¹H-NMR (500 MHz, DMSO) δ 8.55 (d, 1H), 8.04 (s, 1H), 7.70 (d, 1H), 7.25 (m, 2H), 7.15 (m, 1H), 7.10 (d, 2H), 6.87 (d, 1H), 5.52 (m, 1H), 4.95 (m, 1H), 4.87 (m, 2H), 4.53 (m, 2H), 2.20 (m, 1H), 1.90 (m, 1H), 1.37 (m, 4H), 1.21 (m, 1H). LC-MS (m/z) 339.2 (MH⁺), t_R = 0.63 min (method B). Mp = 151-153 °C.

Compound 20: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-cyanomethoxy-pyridin-3-yl)-ethyl]-amide



Compound 20a was prepared analogously to **Compound 1** using **IM46** and **IM35** for the first step. Yield of **Compound 20a** = 1.50 g (71%). Pure on TLC (Eluent EtOAc, R_f = 0.5). This

material (1.50 g, 4.36 mmol) was dissolved in a mixture of DMSO (50 ml) and THF (50 ml) and 1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-Oxide (1.34 g, 4.8 mmol) was added and the mixture was stirred at rt overnight. The mixture was added to a mixture of brine and EtOAc and the phases were separated. The organic phases was dried over $MgSO_4$ and was ro-

tovaped. The crude product was purified by silica gel chromatography (Eluent EtOAc). Yield of **Compound 20b** = 1.08 g (72%). Pure on TLC (Eluent EtOAc, R_f = 0.7). This material (1.05

g, 3.24 mmol) was dissolved in THF (10 ml), and MeCN (50 ml) and added drop wise to a solution of 1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-Oxide (1.36 g, 4.86 mmol) in ammonia in water (13 M, 25 ml) and THF (5 ml) and MeCN (5 ml). The mixture was stirred at rt ON.

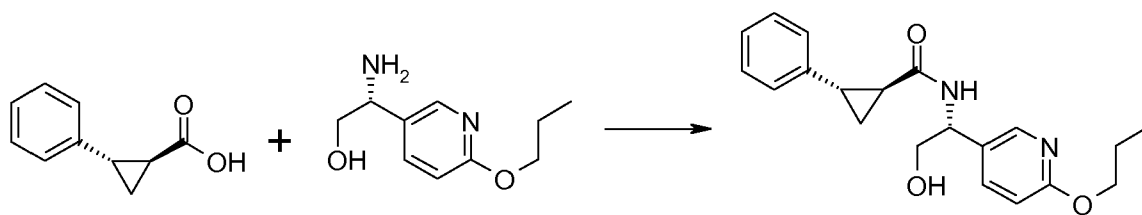
The organic phases was dried over $MgSO_4$ and was rotovaped. The crude product was purified by silica gel chromatography (Eluent EtOAc in heptanes 4:1) to give 177 mg impure prod-

uct. This material was THF (10 ml) and EtOAc (10 ml) and heptanes (10 ml) were added. The mixture was rotovaped until aprox 10 ml solvent was left and then cooled in an ice bath. A solid precipitated and was collected and dried in vac. Yield of **Compound 20** = 0.054 g (5%).

Pure on LCMS and H-NMR. Mp = 163-165 C. LC-MS (m/z) 322.1 (MH^+), t_R = 1.03 min

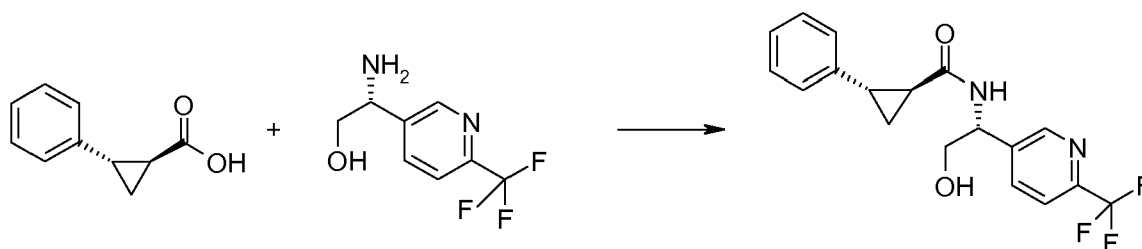
(method A). 1H -NMR (500 MHz, DMSO) δ 8.60 (d, 1H), 8.17 (s, 1H), 7.75 (d, 1H), 7.27 (m, 2H), 7.17 (m, 1H), 7.11 (d, 2H), 6.95 (d, 1H), 5.19 (s, 2H), 4.97 (m, 1H), 2.21 (m, 1H), 1.92 (m, 1H), 1.38 (m, 4H), 1.21 (m, 1H).

Compound 21: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide



Triethylamine (0.384 mL, 2.75 mmol) was added to a mixture of *trans*-2-phenyl-1-cyclopropanecarboxylic acid **IM46** (223 mg, 1.38 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (522 mg, 1.38 mmol) suspended in DMF (2mL) in a small vial. The vial was vigorously agitated for 30 seconds and then left for 5 minutes. This mixture was added drop wise to (*R*)-2-Amino-2-(6-propoxy-pyridin-3-yl)-ethanol **IM36** (270 mg, 1.4 mmol) dissolved in DMF (3 mL). After 1 h the mixture was poured into a mixture of EtOAc (40 mL) and brine (20 mL). The organic layer was dried over MgSO₄ and evaporated to dryness. Flash chromatography (silica, 10-100% EtOAc in heptanes) gave the title compound as a white solid (0.134 g, 29%). LC-MS (*m/z*) 341.0 (MH⁺), *t_R* = 1.52 min (method A). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, *J* = 8.2 Hz, 1H), 8.04 (br s, 1H), 7.64 – 7.57 (m, 1H), 7.30 – 7.23 (m, 2H), 7.19 – 7.14 (m, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.96 – 4.90 (m, 1H), 4.88 – 4.80 (m, 1H), 4.16 (t, *J* = 6.7 Hz, 2H), 3.61 – 3.49 (m, 2H), 2.23 – 2.15 (m, 1H), 2.04 – 1.95 (m, 1H), 1.74 – 1.64 (m, 2H), 1.40 – 1.32 (m, 1H), 1.23 – 1.13 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

Compound 22: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide

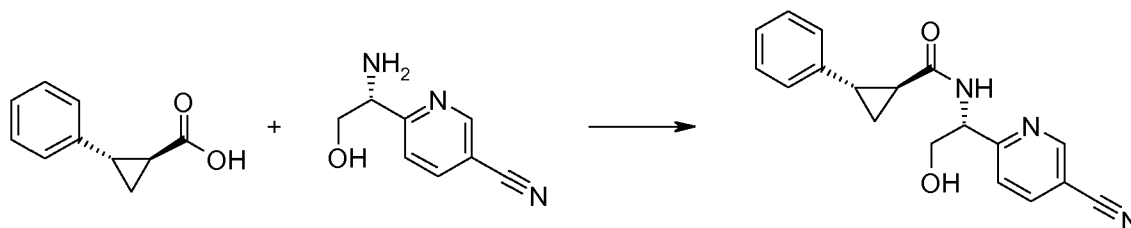


N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.39 g, 2.03 mmol) and 1-hydroxybenzotriazole (0.366 g, 2.71 mmol) were added to a stirred mixture of **IM46** (0.22 g, 1.36 mmol) and commercially available (*R*)-2-amino-2-(6-trifluoromethyl-pyridin-3-yl)-ethanol hydrochloride (Supplier Netchem Inc., Catalog No 517882) (0.494 g, 2.03 mmol) and *N,N*-diisopropylethylamine (0.472 ml, 2.71 mmol) in THF (20 ml). The solution was stirred at rt overnight. Water was added and the mixture was extracted with EtOAc (3x80 ml). The combined organic phases were washed with brine, dried over MgSO₄, filtered and the solvent was evaporated of in vac. The crude product was purified by silica gel chromatography

(EtOAc in heptanes 10:1). Yield of **Compound 22** 475 mg (78%). ¹H-NMR (500 MHz, DMSO) δ 8.77 (d, 1H), 8.74 (s, 1H), 8.00 (d, 1H), 7.88 (d, 1H), 7.27 (m, 2H), 7.18 (m, 1H), 7.13 (d, 2H), 5.04 (m, 2H), 3.64 (m, 2H), 2.22 (m, 1H), 2.07 (m, 1H), 1.37 (m, 1H), 1.37 (m, 1H), 1.23 (m, 1H). LC-MS (m/z) 351.1 (MH⁺), t_R = 1.51 min (method A).

5

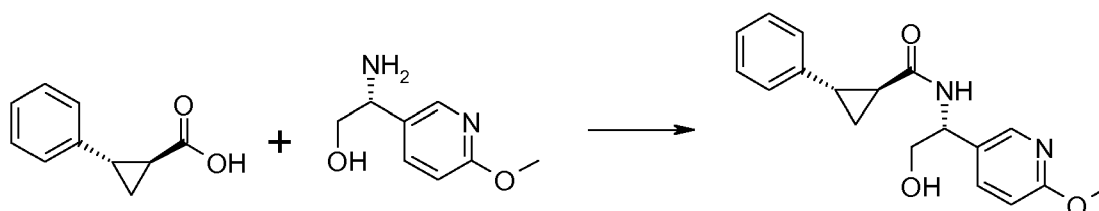
Compound 23: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-1-(5-cyano-pyridin-2-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 22** using **IM46** and commercially available 6-[(*R*)-1-amino-2-hydroxy-ethyl]-nicotinonitrile (Supplier Netchem Inc., Catalog No 549885). Yield of **Compound 23** 230 mg (61%). ¹H-NMR (500 MHz, DMSO) δ 8.97 (s, 1H), 8.72 (d, 1H), 8.26 (d, 1H), 7.52 (d, 1H), 7.27 (m, 2H), 7.18 (t, 1H), 7.11 (d, 2H), 5.05-4.95 (m, 2H), 3.70 (m, 2H), 2.20 (m, 1H), 2.17 (m, 1H), 1.36 (m, 1H), 1.20 (m, 1H). LC-MS (m/z) 308.1 (MH⁺), t_R = 1.21 min (method A).

15

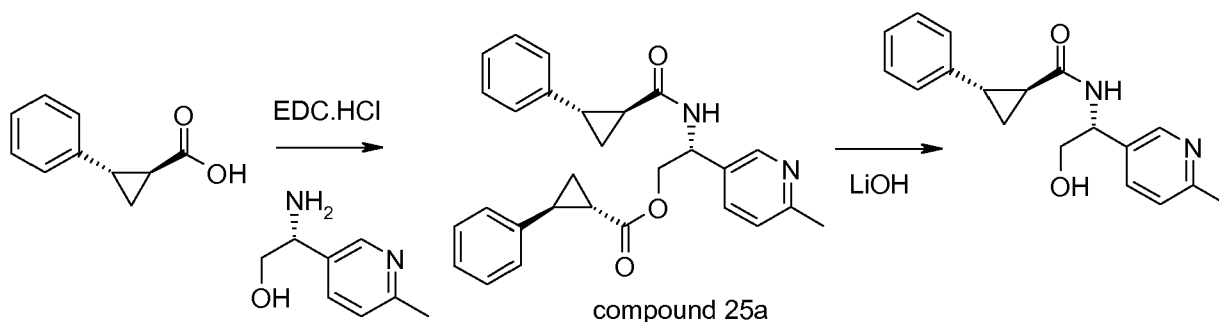
Compound 24: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-methoxy-pyridin-3-yl)-ethyl]-amide



Prepared analogously to **Compound 22** using **IM46** and commercially available (*R*)-2-Amino-2-(6-methoxy-pyridin-3-yl)-ethanol (Supplier Netchem Inc., Catalog No 517926). Yield of **Compound 24** = 763 mg (22%). ¹H-NMR (500 MHz, DMSO) δ 8.53 (d, 1H), 8.09 (s, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.15 (m, 1H), 7.12 (m, 2H), 6.77 (d, 1H), 4.95 (m, 2H), 4.85 (m, 2H), 3.83 (s, 3H), 3.57 (m, 2H), 2.21 (m, 1H), 2.00 (m, 1H), 1.37 (m, 1H), 1.19 (m, 1H). LC-MS (m/z) 313.1 (MH⁺), t_R = 1.53 min (method A).

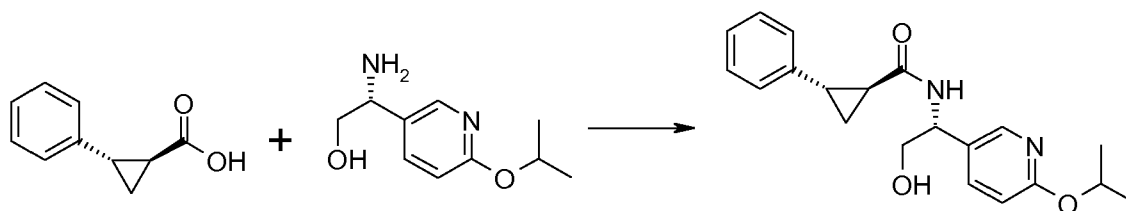
25

Compound 25: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-methyl-pyridin-3-yl)-ethyl]-amide



5 N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.316 g, 1.65 mmol) and 1-hydroxybenzotriazole (0.223 g, 1.65 mmol) were added to a stirred mixture of **IM46** (0.18 g, 1.1 mmol) and commercially available (*R*)-2-Amino-2-(6-methyl-pyridin-3-yl)-ethanol dihydrochloride (Supplier Netchem Inc., Catalog No 549945) (0.128 g, 1.21 mmol) and N,N-diisopropylethylamine (0.575 ml, 3.30 mmol) in THF (10 ml). The solution was stirred at rt overnight. Water was added and the mixture was extracted with EtOAc. The organic phase
10 was rotovaped to produce 140 mg of Compound 25a. LC-MS (*m/z*) 441.4 (*MH*⁺), *t_R* = 1.44 min (method A). Compound 25a was dissolved in THF and LiOH (1M) was added and the mixture was stirred 30 min. A solid precipitated and was isolated by filtration and dried in vac. Yield of **Compound 25** = 110 mg (34%). ¹H-NMR (500 MHz, DMSO) δ 8.53 (d, 1H), 8.09 (s, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.15 (m, 1H), 7.12 (m, 2H), 6.77 (d, 1H), 4.95 (m, 2H), 4.85
15 (m, 2H), 3.83 (s, 3H), 3.57 (m, 2H), 2.21 (m, 1H), 2.00 (m, 1H), 1.37 (m, 1H), 1.19 (m, 1H). LC-MS (*m/z*) 297.3 (*MH*⁺), *t_R* = 0.78 min (method A).

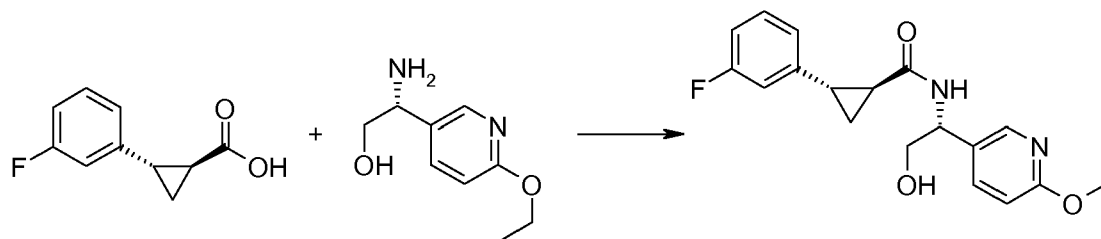
Compound 26: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide



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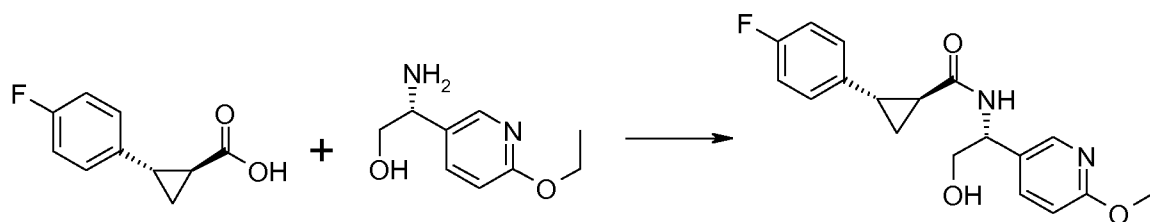
Prepared analogously to **Compound 21** using **IM46** and **IM37**. Yield of **Compound 26** = 667 mg (77%). ¹H-NMR (600 MHz, DMSO) δ 8.52 (d, 1H), 8.03 (s, 1H), 7.60 (d, 1H), 7.25 (m, 2H), 7.15 (m, 1H), 7.10 (d, 2H), 6.67 (d, 1H), 5.20 (m, 1H), 4.92 (t, 1H), 4.83 (m, 1H), 3.55 (m, 2H), 2.20 (m, 1H), 2.00 (m, 1H), 1.35 (m, 1H), 1.24 (d, 6H), 1.19 (m, 1H). LC-MS (*m/z*) 341.0
25 (*MH*⁺), *t_R* = 1.45 min (method A).

Compound 27: (1*S*,2*S*)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



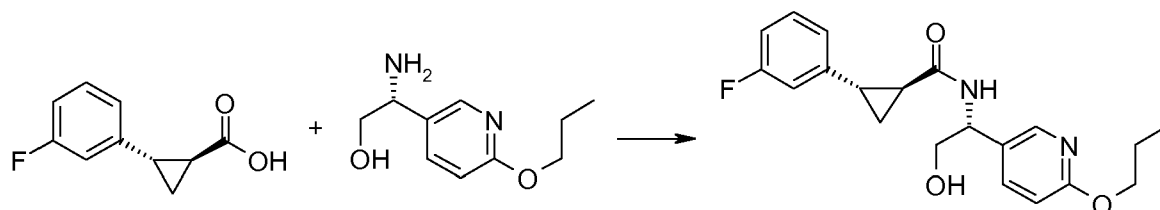
Prepared analogously to **Compound 21** using **IM47** and **IM38**. Yield of **Compound 27** = 90 mg (19%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.05 (s, 1H), 7.62 (m, 1H), 7.28 (m, 1H), 6.97 (m, 3H), 6.73 (d, 1H), 4.83 (m, 1H), 4.24 (m, 2H), 3.55 (m, 2H), 2.22 (m, 1H), 2.03 (m, 1H), 1.37 (m, 1H), 1.28 (t, 3H), 1.22 (m, 1H). LC-MS (*m/z*) 345.0 (MH⁺), *t_R* = 0.63 min (method B).

10 **Compound 28:** (1*S*,2*S*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 21** using **IM48** and **IM38**. Yield of **Compound 28** = 93 mg white solid. (54%). ¹H-NMR (600 MHz, DMSO) δ 8.56 (d, 1H), 8.07 (s, 1H), 7.62 (m, 1H), 7.18 (m, 2H), 7.12 (m, 2H), 6.77 (d, 1H), 4.93 (t, 1H), 4.83 (m, 1H), 4.25 (dd, 2H), 3.52 (m, 2H), 2.27 (m, 1H), 1.97 (m, 1H), 1.30 (m, 4H), 1.15 (m, 1H). LC-MS (*m/z*) 345.0 (MH⁺), LC-MS (*m/z*) 345.0 (MH⁺), *t_R* = 1.36 min (method A).

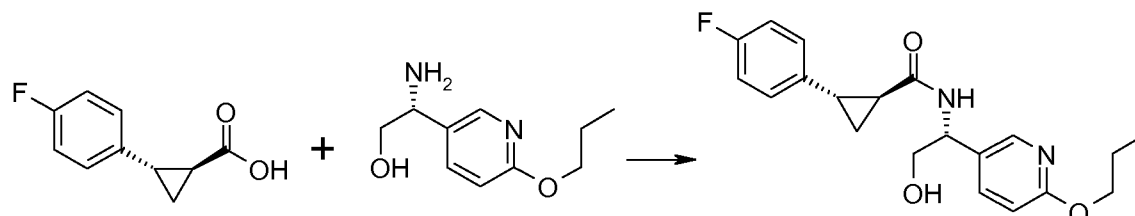
20 **Compound 29:** (1*S*,2*S*)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide



Prepared analogously to **Compound 21** using **IM47** and **IM36**. Yield = 150 mg (30%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.03 (s, 1H), 7.62 (d, 1H), 7.29 (m, 1H), 6.95 (m, 3H),

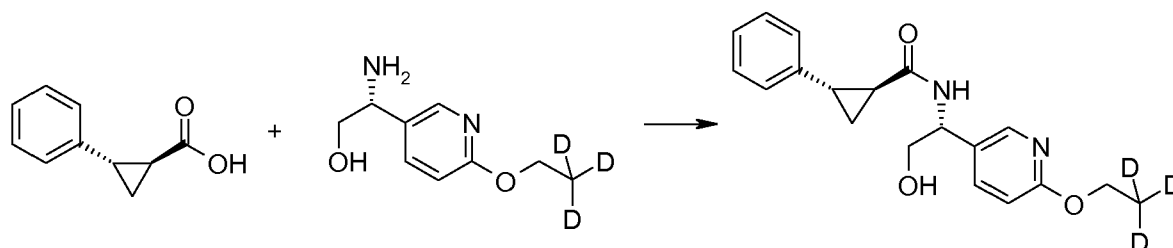
6.74 (d, 1H), 4.93 (m, 1H), 4.84 (m, 1H), 4.16 (t, 2H), 3.55 (m, 2H), 2.23 (m, 1H), 2.03 (m, 1H), 1.68 (m, 2H), 1.37 (m, 1H), 1.25 (m, 1H), 0.93 (t, 3H). LC-MS (m/z) 359.1 (MH⁺), t_R = 1.57 min (method A).

- 5 **Compound 30:** (1*S*,2*S*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide



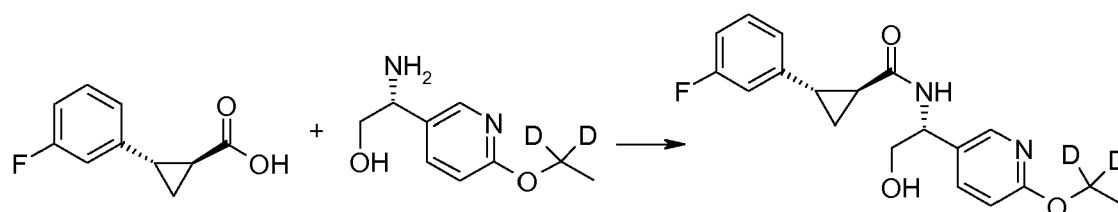
Prepared analogously to **Compound 21** using **IM48** and **IM36**. Yield 176 mg (36%). ¹H-NMR (600 MHz, DMSO) δ 8.52 (d, 1H), 8.05 (s, 1H), 7.63 (d, 1H), 7.14 (m, 2H), 7.09 (m, 2H), 6.74 (d, 1H), 4.92 (t, 1H), 4.85 (m, 1H), 4.15 (t, 2H), 3.55 (m, 2H), 2.22 (m, 1H), 1.97 (m, 1H), 1.70 (m, 2H), 1.34 (m, 1H), 1.18 (m, 1H), 0.92 (t, 3H).

Compound 31: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-1-(6-(2,2,2-*d*₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 21** using **IM46** and **IM40**. Yield = 785 mg (66%). ¹H-NMR (600 MHz, CDCl₃) δ 8.62 (s, 1H), 7.52 (d, 1H), 7.26 (m, 2H), 7.20 (m, 1H), 7.08 (d, 2H), 6.71 (d, 1H), 6.27 (m, 1H), 5.05 (m, 1H), 4.31 (s, 2H), 3.91 (m, 2H), 2.51 (m, 2H), 1.67 (m, 2H), 1.31 (m, 1H). LC-MS (m/z) 330.3 (MH⁺), t_R = 1.32 min (method A).

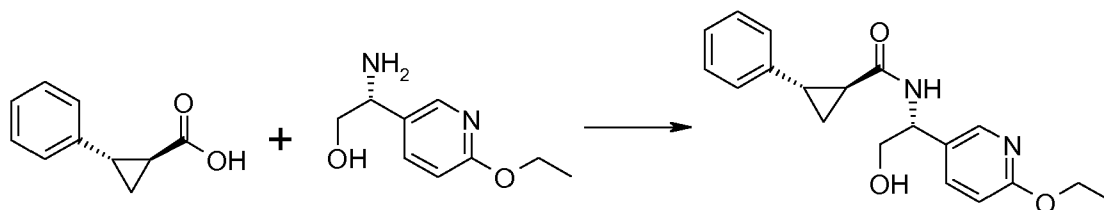
Compound 32: (1*S*,2*S*)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-1-(6-(1,1-*d*₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 21** using **IM47** and **IM41**. Yield = 104 mg (44%). ¹H-NMR (600 MHz, DMSO) δ 8.52 (d, 1H), 8.03 (s, 1H), 7.61 (m, 1H), 7.29 (m, 1H), 6.97 (m, 3H), 6.72 (d, 1H), 4.93 (m, 1H), 4.85 (m, 1H), 3.55 (m, 2H), 2.22 (m, 1H), 2.02 (m, 1H), 1.37 (m, 1H), 1.25 (m, 4H). LC-MS (m/z) 347.2 (MH⁺), t_R = 0.64 min (method A).

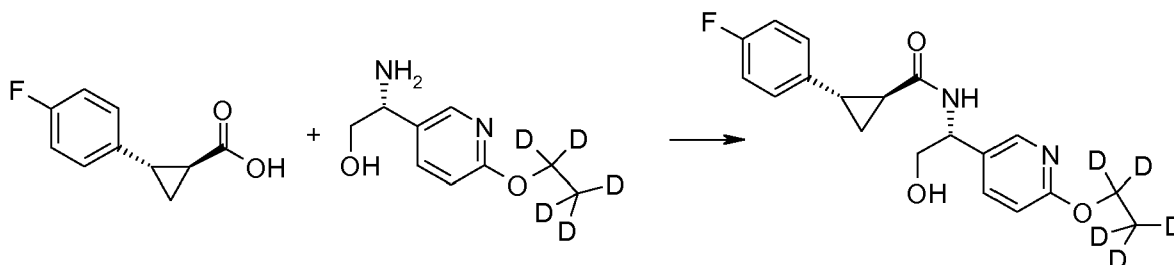
5

Compound 33: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 22** using **IM46** and **IM38**. Yield = 90 mg (28%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.06 (s, 1H), 7.52 (m, 1H), 7.26 (m, 2H), 7.16 (m, 1H), 7.10 (d, 2H), 6.73 (d, 1H), 4.95 (t, 1H), 4.87 (m, 1H), 4.25 (m, 2H), 3.55 (m, 2H), 2.20 (m, 1H), 2.02 (m, 1H), 1.36 (m, 1H), 1.28 (t, 3H), 1.20 (m, 1H). LC-MS (m/z) 327.4 (MH⁺), t_R = 0.57 min (method B).

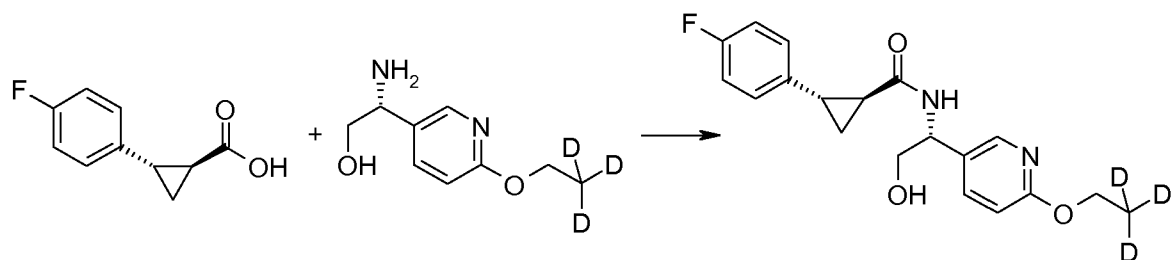
15 **Compound 34:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1,2,2,2-d₅)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 21** using **IM48** and **IM39**. Yield = 130 mg (41%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.06 (s, 1H), 7.62 (m, 1H), 7.14 (m, 2H), 7.10 (m, 2H), 6.73 (d, 1H), 4.95 (br s, 1H), 4.84 (m, 1H), 3.55 (m, 2H), 2.22 (m, 1H), 1.96 (m, 1H), 1.34 (m, 1H), 1.18 (m, 1H). LC-MS (m/z) 350.2 (MH⁺), t_R = 1.41 min (method A).

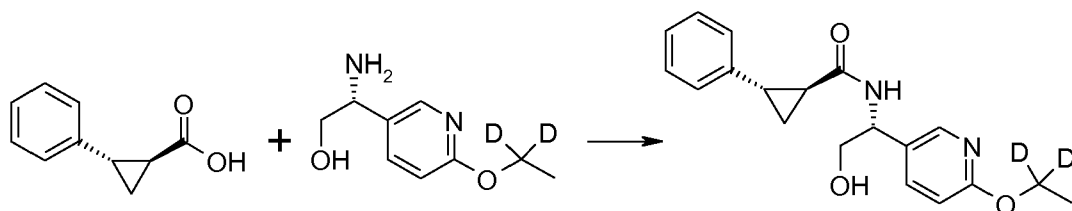
20

Compound 35: (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



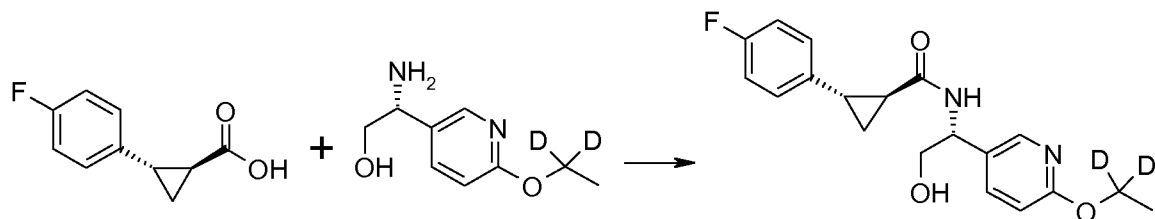
Prepared analogously to **Compound 21** using **IM48** and **IM40**. Yield = 144 mg (41%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.08 (s, 1H), 7.63 (m, 1H), 7.13 (m, 2H), 7.10 (m, 2H), 6.73 (d, 1H), 4.97 (br s, 1H), 4.86 (m, 1H), 4.24 (s, 2H), 3.57 (m, 2H), 2.23 (m, 1H), 1.97 (m, 1H), 1.37 (m, 1H), 1.20 (m, 1H). LC-MS (m/z) 347.9 (MH⁺), t_R = 1.39 min (method A).

Compound 36: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



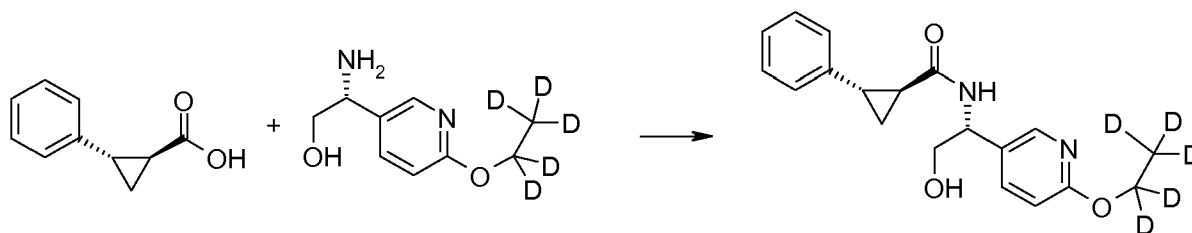
Prepared analogously to **Compound 21** using **IM46** and **IM41**. Yield = 148 mg (67%). ¹H-NMR (600 MHz, DMSO) δ 8.52 (d, 1H), 8.05 (s, 1H), 7.61 (d, 1H), 7.50 (m, 2H), 7.15 (m, 1H), 7.10 (d, 2H), 6.72 (d, 1H), 4.94 (t, 1H), 4.85 (m, 1H), 3.55 (m, 2H), 2.18 (m, 1H), 1.97 (m, 1H), 1.35 (m, 1H), 1.27 (s, 3H), 1.20 (m, 1H). LC-MS (m/z) 329.2 (MH⁺), t_R = 0.61 min (method B).

Compound 37: (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



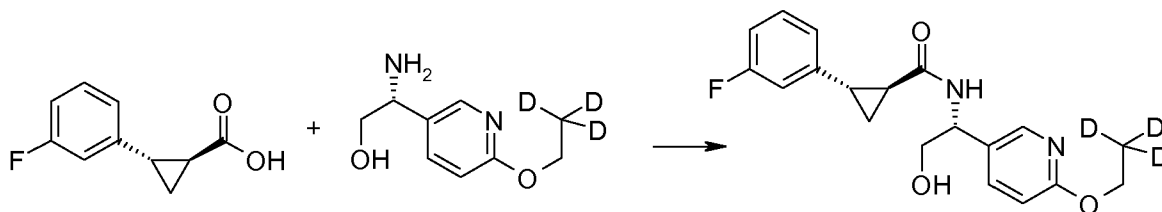
Prepared analogously to **Compound 21** using **IM48** and **IM41**. Yield = 123 mg (52%). ¹H-NMR (600 MHz, DMSO) δ 8.52 (d, 1H), 8.06 (s, 1H), 7.62 (m, 1H), 7.14 (m, 2H), 7.10 (m, 2H), 6.73 (d, 1H), 4.92 (t, 1H), 4.84 (m, 1H), 3.55 (m, 2H), 2.22 (m, 1H), 1.96 (m, 1H), 1.34 (m, 1H), 1.28 (s, 3H), 1.18 (m, 1H). LC-MS (m/z) 347.2 (MH⁺), t_R = 1.41 min (method B).

Compound 38: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-1-(6-(1,1,2,2,2-*d*₅)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



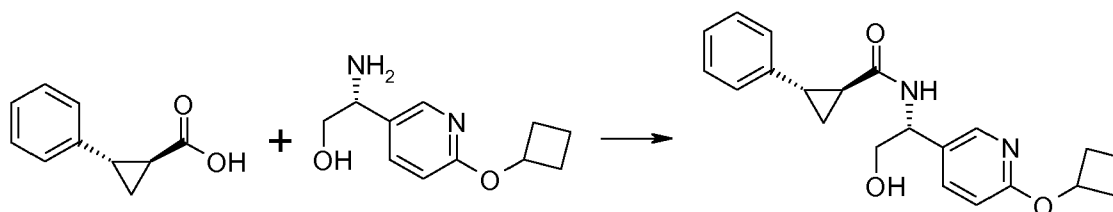
- 5 Prepared analogously to **Compound 21** using **IM46** and **IM39**. Yield = 98 mg (32%). ¹H-NMR (600 MHz, DMSO) δ 8.52 (d, 1H), 8.05 (s, 1H), 7.61 (d, 1H), 7.26 (t, 2H), 7.16 (t, 1H), 7.10 (d, 2H), 6.72 (d, 1H), 4.93 (t, 1H), 4.83 (m, 1H), 3.55 (m, 2H), 2.18 (m, 1H), 1.99 (m, 1H), 1.35 (m, 1H), 1.20 (m, 1H). LC-MS (m/z) 332.2 (MH⁺), t_R = 0.61 min (method B).

- 10 **Compound 39:** (1*S*,2*S*)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-1-(6-(2,2,2-*d*₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



- Prepared analogously to **Compound 21** using **IM47** and **IM40**. Yield = 101 mg (29%). ¹H-NMR (600 MHz, DMSO) δ 8.53 (d, 1H), 8.05 (s, 1H), 7.61 (d, 1H), 7.28 (m, 1H), 7.0-6.95 (m, 3H), 6.72 (d, 1H), 4.93 (t, 1H), 4.83 (m, 1H), 4.22 (s, 2H), 3.55 (m, 2H), 2.23 (m, 1H), 2.02 (m, 1H), 1.37 (m, 1H), 1.27 (m, 1H). LC-MS (m/z) 348.0 (MH⁺), t_R = 1.43 min (method A).
- 15

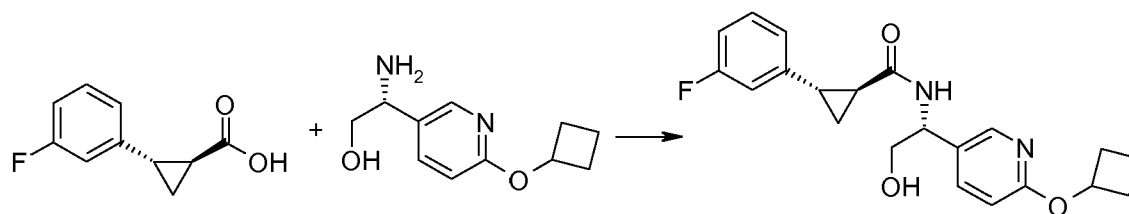
Compound 40: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



- 20 Prepared analogously to **Compound 21** using **IM46** and **IM44**. Yield = 53 mg (30%). ¹H-NMR (600 MHz, DMSO) δ 8.50 (d, 1H), 8.03 (s, 1H), 7.61 (d, 1H), 7.25 (m, 2H), 7.16 (m, 1H), 7.10 (m, 2H), 6.71 (d, 1H), 5.09 (m, 1H), 4.90 (t, 1H), 4.82 (m, 1H), 3.55 (m, 2H), 2.37 (m, 2H),

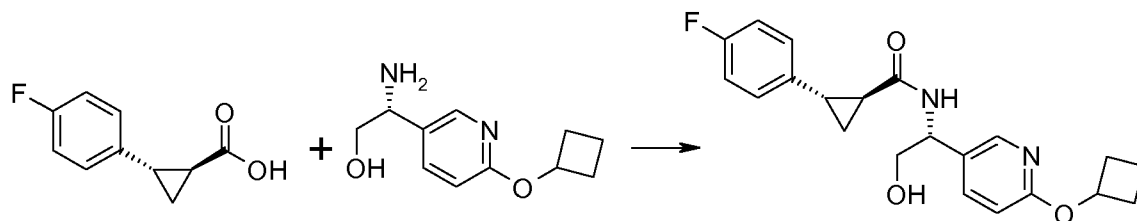
2.21 (m, 1H), 2.00 (m, 4H), 1.76 (m, 1H), 1.61 (m, 1H), 1.32 (m, 1H), 1.20 (m, 1H). LC-MS (m/z) 353.1 (MH⁺), t_R = 0.70 min (method B).

Compound 41: (1*S*,2*S*)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



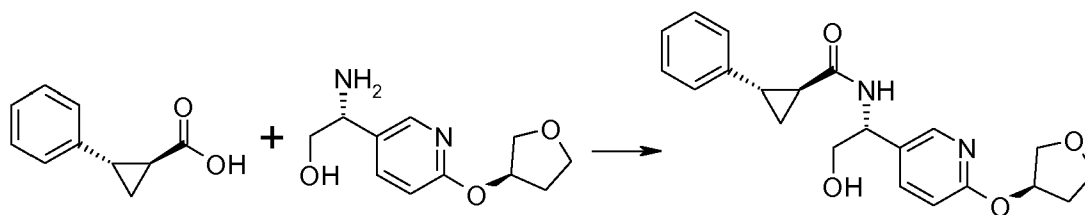
Prepared analogously to **Compound 21** using **IM47** and **IM44**. Yield = 38 mg (20%). ¹H-NMR (600 MHz, DMSO) δ 8.50 (d, 1H), 8.03 (s, 1H), 7.61 (d, 1H), 7.27 (m, 1H), 6.95 (m, 3H), 6.71 (d, 1H), 5.08 (m, 1H), 4.95 (br. s, 1H), 4.82 (m, 1H), 3.55 (m, 2H), 2.37 (m, 2H), 2.22 (m, 1H), 2.02 (m, 4H), 1.75 (m, 1H), 1.61 (m, 1H), 1.37 (m, 1H), 1.27 (m, 1H). LC-MS (m/z) 371.1 (MH⁺), t_R = 0.71 min (method B).

Compound 42: (1*S*,2*S*)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(*R*)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide



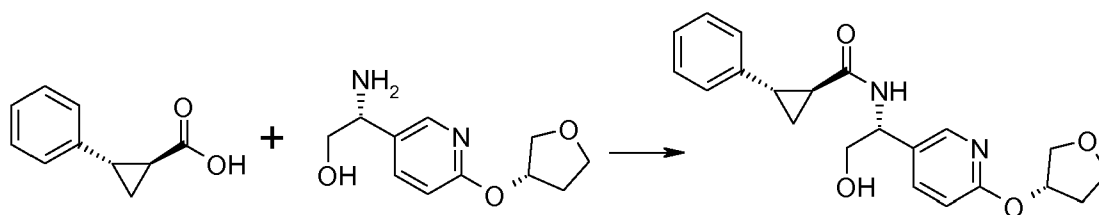
Prepared analogously to **Compound 21** using **IM48** and **IM44**. Yield = 84 mg (45%). ¹H-NMR (600 MHz, DMSO) δ 8.50 (d, 1H), 8.03 (s, 1H), 7.61 (d, 1H), 7.14 (m, 2H), 7.09 (m, 2H), 6.71 (d, 1H), 5.08 (m, 1H), 4.92 (t, 1H), 4.82 (m, 1H), 3.55 (m, 2H), 2.37 (m, 2H), 2.21 (m, 1H), 2.05-1.95 (m, 4H), 1.75 (m, 1H), 1.61 (m, 1H), 1.32 (m, 1H), 1.17 (m, 1H). LC-MS (m/z) 371.1 (MH⁺), t_R = 0.71 min (method B).

Compound 43: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-2-hydroxy-1-{6-[(*R*)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl]-amide



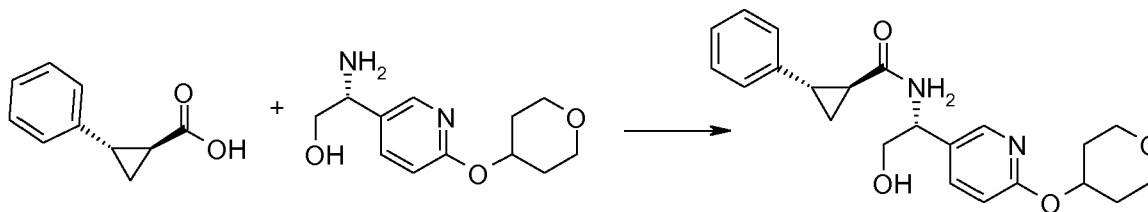
Prepared analogously to **Compound 21** using **IM46** and **IM43**. Yield = 1.34 g white solid (60%). ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.18-7.25 (m, 3 H), 7.04-7.06 (m, 2 H), 6.68-6.71 (m, 1 H), 6.36-6.39 (m, 1 H), 5.50-5.53 (m, 1 H), 5.04-5.05 (m, 1 H), 3.88-4.01 (m, 6 H), 2.48-2.50 (m, 1 H), 2.21-2.26 (m, 1 H), 2.11-2.13 (m, 1 H), 1.62-1.71 (m, 2 H), 1.27-1.31 (m, 1 H). LC-MS (*m/z*) 369.2 (MH⁺), *t_R* = 2.04 min (method WXE-AB01). [α]_D²⁰ = 178.6 (C=0.2, CHCl₃)

Compound 44: (1*S*,2*S*)-*N*-[(1*R*)-2-hydroxy-1-[6-[(3*S*)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide



Prepared analogously to **Compound 21** using **IM46** and **IM42**. Yield = 2.10 g white solid (50%). ¹H NMR (400 MHz, CDCl₃): δ 8.09 (m, 1 H), 7.52-7.55 (m, 1 H), 7.29 (m, 1 H), 7.25-7.27 (m, 1 H), 7.20-7.21 (m, 1 H), 7.17-7.19 (d, *J* = 7.2 Hz, 2 H), 6.70-6.73 (d, *J* = 8.8 Hz, 1 H), 6.34-6.36 (d, *J* = 7.2 Hz, 1 H), 5.50-5.53 (m, 1 H), 5.04-5.05 (d, *J* = 6.8 Hz, 1 H), 3.94-4.03 (m, 2 H), 3.85-3.91 (m, 4 H), 2.48-2.50 (m, 1 H), 2.21-2.26 (m, 1 H), 2.11-2.13 (m, 1 H), 1.62-1.71 (m, 2 H), 1.27-1.31 (m, 1 H). LC-MS (*m/z*) 369.2 (MH⁺), *t_R* = 2.03 min (method WXE-AB01). [α]_D²⁰ = 160.9 (C=0.21, CHCl₃).

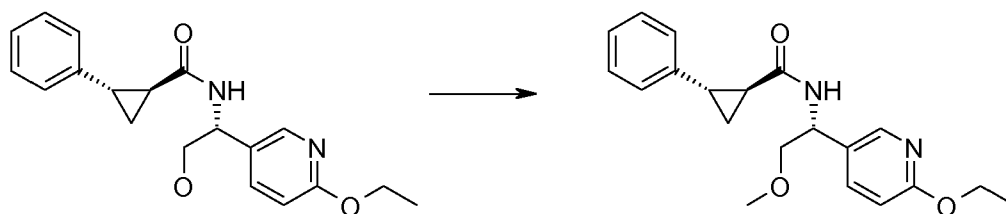
Compound 45: (1*S*,2*S*)-2-[(*Z*)-1-Methylene-penta-2,4-dienyl]-cyclopropanecarboxylic acid {(*R*)-2-hydroxy-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethyl}-amide



Prepared analogously to **Compound 1** using **IM46** and **IM45**. Yield = 2.5 g white solid (44%). ¹H NMR ((400 MHz, CDCl₃): δ 8.09 (s, 1 H), 7.52-7.55 (m, 1 H), 7.27-7.28 (m, 1 H), 7.25-7.26 (m, 1 H), 7.20 (m, 1 H), 7.06-7.08 (t, *J* = 4.2 Hz, 2 H), 6.70-6.72 (d, *J* = 8.4 Hz, 1 H), 6.34-6.36 (d, *J* = 7.2 Hz, 1 H), 5.18-5.21 (m, 1 H), 5.04-5.05 (d, *J* = 6.8 Hz, 1 H), 3.62-3.99 (m, 4 H),

3.56-3.62 (m, 2 H), 2.46-2.50 (m, 1 H), 2.01-2.06 (m, 2 H), 1.74-1.80 (m, 2 H), 1.62-1.70 (m, 2 H), 1.27-1.30 (m, 1 H). $[\alpha]_D^{20} = 144.3$ (c = 0.204 g/100mL, CHCl_3).

Compound 46: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-methoxy-ethyl]-amide

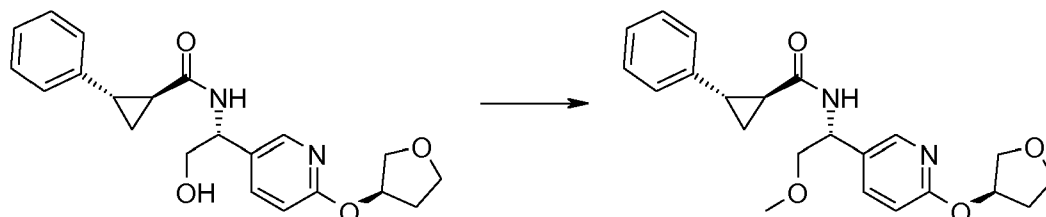


NaH (60 % suspension in mineral oil) (2.06 g, 51.5 mmol) was suspended in DMF and the reaction vessel was cooled in an ice bath. (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide (**Compound 33**) (15 g, 46 mmol) was dissolved in DMF (50 ml) and added drop wise to the sodium hydride suspension at 5-8 C over 20 minutes. The solution was stirred 30 minutes. Methyl iodide (3.30 ml, 53.0 mmol) dissolved in DMF (25 ml) was added drop wise at 5-12 C over 10 minutes and the mixture was stirred at 7-8 C for 30 minutes. The mixture was added to a brine solution and extracted with EtOAc. The organic layer was washed with more brine, dried (MgSO_4) filtered and the solvent was evaporated off. The crude product was purified by silica gel chromatography (eluent EtOAc in heptanes 4:1). The fractions that contained the product was collected and the solvent was removed in vac. The residue was redissolved in THF (50 ml) EtOAc (100 ml) and heptanes (25 ml). The mixture was concentrated until 40 ml remained and cooled in ice. A white solid precipitated and was collected by filtration. Yield: 6.75 g (43%) of **Compound 46**.

LC-MS (m/z) 341.2 (MH^+), $t_R = 0.64$ min (method B).

$^1\text{H-NMR}$ (500 MHz, DMSO) δ 8.62 (d, 1H), 8.08 (br s, 1H), 7.63 (d, 1H), 7.27 (m, 2H), 7.17 (m, 1H), 7.10 (d, 2H), 6.74 (d, 1H), 5.05 (m, 1H), 4.26 (m, 2H), 3.55 – 3.46 (m, 2H), 3.26 (s, 3H), 2.20 (m, 1H), 1.99 (m, 1H), 1.38 (m, 1H), 1.29 (t, 3H), 1.20 (m, 1H).

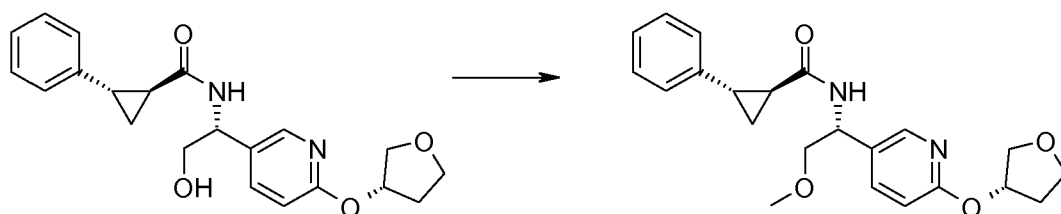
Compound 47: (1S,2S)-N-[(1R)-2-methoxy-1-[6-[(3R)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide



Prepared analogously to **Compound 46** using **Compound 43** (0.90 g).

Yield = 490 mg (53%) as a solid. ^1H NMR (400 MHz, CDCl_3): δ 8.12 (d, $J = 2.4$ Hz, 1 H), 7.54-7.57 (m, 1 H), 7.25-7.28 (m, 2 H), 7.18-7.21 (m, 1 H), 7.05-7.07 (m, 2 H), 6.68-6.70 (d, $J = 8.8$ Hz, 1 H), 6.37-6.39 (d, $J = 8.0$ Hz, 1 H), 5.51-5.54 (m, 1 H), 5.10-5.12 (m, 1 H), 3.87-4.04 (m, 4 H), 3.66-3.69 (m, 1 H), 3.60-3.63 (m, 1 H), 3.38 (s, 3 H), 2.45-2.46 (m, 1 H), 2.21-2.26 (m, 1 H), 1.60-1.68 (m, 2 H), 1.25-1.28 (m, 1 H). LC-MS: $t_R = 0.53$ min (method B), $m/z = 383.2$ [$M + H$] $^+$. $[\alpha]_D^{20} = 188.2$ ($C=0.176$, CHCl_3).

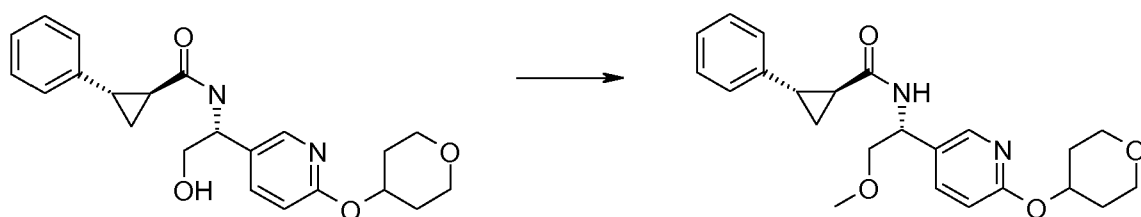
Compound 48: (1*S*,2*S*)-*N*-[(1*R*)-2-methoxy-1-[6-[(3*S*)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide



Prepared analogously to **Compound 46** using **Compound 44** (841 mg).

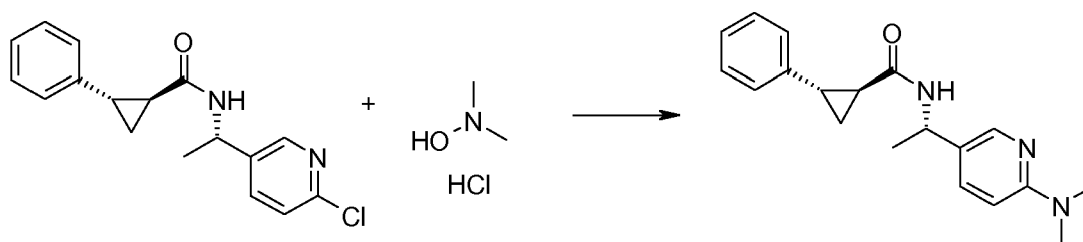
Yield = 645 mg (44%) as a solid. ^1H NMR (400 MHz, CDCl_3): δ 8.10-8.11 (d, $J = 2.4$ Hz, 1 H), 7.54-7.57 (m, 1 H), 7.25-7.28 (m, 2 H), 7.18-7.21 (m, 1 H), 7.05-7.07 (m, 2 H), 6.68-6.70 (d, $J = 8.8$ Hz, 1 H), 6.37-6.39 (d, $J = 8.0$ Hz, 1 H), 5.51-5.54 (m, 1 H), 5.10-5.12 (m, 1 H), 3.87-4.04 (m, 4 H), 3.66-3.69 (m, 1 H), 3.60-3.63 (m, 1 H), 3.38 (s, 3 H), 2.45-2.46 (m, 1 H), 2.21-2.26 (m, 1 H), 1.60-1.68 (m, 2 H), 1.25-1.28 (m, 1 H). LC-MS: $t_R = 0.62$ min (method B), $m/z = 383.2$ [$M + H$] $^+$. $[\alpha]_D^{20} = 162.5$ ($C=0.225$, CHCl_3).

Compound 49: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid {(*R*)-2-methoxy-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethyl}-amide



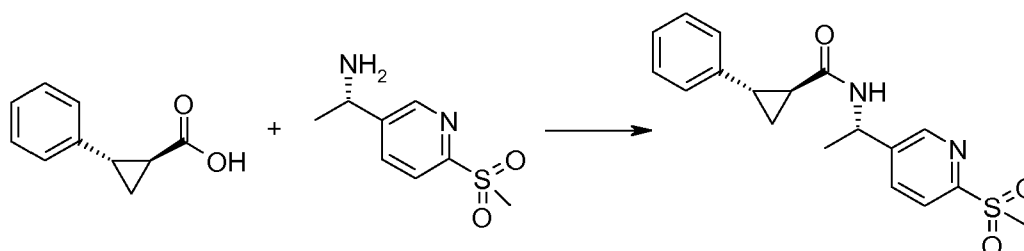
Prepared analogously to **Compound 46** using **Compound 45**. Yield = 343 mg (20%) as a solid. ^1H NMR (400 MHz, CDCl_3): δ 8.10-8.11 (d, $J = 2.4$ Hz, 1 H), 7.54-7.57 (m, 1 H), 7.25-7.29 (m, 2 H), 7.18-7.21 (m, 1 H), 7.05-7.07 (m, 2 H), 6.66-6.68 (t, $J = 4.2$ Hz, 1 H), 6.38-6.40 (d, $J = 7.2$ Hz, 1 H), 5.20-5.21 (m, 1 H), 5.10-5.12 (m, 1 H), 3.94-3.99 (m, 2 H), 3.57-3.69 (m, 4 H), 3.37 (s, 3 H), 2.42-2.49 (m, 1 H), 2.02-2.08 (m, 2 H), 1.61-1.79 (m, 4 H), 1.25-1.28 (m, 1 H). $[\alpha]_D^{20} = 159.3$ ($c = 0.198$ g/100mL, CHCl_3). LC-MS (m/z) 383.15 (MH^+), $t_R = 0.54$ min (method B).

Compound 50: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-[6-(oxetan-3-yloxy)-pyridin-3-yl]-ethyl]-amide



- 5 (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-chloro-pyridin-3-yl)-ethyl]-amide (**Compound 18**) (2.00 g, 6.65 mmol) was dissolved in DMF (40 ml). *N,N*-dimethylhydroxylaminehydrochloride (5.00 g, 51.2 mmol) and dicesium carbonate (25 g, 76.7 mmol) were added and the mixture was heated at 95 C 3 days. The mixture was poured out into brine and extracted with EtOAc. The organic layer was washed with brine, dried (MgSO₄)
- 10 and was filtered and then evaporated to dryness. The residue was transferred to a silica gel column and eluted with EtOAc to give **Compound 50** as a solid. This solid was dissolved in a mixture of THF (10 ml), EtOAc (10 ml) and heptanes (10 ml). The mixture was concentrated to approx. 10 ml volume and this solution was cooled in an ice/water bath. A white precipitate formed. The solids was collected by filtration and dried in vacuo to give the title compound as
- 15 a white solid (0.044 g, 2%). ¹H-NMR (500 MHz, DMSO) δ 8.43 (d, 1H), 8.02 (s, 1H), 7.45 (d, 1H), 7.25 (m, 2H), 7.17 (m, 1H), 7.10 (d, 2H), 6.61 (d, 1H), 4.83 (m, 1H), 3.98 (m, 6H), 2.19 (m, 1H), 1.90 (m, 1H), 1.35 (m, 4H), 1.21 (m, 1H). LC-MS (*m/z*) 310.2 (MH⁺), *t_R* = 0.46 min (method B). Mp = 171-181 C.

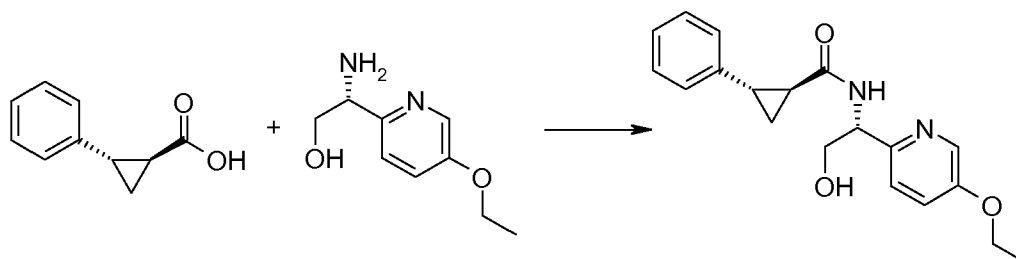
- 20 **Compound 51:** (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*S*)-1-(6-ethanesulfonyl-pyridin-3-yl)-ethyl]-amide



- Prepared analogously to **Compound 1** using **IM46** and (*S*)-1-(6-Methanesulfonyl-pyridin-3-yl)-ethylamine (prepared from 1-(6-Methanesulfonyl-pyridine-3-yl)-ethanone analogously to
- 25 **IM24**, which was prepared from commercially available 5-Bromo-2-methanesulfonyl-pyridine CAS 98626-95-0). Yield from **IM46** = 1.54 g (68%). ¹H-NMR (500 MHz, DMSO) δ 8.80 (d, 1H), 8.72 (s, 1H), 8.02 (m, 2H), 7.27 (m, 2H), 7.20 (s, 1H), 7.12 (d, 2H), 5.08 (m, 1H), 3.27

(s, 3H), 2.20 (m, 1H), 1.95 (m, 1H), 1.42 (d, 3H), 1.37 (m, 1H), 1.22 (m, 1H). LC-MS (m/z) 345.1 (MH⁺), t_R = 1.21 min (method A).

Compound 52: (1*S*,2*S*)-2-Phenyl-cyclopropanecarboxylic acid [(*R*)-1-(5-ethoxy-pyridin-2-yl)-2-hydroxy-ethyl]-amide



Prepared analogously to **Compound 21** using **IM46** and (*R*)-2-Amino-2-(5-ethoxy-pyridin-2-yl)-ethanol (prepared from commercially available 2-Bromo-5-ethoxy-pyridine CAS 42834-01-5 analogously to IM36). **Compound 52** was further purified by SFC (Column: Chiralpack OJ250x30 mm, Mobile phase: Supercritical CO₂/MeOH+NH₄OH = 55/45 at 50 mL/min, column temperature: 38°C, Nozzle Pressure: 100 Bar, Nozzle Temp = 60°C, Evaporator temp = 20 C, Trimmer temp = 25°C, Detector: 220 nm). Yield = 163 mg. ¹H NMR (CDCl₃ 400MHz, TMS): δ 8.15 (d, J = 2.8 Hz, 1 H), 7.08-7.31 (m, 6 H), 7.06 (d, J = 7.2 Hz, 2 H), 5.11-5.15 (m, 1 H), 4.00-4.08 (m, 3 H), 3.87-3.90 (m, 1 H), 2.47-2.52 (m, 1 H), 1.63-1.76 (m, 3 H), 1.43 (t, J = 7.2 Hz, 3 H), 1.27-1.31 (m, 1 H); [α]_{20,D} = 182.0 (c = 0.234 g/100mL, EtOH)

In vitro assays

The nicotinic acetylcholine receptor α7 is a calcium-permeable ion channel, whose activity can be measured by over expression in mammalian cells or oocytes. These two individual assays are described in Example 2 and 3, respectively.

Example 2: α7 NNR flux assay

The nicotinic acetylcholine receptor α7 is a calcium-permeable ion channel, whose activity can be measured by over expression in mammalian cells or oocytes. In this version of the assay, the human α7 receptor is stably expressed in the rat GH4C1 cell line. The assay was used to identify positive allosteric modulators (PAMs) of the α7 receptor. Activation of the channel was measured by loading cells with the calcium-sensitive fluorescent dye Calcium-4 (Assay kit from Molecular Devices), and then measuring real-time changes in fluorescence upon treatment with test compounds.

The cell line ChanClone GH4C1-nAChR α 7 from Genionics was seeded from frozen stock in 384-well plates in culture media 2-3 days before experiment to form an approximately 80% confluent layer on the day of experiment.

5 Cell plating and dye loading

The cell culture were split into "22.5cm x 22.5cm"-plates with approximately 100×10^3 cells/cm². After four days incubation in a humidified incubator at 37°C and 5% CO₂, it had grown to an 80-90% confluent layer, and the cells were harvested.

Culture media:

10 500 mL DMEM/F12 (Gibco 31331)

50 mL FBS (Gibco 10091-155, lot 453269FD)

5 mL Sodium Pyruvate (Gibco 11360)

5 mL Pen/Strep (Gibco 15140)

0.1 mg/mL G-418 (Gibco 11811-064)

15 Two or three days before the experiment the cells were seeded in 384 well plates from Greiner bio-one (781946, CELLCOAT, Poly-D-Lysine, black, μ Clear).

The media was poured off and the plate washed with PBS and left to drain. 5 mL Trypsin was added, cells were washed and incubated (at room temperature) for about 10 seconds. Trypsin was poured off quickly and the cells were incubated for 2 minutes at 37°C (if the cells were not already detached). Cells were resuspended in 10 mL culture media and transferred to 50 mL tubes.

The cell suspension was counted (NucleoCounter, total cell count) from the first plates to estimate the total cell number of the whole batch.

The cells were seeded in 384 well plates with 30 μ L/well (30000 cells/well) while stirring the cell suspension or otherwise preventing the cells from precipitating.

The plates were incubated at room temperature for 30-45 minutes.

The plates were placed in incubator for two days (37°C and 5% CO₂).

Loading the Cells

30 The loading buffer was 5% v/v Calcium-4 Kit and 2.5 mM Probenecid in assay buffer.

190 mL assay buffer

10 mL Kit-solution

2 mL 250 mM Probenecid

This volume was enough for 3 x 8 cell plates.

35 Culture media were removed from the cell plates and 20 μ L loading buffer was added in each well. The cell plates were placed in trays and incubated 90 minutes in the incubator

(37°C). Thereafter the plates were incubated 30 minutes at room temperature, still protected from light.

Now the cell plates were ready to run in the Functional Drug Screening System (FDSS).

- 5 The assay buffer was HBSS with 20 mM HEPES, pH 7.4 and 3 mM CaCl₂.

FDSS Ca assay

200 nL 10 mM compound solution in DMSO was diluted in 50 µL assay buffer. The final test concentrations in the cell plates were 20-10-5-2.5-1.25-0.625-0.312-0.156-0.078-

- 10 0.039 µM. Assay buffer and 3 µM PNU-120596 were used for control.

The agonist acetylcholine was added to a final concentration of 20 µM (~EC₁₀₀).

In the FDSS7000 the Ex480-Em540 was measured with 1 second intervals. The baseline was made of 5 frames before addition of test compounds, and 95 frames more were made before addition of acetylcholine. The measurement stopped 30 frames after the 2nd addition.

- 15 Raw data for each well were collected as "the maximum fluorescence count" in the interval 100-131 seconds and as "the average fluorescence count" in the interval 96-100 seconds. The positive allosteric modulation in the 2nd addition was the enhancement of agonist response with test compound compared to agonist alone.

- 20 Results were calculated as % modulation of test compound compared to the reference PNU-120596 set to 100%. From these data EC₅₀ curves were generated giving EC₅₀, hill and maximum stimulation.

- 25 The compounds of the invention were shown to be PAMs of the α₇ receptor. The compounds of the present invention characterized in the flux assay generally possess EC₅₀ values below 20.000 nM or less such as below 10.000 nM. Many compounds, in fact have EC₅₀ values below 5.000 nM. Table 1 shows EC₅₀ values for exemplified compounds of the invention.

Table 1

Compound	EC ₅₀ (nM)	Compound	EC ₅₀ (nM)	Compound	EC ₅₀ (nM)
1	670	19	2400	37	700
2	5600	20	2000	38	970
3	5800	21	640	39	720
4	8100	22	5500	40	890
5	7700	23	7600	41	1600

6	5200	24	5200	42	790
7	960	25	7300	43	2900
8	3700	26	390	44	4600
9	6200	27	390	45	2900
10	1900	28	620	46	460
11	3800	29	860	47	1000
12	1200	30	560	48	1700
13	1600	31	1700	49	1200
14	1600	32	530	50	3200
15	5600	33	1000	51	7200
16	6800	34	700	52	2000
17	3700	35	710		
18	3700	36	1600		

Example 3: $\alpha 7$ NNR oocyte assay

Expression of $\alpha 7$ nACh receptors in *Xenopus* oocytes.

Oocytes were surgically removed from mature female *Xenopus laevis* anaesthetized in 0.4% MS-222 for 10 – 15 min. The oocytes were then digested at room temperature for 2-3 hours with 0.5 mg/mL collagenase (type IA Sigma-Aldrich) in OR2 buffer (82.5 mM NaCl, 2.0 mM KCl, 1.0 mM $MgCl_2$ and 5.0 mM HEPES, pH 7.6). Oocytes avoid of the follicle layer were selected and incubated for 24 hours in Modified Barth's Saline buffer (88 mM NaCl, 1 mM KCl, 15 mM HEPES, 2.4 mM $NaHCO_3$, 0.41 mM $CaCl_2$, 0.82 mM $MgSO_4$, 0.3 mM $Ca(NO_3)_2$) supplemented with 2 mM sodium pyruvate, 0.1 U/l penicillin and 0.1 $\mu g/l$ streptomycin. Stage IV oocytes were identified and injected with 4.2 - 48 nl of nuclease free water containing 0.1 – 1.2 ng of cRNA coding for human $\alpha 7$ nACh receptors or 3.0 – 32 ng of cRNA coding for rat $\alpha 7$ nACh receptors and incubated at 18°C for 1 – 10 days when they were used for electrophysiological recordings.

Electrophysiological recordings of $\alpha 7$ nACh receptors expressed in oocytes.

Oocytes were used for electrophysiological recordings 1 – 10 days after injection. Oocytes were placed in a 1 mL bath and perfused with Ringer buffer (115 mM NaCl, 2.5 mM KCl, 10 mM HEPES, 1.8 mM $CaCl_2$, 0.1 mM $MgCl_2$, pH 7.5). Cells were impaled with agar plugged 0.2 – 1 M Ω electrodes containing 3 M KCl and voltage clamped at -90 mV by a GeneClamp 500B amplifier. The experiments were performed at room temperature. Oocytes were continuously perfused with Ringer buffer and the drugs were applied in the perfusate. ACh (30 μM) applied for 30 sec were used as the standard agonist for activation of the $\alpha 7$

nACh receptors. In the standard screening set-up the new test compound (10 μ M or 30 μ M) were applied for 1 min of pre-application allowing for evaluation of agonistic activity followed by 30 sec of co-application with ACh (30 μ M) allowing for evaluation of PAM activity. The response of co-application was compared to the agonistic response obtained with ACh alone.

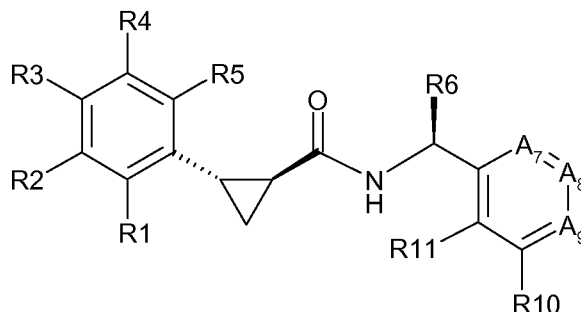
- 5 The drug induced effects on both the peak response and the total charge (AUC) response were calculated thus giving the effect of drug induced PAM activity as fold modulation of the control response.

For more elaborate studies doses-response curves can be performed for evaluation of max-fold modulation and EC₅₀ values for both peak and AUC responses.

10

CLAIMS

1. A compound according to formula [I]



[I]

wherein R1, R2, R3, R4 and R5 are selected independently of each other from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano and halogen, wherein said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl is optionally substituted with one or more substituents independently selected from chlorine and fluorine;

R6 is selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆alkoxy, wherein said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl is optionally substituted with one or more substituents independently selected from hydroxy, C₁₋₆alkoxy and fluorine;

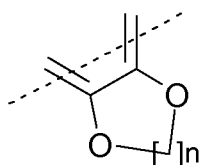
A7 is C-R7 or N, A8 is C-R8 or N and A9 is C-R9 or N, provided that at least one of A7, A8 or 9 is N and no more than two of A7, A8 and A9 is N;

R7, R8, R9, R10 and R11 are selected independently of each other from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano, NR₁₂R₁₃, C₁₋₆alkylsulfonyl, halogen and OR₁₄, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₆alkoxy is optionally substituted with one or more substituents selected from chlorine, fluorine, C₁₋₆alkoxy, cyano and NR₁₂R₁₃;

R12 and R13 independently represent hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl;

R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C;

or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1, 2 or 3;

and pharmaceutically acceptable salts thereof;

with the proviso that the compound of formula [I] is other than

(1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide;

(1S,2S)-2-(2-Chloro-4-fluoro-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide;

- 5 (1S,2S)-2-(2-Fluoro-4-methoxy-phenyl)-cyclopropanecarboxylic acid {(S)-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-yl]-ethyl}-amide.

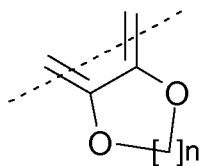
2. The compound according to claim 1, wherein R1, R2, R3, R4 and R5 are selected independently of each other from H, methyl, fluorine and chlorine;

- 10 R6 is selected from methyl, hydroxymethyl, methoxymethyl and fluoromethyl;

R7, R8, R9, R10 and R11 are selected independently of each other from H, C₁₋₄alkyl, C₁₋₄alkoxy, cyano, -N(CH₃)₂, methylsulfonyl, fluorine, chlorine and OR14, wherein said C₁₋₄alkyl or C₁₋₄alkoxy is optionally substituted with one or more substituents selected from fluorine, C₁₋₄alkoxy and cyano;

- 15 R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C;

or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1 or 2.

20

3. The compound according to any of claims 1-2, wherein four or more of R1, R2, R3, R4 and R5 are H.

4. The compound according to any of claims 1-5, wherein R6 is selected from methyl, hydroxymethyl, methoxymethyl and fluoromethyl.

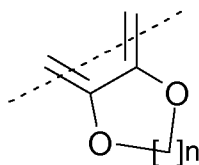
25

5. The compound according to any of claims 1-4, wherein R7, R8, R9, R10 and R11 are selected independently of each other from H, C₁₋₄alkyl, C₁₋₄alkoxy, cyano, -N(CH₃)₂, methylsulfonyl, fluorine, chlorine and OR14, wherein said C₁₋₄alkyl or C₁₋₄alkoxy is optionally substituted with one or more substituents selected from fluorine, C₁₋₄alkoxy and cyano;

30

R14 represents a monocyclic saturated ring moiety having 4-6 ring atoms wherein one of said ring atoms is O and the others are C;

or R9 and R10 may be linked together to form the moiety indicated below



wherein n is 1 or 2;

6. The compound according to any of embodiments 1-12, wherein R7, R8, R9, R10 and
5 R11 are selected independently from H, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, cyano and halogen, wherein said C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl or C₁₋₄alkoxy is optionally substituted with one or more substituents selected from fluorine and C₁₋₄alkoxy.
7. The compound according to any of claims 1-6, wherein one or more of the hydrogen
10 atoms are represented by deuterium.
8. The compound according to claim 7, wherein at least about 85% of the compound has a deuterium atom at each position designated as deuterium, and any atom not designated as deuterium is present at about its natural isotopic abundance.
- 15 9. The compound according to any of claims 1-8, wherein no more than one of A7, A8 or A9 is N.
10. The compound according to any of claims 1-9 having a diastereomeric excess of at
20 least 80% such as at least 85%, such as at least 90%, such as at least 95%.
11. The compound according to claim 1 selected from
 - 1: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide;
 - 25 2: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(5-methyl-pyridin-2-yl)-ethyl]-amide;
 - 3: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methoxy-pyridin-3-yl)-ethyl]-amide;
 - 4: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methyl-pyridin-3-yl)-ethyl]-amide;
 - 5: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-cyano-pyridin-3-yl)-ethyl]-amide;
 - 6: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide;
 - 30 7: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethoxy-pyridin-3-yl)-ethyl]-amide;
 - 8: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethyl-pyridin-3-yl)-ethyl]-amide;

- 9:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-methoxymethyl-pyridin-3-yl)-ethyl]-amide;
- 10:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-ethyl}-amide;
- 5 **11:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-ethyl}-amide;
- 12:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2-ethoxy-pyridin-4-yl)-ethyl]-amide;
- 13:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((S)-1-{6-[(S)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide;
- 10 **14:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((S)-1-{6-[(R)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide;
- 15:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((S)-1-[1,3]dioxolo[4,5-b]pyridin-6-yl-ethyl)-amide;
- 16:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2,3-dihydro-[1,4]dioxino[2,3-
15 b]pyridin-7-yl)-ethyl]-amide;
- 17:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(2-ethoxy-pyrimidin-5-yl)-ethyl]-amide;
- 18:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-chloro-pyridin-3-yl)-ethyl]-amide;
- 19:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(oxetan-3-yloxy)-pyridin-3-yl]-
20 ethyl}-amide;
- 20:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-cyanomethoxy-pyridin-3-yl)-ethyl]-amide;
- 21:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide;
- 25 **22:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl]-amide;
- 23:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(5-cyano-pyridin-2-yl)-2-hydroxy-ethyl]-amide;
- 24:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-methoxy-pyridin-3-yl)-
30 ethyl]-amide;
- 25:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-methyl-pyridin-3-yl)-ethyl]-amide;
- 26:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-ethyl]-amide;
- 35 **27:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

28: (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

29: (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide;

5 **30:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-2-hydroxy-1-(6-propoxy-pyridin-3-yl)-ethyl]-amide;

31: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

10 **32:** (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

33: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

34: (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1,2,2,2-d₅)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

15 **35:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

36: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

20 **37:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(1,1-d₂)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

38: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-(1,1,2,2,2-d₅)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

39: (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-(2,2,2-d₃)-ethoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

25 **40:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

41: (1S,2S)-2-(3-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

30 **42:** (1S,2S)-2-(4-Fluoro-phenyl)-cyclopropanecarboxylic acid [(R)-1-(6-cyclobutoxy-pyridin-3-yl)-2-hydroxy-ethyl]-amide;

43: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid ((R)-2-hydroxy-1-{6-[(R)-(tetrahydro-furan-3-yl)oxy]-pyridin-3-yl}-ethyl)-amide;

44: (1S,2S)-N-[(1R)-2-hydroxy-1-[6-[(3S)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide;

35 **45:** (1S,2S)-2-((Z)-1-Methylene-penta-2,4-dienyl)-cyclopropanecarboxylic acid {(R)-2-hydroxy-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethyl}-amide;

46: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(6-ethoxy-pyridin-3-yl)-2-methoxy-ethyl]-amide;

47: (1S,2S)-N-[(1R)-2-methoxy-1-[6-[(3R)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide;

5 **48:** (1S,2S)-N-[(1R)-2-methoxy-1-[6-[(3S)-tetrahydrofuran-3-yl]oxy-3-pyridyl]ethyl]-2-phenyl-cyclopropanecarboxamide;

49: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(R)-2-methoxy-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-ethyl}-amide;

10 **50:** (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid {(S)-1-[6-(oxetan-3-yloxy)-pyridin-3-yl]-ethyl}-amide;

51: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(S)-1-(6-ethanesulfonyl-pyridin-3-yl)-ethyl]-amide;

52: (1S,2S)-2-Phenyl-cyclopropanecarboxylic acid [(R)-1-(5-ethoxy-pyridin-2-yl)-2-hydroxy-ethyl]-amide;

15 and pharmaceutically acceptable salts of any of these compounds.

12. A compound according to any of claims 1-11, for use as a medicament.

13. A compound according to any of claims 1-11, for use in the treatment of a disease or
20 disorder selected from Psychosis; Schizophrenia; cognitive disorders; cognitive impairment associated with schizophrenia; Attention Deficit Hyperactivity Disorder (ADHD); autism spectrum disorders, Alzheimer's disease (AD); mild cognitive impairment (MCI); age associated memory impairment (AAMI); senile dementia; AIDS dementia; Pick's disease; dementia associated with Lewy bodies; dementia associated with Down's syndrome; Huntington's Disease;
25 Parkinson's disease (PD); obsessive-compulsive disorder (OCD); traumatic brain injury; epilepsy; post-traumatic stress; Wernicke-Korsakoff syndrome (WKS); post-traumatic amnesia; cognitive deficits associated with depression; diabetes, weight control, inflammatory disorders, reduced angiogenesis; amyotrophic lateral sclerosis and pain.

30 14. A pharmaceutical composition comprising a compound according to any of claims 1-11, and one or more pharmaceutically acceptable carrier or excipient.

15. A kit comprising a compound according to any of claims 1-11, together with a second compound selected from the list consisting of acetylcholinesterase inhibitors; glutamate re-
35 ceptor antagonists; dopamine transport inhibitors; noradrenalin transport inhibitors; D2 an-

tagonists; D2 partial agonists; PDE10 antagonists; 5-HT2A antagonists; 5-HT6 antagonists; KCNQ antagonists; lithium; sodium channel blockers and GABA signaling enhancers.