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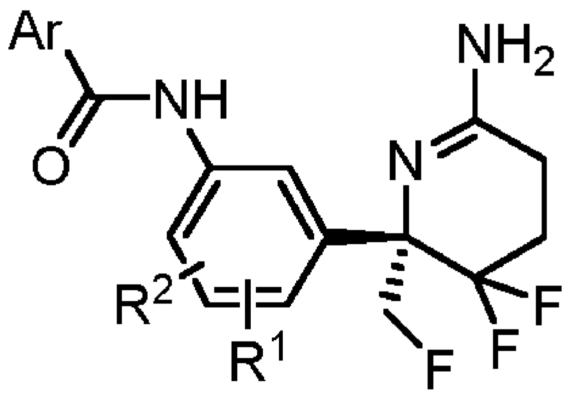
(54) **Title**: 2-AMINO-5,5-DIFLUORO-6-(FLUOROMETHYL)-6-PHENYL-3,4,5,6-TETRAHYDROPYRIDINES AS BACE1 INHIBITORS



(I)

(57) **Abstract**: The present invention is directed to compounds of Formula (I) which are inhibitors of the BACE1 enzyme. Separate aspects of the invention are directed to pharmaceutical compositions comprising said compounds and uses of the compounds to treat disorders for which the reduction of Aβ deposits is beneficial such as Alzheimer's disease.

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2-Amino-5,5-difluoro-6-(fluoromethyl)-6-phenyl-3,4,5,6-tetrahydropyridines as BACE1 inhibitors

FIELD OF THE INVENTION

The present invention provides compounds which are BACE1 inhibitors. Separate aspects of the invention are directed to pharmaceutical compositions comprising said compounds and uses of the compounds to treat neurodegenerative and cognitive disorders.

BACKGROUND ART

Dementia is a clinical syndrome characterized by deficits in multiple areas of cognition that cannot be explained by normal aging, a noticeable decline in function, and an absence of delirium. In addition, neuropsychiatric symptoms and focal neurological findings are usually present. Dementia is further classified based on etiology. Alzheimer's disease (AD) is the most common cause of dementia, followed by mixed AD and vascular dementia, Lewy body dementia (DLB), and fronto-temporal dementia.

β-Amyloid deposits and neurofibrillary tangles are considered to be major pathologic characterizations associated with AD which is characterized by the loss of memory, cognition, reasoning, judgment, and orientation. Also affected, as the disease progresses, are motor, sensory and linguistic abilities until global impairment of multiple cognitive functions occurs. β-Amyloid deposits are predominantly an aggregate of Aβ peptide, which in turn is a product of the proteolysis of amyloid precursor protein (APP) as part of the β-amyloidogenic pathway. Aβ peptide results from the cleavage of APP at the C-terminals by one or more γ-secretases and at the N-terminus by β-secretase 1 (BACE1) also known as aspartyl protease 2. BACE1 activity is correlated directly to the generation of Aβ peptide from APP.

Studies indicate that the inhibition of BACE1 impedes the production of Aβ peptide. Further, BACE1 co-localizes with its substrate APP in Golgi and endocytic compartments (Willem M, et al. *Semin.Cell Dev. Biol*, 2009, 20, 175-182). Knock-out studies in mice have demonstrated the absence of amyloid peptide formation while the animals are healthy and fertile (Ohno M, et al. *Neurobiol. Dis*., 2007, 26, 134-145). Genetic ablation of BACE1 in APP-overexpressing mice has demonstrated absence of plaque formation, and the reverse of cognitive deficits (Ohno M, et al. *Neuron*; 2004, 41, 27-33). BACE1 levels are elevated in the brains of sporadic AD patients (Hampel and Shen, *Scand. J. Clin. Lab. Invest*. 2009, 69, 8-12).

These convergent findings indicate that the inhibition of BACE1 may be a therapeutic target for the treatment of AD as well as disorders for which the reduction of Aβ deposits is beneficial.

AstraZeneca announced the discovery of AZD3839, a potent BACE1 inhibitor clinical candidate for the treatment of AD (Jeppsson, F., et al. *J. Biol. Chem.*, 2012, 287, 41245-41257) in October 2012. The effort which led to the discovery of AZD3839 was further described in Ginman, T., et al. *J. Med. Chem.*, 2013, 56, 4181-4205. The Ginman publication describes the issues which were overcome in connection with the discovery and identification of AZD3839. These issues related to poor blood brain barrier penetration and P-glycoprotein mediated efflux of the compounds resulting in lack of brain exposure.

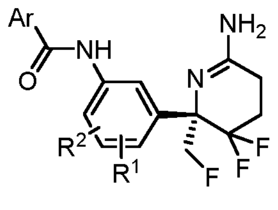
The Ginman manuscript hypothesized that the differences in brain exposure would largely be due to the core structures and Structure Activity Relationship data was provided wherein the in vitro properties on the reported compounds were given in four tables according to core sub-types. In table 4, a series of amidine containing compounds are described that were considered interesting from an activity perspective. However, the data suggests that the amidine containing core did not exhibit a favourable blood brain barrier permeability profile.

Researchers from Hoffmann-La Roche and Siena Biotech also reported the discovery of amidine containing compounds (Woltering, T. J., et al. *Bioorg. Med. Chem. Lett.* 2013, 23, 4239-4243). These compounds (compounds 17 and 18 in the paper) were found not to have any in vivo effect (lack of Aβ40 reduction in brain in wild type mice).

Contrary to the teachings of Ginman, et al. and Woltering, T. J., et al., the present inventors have discovered a series of amidine compounds which are brain penetrating. Accordingly, the present invention relates to novel compounds having BACE1 inhibitory activity, to their preparation, to their medical use and to medicaments comprising them.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide compounds that inhibit BACE1. Accordingly, the present invention relates to compounds of Formula I



Formula I

wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl and isoxazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy; and R^1 and R^2 independently are hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof.

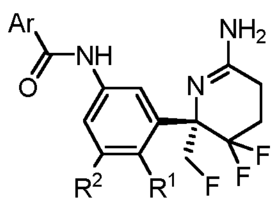
In separate embodiments of the invention, the compound is selected from one of the exemplified compounds disclosed in the Experimental Section.

The present invention further provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention provides a method of treating a subject suffering from neurodegenerative or cognitive disorder comprising administering to said subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder.

In one embodiment, the compound of the present invention is according to Formula Ia



Formula Ia;

or a pharmaceutically acceptable salt thereof.

In one embodiment, R^1 and R^2 independently are H or F, in particular R^1 if F and R^2 is H or both R^1 and R^2 are F.

In one embodiment, Ar is optionally substituted with one or more substituents selected from F, Cl, CN, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl or C_1-C_3 alkoxy.

In one embodiment, Ar is optionally substituted phenyl.

In one embodiment, Ar is optionally substituted pyridyl.

In one embodiment, Ar is optionally substituted pyrimidyl.

In one embodiment, Ar is optionally substituted pyrazinyl.

In one embodiment, Ar is optionally substituted imidazolyl.

In one embodiment, Ar is optionally substituted pyrazolyl.

In one embodiment, Ar is optionally substituted thiazolyl.

In one embodiment, Ar is optionally substituted oxazolyl.

In one embodiment, Ar is optionally substituted isoxazolyl.

In one embodiment, the compound is selected from the group consisting of:
(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-chloropicolinamide
(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-fluoropicolinamide
(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide
(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1H-pyrazole-3-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyanopicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-2-methyloxazole-4-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-methoxypyrazine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-fluoropicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-chloropicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-cyanopicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-methoxypicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-(methoxy-d_3)picolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide

S)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(methoxy-d_3)picolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-bromopicolinamide

or a pharmaceutically acceptable salt thereof.

A separate embodiment is directed to a pharmaceutical composition comprising a compound from the above list or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Another embodiment of the invention is directed to a method of treating a neurodegenerative or cognitive disorder comprising administering a therapeutically effective amount of a compound from the above list or a pharmaceutically acceptable salt thereof to a patient in need thereof. In another embodiment the invention is directed to a use of a compound from the above list or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a neurodegenerative or cognitive disorder.

In one embodiment the invention is directed to a compound from the above list or a pharmaceutically acceptable salt thereof for use in a method for the treatment of a neurodegenerative or cognitive disorder.

In one embodiment the invention is directed to a compound from the above list or a pharmaceutically acceptable salt thereof for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that compounds of Formula I are inhibitors of BACE1, and as such, are useful for the treatment of related disorders. Certain aspects of the invention are explained in greater detail below but this description is not intended to be a detailed catalog of all the different ways in which the invention may be implemented, or all the features that may be added to the instant invention. Hence, the following specification is intended to illustrate some embodiments of the invention, and not to exhaustively specify all permutations, combinations and variations thereof.

As used herein, the term "C_1-C_6 alkyl" refers to a straight chained or branched saturated hydrocarbon having from one to six carbon atoms inclusive. Examples of C_1-C_6 alkyl include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, n-pentyl and n-hexyl. Similarly, the term "C_1-C_3 alkyl" refers to a straight chained or branched saturated hydrocarbon having from one to three carbon atoms inclusive. Examples of such substituents include, but are not limited to, methyl, ethyl and n-propyl.

Likewise, the term "C_1-C_6 alkoxy" refers to a straight chained or branched saturated alkoxy group having from one to six carbon atoms inclusive with the open valency on the oxygen. Examples of C_1-C_6 alkoxy include, but are not limited to, methoxy, ethoxy, n-butoxy, t-butoxy and n-hexyloxy. The "C_1-C_6 alkoxy" is optionally substituted with one or more fluorine atoms.

As used herein, the term "C_1-C_6 fluoroalkyl" refers to a straight chained or branched saturated hydrocarbon having from one to six carbon atoms inclusive substituted with one or more fluorine atoms. Examples of C_1-C_6 fluoroalkyl include, but are not limited to, trifluoromethyl, pentafluoroethyl, 1-fluoroethyl, monofluoromethyl, difluoromethyl, 1,2-difluoroethyl and 3,4 difluorohexyl. Similarly, the term "C_1-C_3 fluoroalkyl" refers to a straight chained or branched saturated hydrocarbon having from one to three carbon atoms inclusive substituted with one or more fluorine atoms per carbon atom.

The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The term "C_2- C_6-alkenyl" refers to a branched or unbranched alkenyl group having from two to six carbon atoms and one double bond, including but not limited to ethenyl, propenyl, and butenyl.

The term "C_2- C_6-alkynyl" shall mean a branched or unbranched alkynyl group having from two to six carbon atoms and one triple bond, including but not limited to ethynyl, propynyl and butynyl.

As used herein, the phrase "effective amount" when applied to a compound of the invention, is intended to denote an amount sufficient to cause an intended biological effect. The phrase "therapeutically effective amount" when applied to a compound of the invention is intended to denote an amount of the compound that is sufficient to ameliorate, palliate, stabilize, reverse, slow or delay the progression of a disorder or disease state, or of a symptom of the disorder or disease. In an embodiment, the method of the present invention provides for administration of combinations of compounds. In such instances, the "effective amount" is the amount of the compound of the present invention in such combination sufficient to cause the intended biological effect.

The term "treatment" or "treating" as used herein means ameliorating or reversing the progress or severity of a disease or disorder, or ameliorating or reversing one or more symptoms or side effects of such disease or disorder. "Treatment" or "treating", as used herein, also means to inhibit or block, as in retard, arrest, restrain, impede or obstruct, the progress of a system, condition or state of a disease or disorder. For purposes of this invention, "treatment" or "treating" further means an approach for obtaining beneficial or desired clinical results, where "beneficial or desired clinical results" include, without limitation, alleviation of a symptom, diminishment of the extent of a disorder or disease, stabilized (i.e., not worsening) disease or disorder state, delay or slowing of a disease or disorder state, amelioration or palliation of a disease or disorder state, and remission of a disease or disorder, whether partial or total.

The present invention also provides a method of treating a disease or disorder, the method comprises administering a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof to a mammal in need thereof, wherein the disease or disorder is a neurodegenerative or cognitive disease or disorder.

The compounds of the present invention are, as discussed above, expected to be useful in the treatment of Alzheimer's disease due to their effects on β-amyloid deposits and neurofibrillary tangles. This includes familial Alzheimer's disease where patients carry mutations on specific genes intimately involved in the production of Aβ peptide. It is, however, important to note that aggregates of Aβ peptide is not limited to familial Alzheimer's disease but is similarly an important pathophysiological characteristics of the more common sporadic Alzheimer's disease [*Mol Cell Neurosci*, 66, 3-11, 2015].

The compounds of the present invention are also believed to be useful in the treatment of early-stage Alzheimer's disease, i.e. disease stages where the biological and structural changes have started but the clinical manifestations of the disease have not yet become evident or are not yet well developed. Early-stage Alzheimer's disease may, in fact, start years before any clinical manifestation of the disease becomes manifest. Early-stage Alzheimer's disease include prodromal Alzheimer's disease, preclinical Alzheimer's disease and mild cognitive impairment. Although mild cognitive impairment may be unrelated to Alzheimer's disease it is often a transitional stage to Alzheimer's disease or due to Alzheimer's disease. Preclinical and prodromal Alzheimer's disease are asymptomatic stages, and they are typically diagnosed by the presence of Alzheimer's disease related biomarkers. In this context the compounds of the present invention are believed to be useful in slowing down the progression of early-stage Alzheimer's disease, such as mild cognitive impairment, to Alzheimer's disease. The compounds of the present invention are also believed to be useful in the treatment of memory loss, attention deficits and dementia associated with Alzheimer's disease.

Other diseases, in addition to the continuum of Alzheimer's disease, are characterized by β-amyloid deposits and neurofibrillary tangles. This includes e.g. Trisomy 21 also known as Down's syndrome. Patients suffering from Down's syndrome have an extra chromosome 21 which chromosome contains the gene for the amyloid precursor protein (APP). The extra chromosome 21 leads to overexpression of APP, which leads to increased levels of Aβ peptide, which eventually causes the markedly increased risk of developing Alzheimer's disease seen in Down's syndrome patients[*Alzheimer's & Dementia*, 11, 700-709, 201]. Cerebral amyloid angiopathy is also characterized by β-amyloid deposits and neurofibrillary tangles in blood vessels of the central nervous system [*Pharmacol Reports*, 67, 195-203, 2015] and is as such expected to be treatable with compounds of the present invention.

In one embodiment, the present invention provides a method of treating a disease selected from Alzheimer's disease (familial or sporadic), preclinical Alzheimer's disease, prodromal Alzheimer's disease, mild cognitive impairment, Down's syndrome and cerebral amyloid angiopathy, the method comprising the administration of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof to a patient in need thereof.

The present invention further provides a method of inhibiting BACE1 in a patient comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of inhibiting β-secretase mediated cleavage of amyloid precursor protein comprising administering to a patient in need of such treatment a therapeutically effective amount a compound of Formula I or a pharmaceutically acceptable salt thereof.

In further embodiments, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disease selected from Alzheimer's disease (familial or sporadic), preclinical Alzheimers's disease, prodromal Alzheimer's disease, mild cognitive impairment, Down's syndrome or cerebral amyloid angiopathy.

The present invention also provides the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the inhibition of BACE1. The present invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the inhibition of production or accumulation of Aβ peptide.

In one embodiment, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in a method for the treatment of a disease selected form Alzheimer's disease (familial or sporadic), preclinical Alzheimer's disease, prodromal Alzheimer's disease, mild cognitive impairment, Down's syndrome or cerebral amyloid angiopathy.

In one embodiment, the present invention relates to a compound of formula I or a pharmaceutically acceptable salt thereof for use in a method for inhibiting of BACE1 or a in method for inhibiting of production or accumulation of Aβ peptide.

In a further embodiment, the invention provides a pharmaceutical formulation adapted for any of the above treatments and uses.

In one embodiment, a mammal is a human.

In one embodiment, the patient is a human patient.

The compounds of the present invention are as demonstrated in the examples potent inhibitors of BACE1 and capable of lowering the level of Aβ peptide in rat brain and plasma, and said compounds are thus believed to be useful in the treatment of neurodegenerative and cognitive disorders which pathological characteristics comprise Aβ deposits and neurofibrilary tangles, such as e.g. Alzheimer's disease. It may be beneficial to combine a compound of the present invention with another treatment paradigm useful in the treatment of such disease, e.g. Alzheimer's disease.

Tau proteins are abundant in neurons. Tau proteins are soluble and highly phosphorylation labile and bind to tubulin providing regulation and modulation of tubulin assembly, i.e. eventually the microtubular structure and stability. Tau proteins can only associate with tubulin in the most de-phosphorylated state, and phosphorylation/de-phosphorylation acts as a switch controlling the tubulin association. Phosphorylated Tau constitutes an important part of the neurofibrillary tangles which are one of the hallmarks of Alzheimer's disease. The so-called Tau hypothesis suggests targeting these pathological tangles, a main constituent of which is phosphorylated Tau protein, as a treatment paradigm for Alzheimer's disease. In particular, immunotherapies, both active and passive, have been suggested as a way to target Tau neurofibrillary tangles. In active immunotherapy, a pathogenic antigen is injected into the patient and the innate immune system elicits an immune response. This triggers the maturation of B-cells generating high affinity antibodies against the administered antigen. In a passive immunotherapy, the triggering of the innate immune system is circumvented by infusing a specific antibody against the antigen. It is suggested that the inherent clearance system then removes antibody bound ligand. Substantial evidence for the efficacy of both active and passive immunotherapy targeting phosphorylated Tau protein as a treatment for Alzheimer's disease exists [Alzheimer's &Dementia, 7(4, suppl) S480-481; J Neurosci 30, 16559-16556, 2010; J Neurosci, 27, 9115-9129, 2007].

In one embodiment the invention provides a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer's disease, the method comprising the administration of a therapeutically effect amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) a compound useful in active or passive Tau immunotherapy to a patient in need thereof. Said compound useful in passive Tau immunotherapy may be an antibody directed against phosphorylated Tau protein. Said compound useful in active Tau immunotherapy may be a fragment of the Tau protein amino acid sequence which upon injection in a patient elicits generation of an anti-phosphorylated Tau protein antibody in said patient. The administration according to this embodiment of the invention may be simultaneous, or there may be a time gap between the administration of the two components.

In one embodiment, the invention relates to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof and a compound useful in active or passive Tau immunotherapy in the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder, e.g. Alzheimer's disease.

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof and a compound useful in active or passive Tau immunotherapy for use in a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer's disease.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a compound useful in active or passive Tau immunotherapy and a pharmaceutically acceptable carrier.

Another paradigm to treat neurodegenerative and cognitive disorder, e.g. Alzheimer's disease is to target the Aβ peptides. It has been suggested that this can be achieved by either passive or active immunotherapy targeting Aβ peptides [J Neurosci, 34, 11621-11630, 2014; J Neurosci 33, 4923-4934, 2013]. In combination with compounds of the present invention this would attempt to target the same pathological mechanism via two different routes. Anti-Aβ antibodies (either injected directly into the patient or generated in the patient as a result of active immunotherapy) clear Aβ deposits in the brain, while further accumulation of Aβ peptide is blocked or reduced by the compounds of the present invention.

In one embodiment the invention provides a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer's disease, the method comprising the administration of a therapeutically effect amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) a compound useful in active or passive Aβ peptide immunotherapy to a patient in need thereof. Said compound useful in passive Aβ peptide immunotherapy may be an anti-Aβ peptide antibody, such as gantenerumab, solanezumab, aducanumab or crenezumab. Said compound useful in active Aβ peptide immunotherapy may be a fragment of the Aβ peptide amino acid sequence which upon injection into a patient elicits anti-Aβ peptide antibodies in said patient. The administration according to this embodiment of the invention may be simultaneous, or there may be a time gap between the administration of the two components.

In one embodiment, the invention relates to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof and a compound useful in active or passive Aβ peptide immunotherapy in the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder, e.g. Alzheimer's disease.

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof and a compound useful in active or passive Aβ peptide immunotherapy for use in a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a compound useful in active or passive Aβ peptide immunotherapy and a pharmaceutically acceptable carrier.

The NMDA (N-Methyl-D-Aspartate) receptor antagonist memantine and the acetylcholine esterase inhibitors donepezil, rivastigmine and galantamine are approved drugs for the treatment of Alzheimer’s disease.

In one embodiment the invention provides a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease, the method comprising the administration of a therapeutically effect amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) an NMDA receptor antagonist or an acetylcholine esterase inhibitor to a patient in need thereof. The administration according to this embodiment of the invention may be simultaneous, or there may be a time gap between the administration of the two components.

In one embodiment, the invention relates to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof and an NMDA receptor antagonist or an acetylcholine esterase inhibitor in the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof and an NMDA receptor antagonist or an acetylcholine esterase inhibitor for use in a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and an NMDA receptor antagonist or an acetylcholine esterase inhibitor and a pharmaceutically acceptable carrier.

Seizures or epileptiform activity are also associated with Alzheimer’s disease, including early stages of Alzheimer’s disease, and treatment of said epileptic activity, which seeks to normalise hippocampal hyperactivity, may form part of an Alzheimer’s disease treatment paradigm [JAMA Neurol, 70, 1158-1166, 2013; J Neurosci Res, 93, 454, 465, 2015; Neuron, 74, 647-474, 2012; Neurepsychpharm, 35, 1016-1025, 2010; CNS Neurosci Ther, 19, 871-881, 2013]. Useful antiepileptics include NMDA receptor antagonists and ion channel modulators, such as topiramate, levetiracetam and lamotrigine.

In one embodiment the invention provides a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease, the method comprising the administration of a therapeutically effect amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) an antiepileptic to a patient in need thereof. The administration according to this embodiment of the invention may be simultaneous, or there may be a time gap between the administration of the two components.

In one embodiment, the invention relates to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof and an antiepileptic in the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof and an antiepileptic for use in a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and an antiepileptic and a pharmaceutically acceptable carrier.

Emerging evidence suggests that inflammation has a causal role in Alzheimer’s disease pathogenesis and that neuroinflammation is not a passive system activated by emerging β-amyloid deposits and neurofibrilary tangles, but also contributes to pathogenesis itself [Lancet Neurol, 14, 388-405, 2015; J Alz Dis, 44, 385-396, 2015; Neurol, 84, 2161-2168, 2015]. It follows from this that anti-inflammatory drugs, such as NSAID (non-steriod anti-inflammatory drugs), TNFα inhibitors, such as etanercept and p38 MAP kinase inhibitors, such as VX-745 (5-(2,6-Dichlorophenyl)-2-((2,4-difluorophenyl)thio)-6H-pyrimido[1,6-b]pyridazin-6-one) may be useful in the treatment of Alzheimer’s disease.

In one embodiment the invention provides a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease, the method comprising the administration of a therapeutically effect amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) an anti-inflammatory drug to a patient in need thereof. The administration according to this embodiment of the invention may be simultaneous, or there may be a time gap between the administration of the two components.

In one embodiment, the invention relates to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof and anti-inflammatory drug in the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof and an anti-inflammatory drug for use in a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer’s disease.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and an anti-inflammatory drug and a pharmaceutically acceptable carrier.

In addition, efficacy in the treatment of Alzheimer's disease has been demonstrated for Tau protein aggregation inhibitors, such as TRX-0237, also known as Methylene Blue, and SSRIs (Selective Serotonin Reuptake Inhibitor), such as citalopram [Behav Pharmacol, 26, 353-368, 2015; Sci Transl Med, 6(236re4), 2014].

In one embodiment the invention provides a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer's disease, the method comprising the administration of a therapeutically effect amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) Tau protein aggregation inhibitor or an SSRI to a patient in need thereof. The administration according to this embodiment of the invention may be simultaneous, or there may be a time gap between the administration of the two components.

In one embodiment, the invention relates to the use of a compound of Formula I or a pharmaceutically acceptable salt thereof and a Tau protein aggregation inhibitor or an SSRI in the manufacture of a medicament for the treatment of neurodegenerative or cognitive disorder, e.g. Alzheimer's disease.

In one embodiment, the invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof and a Tau protein aggregation inhibitor or an SSRI drug for use in a method for the treatment of a neurodegenerative or cognitive disorder, e.g. Alzheimer's disease.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a Tau protein aggregation inhibitor or an SSRI drug and a pharmaceutically acceptable carrier.

Pharmaceutically Acceptable Salts

The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutically acceptable acid addition salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Representative 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-halotheophyllines (for example, 8-bromotheophylline and the like). Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in S. M. Berge, et al., J. Pharm. Sci., 1977, 66, 2.

Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures, i.e. a mixture of stereoisomeres, are included within the scope of the invention.

In this context it is understood that when specifying the enantiomeric form, then the compound is in enantiomeric excess, e.g. essentially in a pure form. Accordingly, one embodiment of the invention relates to a compound of the invention having an enantiomeric excess of at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 96%, preferably at least 98%.

Racemic forms may 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. Separation of such diastereomeric salts can be achieved, e.g. by fractional crystallization. The optically active acids suitable for this purpose may include, but are not limited to d- or l- tartaric, mandelic or camphorsulfonic acids. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. The compounds of the present invention may also be resolved by the formation and chromatographic separation of diastereomeric derivatives from chiral derivatizing reagents, such as, chiral alkylating or acylating reagents, followed by cleavage of the chiral auxiliary. Any of the above methods may be applied either to resolve the optical antipodes of the compounds of the invention per se or to resolve the optical antipodes of synthetic intermediates, which can then be converted by methods described herein into the optically resolved final products which are the compounds of the invention.

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.

Pharmaceutical compositions

The present invention further provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The present invention also provides a pharmaceutical composition comprising a specific compounds disclosed in the Experimental Section or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of the invention may be administered alone 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, 22th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 2013.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, the compositions may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art. 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 powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Other suitable administration forms include, but are not limited to, suppositories, sprays, ointments, creams, gels, inhalants, dermal patches and implants.

Typical oral dosages range from about 0.01 to about 100 mg/kg body weight per day.

The compounds of this invention are generally utilized as the free base or as a pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts of a compound of Formula I are prepared e.g. in a conventional manner by treating a solution or suspension of a free base of Formula I with a molar equivalent of a pharmaceutically acceptable acid. Representative examples of suitable organic and inorganic acids are described above.

Suitable 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 limited to, syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compounds of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier are readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it may be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will range from about 25 mg to about 1 g per dosage unit. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

EXPERIMENTAL SECTION

The compounds of formula I, wherein R^1, R^2 and Ar are as defined above can be prepared by the methods outlined in the following reaction schemes 1-7 and in the examples. In the described methods, it is possible to make use of variants or modifications, which are themselves known to chemists skilled in the art or could be apparent to the person of ordinary skill in this art. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person skilled in the art in light of the following reaction schemes and examples.

For example, Scheme 5 describe the use of selective protecting groups during the synthesis of the compounds of the invention. One skilled in the art would be able to select the appropriate protecting group for a particular reaction. Moreover, it may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, keto and hydroxyl groups in the synthetic methods described below to synthesize the compounds of Formula I. Methods for protection and deprotection of such groups are well known in the art, and may be found in T. Green, et al., Protective Groups in Organic Synthesis, 1991, 2nd Edition, John Wiley & Sons, New York.

For compounds, which can exist as a mixture or equilibrium between two or more tautomers, only one tautomer is represented in the schemes, although it may not be the most stable tautomer. For compounds, which can exist in enantiomeric, stereoisomeric or geometric isomeric forms their geometric configuration is specified; otherwise the structure represents a mixture of stereoisomers.

Analytical LC-MS data was obtained using the following methods.

Method A:

LC-MS was run on Waters Aquity UPLC-MS consisting of Waters Aquity including column mamager, binary solvent manager, sample organizer, PDA detector (operating at 254 nM), ELS detector, and SQ-MS equipped with APPI-source operating in positive ion mode.

LC-conditions: The column was Acquity UPLC BEH C18 1.7µm ; 2.1x150mm operating at 60°C with 0.6 ml/min of a binary gradient consisting of water + 0.05 % trifluoroacetic acid (A) and acetonitrile + 5% water + 0.03 % trifluoroacetic acid (B). Gradient: 0.00 min: 10% B; 3.00 min: 99.9% B; 3.01 min: 10% B; 3.60 min: 10% B. Total run time: 3.60 min.

Method B:

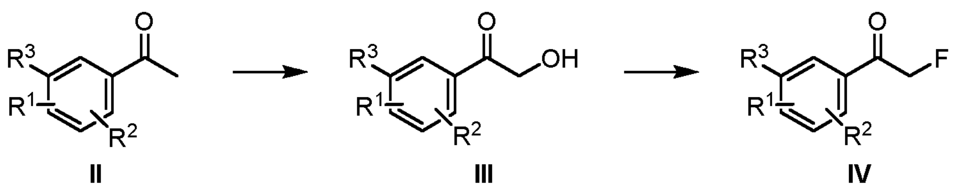
LC-MS were run on Waters Acquity UPLC-MS consisting of Waters Acquity including column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nm), ELS detector, and TQ-MS equipped with APPI-source operating in positive ion mode.

LC-conditions: The column was Acquity UPLC BEH C18 1.7µm ; 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 + 0.05 % trifluoroacetic acid (B). Gradient: 0.00 min: 10% B; 1.00 min: 100% B; 1.01 min: 10% B; 1.15 min: 10% B. Total run time: 1.15 min.

^{1}H NMR spectra were recorded at 600 MHz on a Bruker Avance AV-III-600 instrument or at 400 MHz on a Bruker Avance AV-III-400 instrument or a Varian 400 instrument. Chemical shift values are expressed in ppm-values relative. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, dt = double triplet, br = broad, and m = multiplet.

Compounds of the general formula IV may be prepared as shown in Scheme 1.

Scheme 1

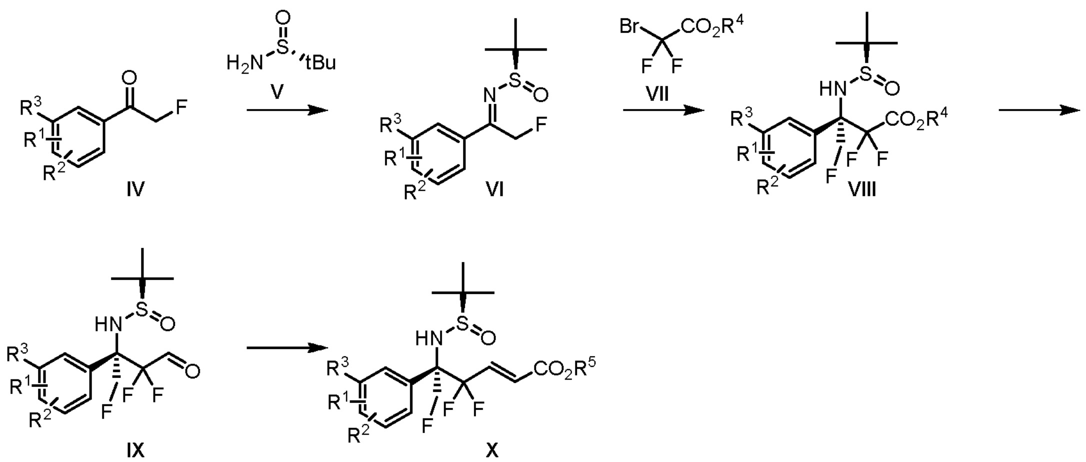


where R^1 is as defined under formula I and R^3 is a hydrogen or a nitro group

Compounds of the general formula III (Scheme 1) may be prepared by reacting compounds of the general formula II with an oxidant such as bis(acetoxy)iodobenzene in a solution of a base such as potassium hydroxide in methanol, followed by deprotection of the formed dimethyl ketal. Compounds of the general formula IV can then be obtained by substitution of the hydroxy moiety of compound III with fluorine using standard procedures.

Compounds of the general formula X may be prepared as shown in Scheme 2.

Scheme 2

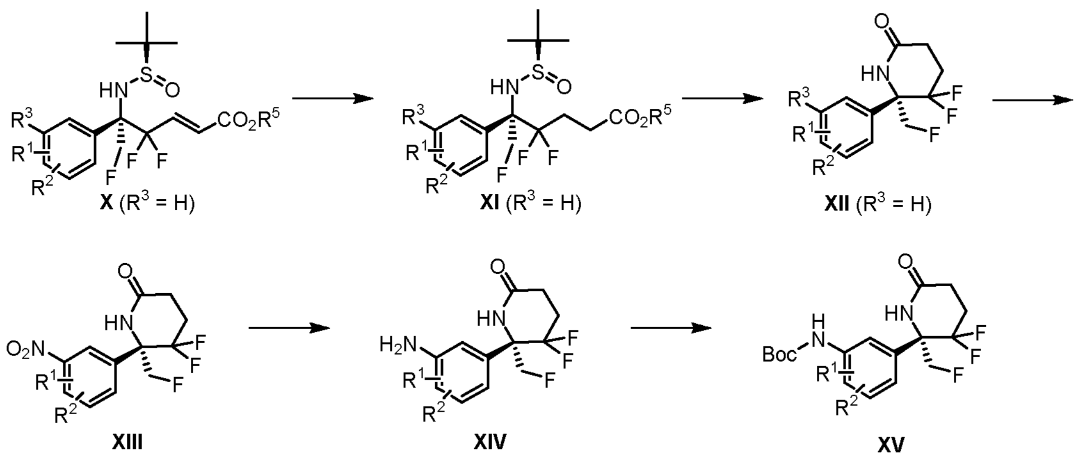


where R^1 and R^2 as defined under formula I, R^3 is hydrogen or a nitro group and R^4 and R^5 are an alkyl group such as methyl or ethyl.

Compounds of the general formula VI (Scheme 2) may be prepared by reacting compounds of the general formula IV with a sulfinamide such as V in the presence of a Lewis acid/dehydrating agent such as titanium tetraethoxide. Treatment of compounds of the general formula VI with compounds of the general formula VII such as ethyl bromodifluoroacetate in the presence of Zn powder or in the presence of diethyl zinc and tris(triphenylphosphine)rhodium(I) chloride gives compounds of the general formula VIII. Compounds of the general formula IX are obtained from compounds of the general formula VIII by treatment with a reducing agent such as diisobutylaluminium hydride. In some cases compound IX might be in equilibrium with the hydrate form. Treatment of compounds of the general formula IX with conditions such as methyl 2-(dimethoxyphosphoryl)-acetate in the presence of lithium chloride and a base such as N,N-diisopropylethylamine gives compounds of the general formula X.

Compound of the general formula XV may be prepared as shown in Scheme 3.

Scheme 3

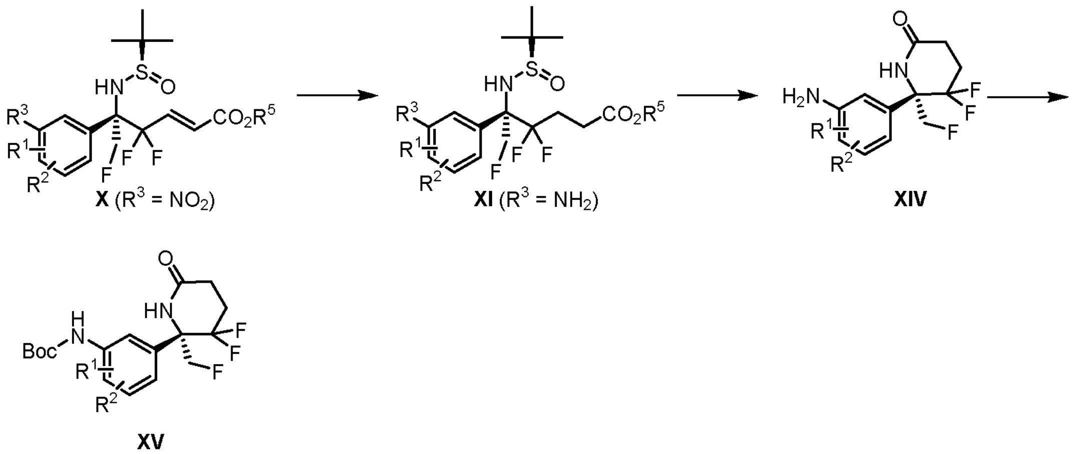


where R^1 and R^2 as defined under formula I and R^5 is an alkyl group such as methyl or ethyl.

Compounds of the general formula XI are obtained by hydrogenation of compounds of the general formula X in the presence of a catalyst such as palladium on carbon. Compounds of the general formula XII are obtained by treatment of compounds of the general formula XI with an acid such as hydrochloric acid in methanol followed by treatment with a base such as triethylamine or potassium carbonate in methanol. Compounds of the general formula XII (when R^3 is hydrogen) can be nitrated using nitric acid to give compounds of the general formula XIII. Reduction of the nitro group of compounds of the general formula XIII followed by protection of the formed aniline moiety (XIV) gives compounds of the general formula XV.

Compound of the general formula XV may be prepared as shown in Scheme 4.

Scheme 4

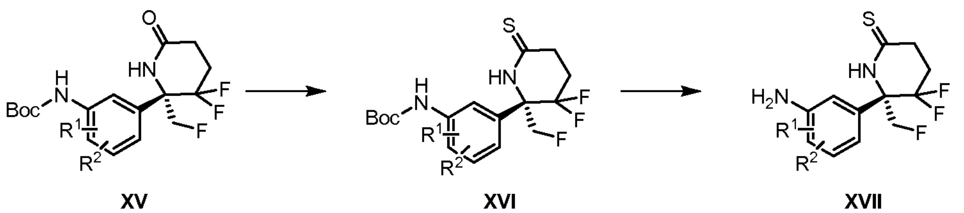


where R^1 and R^2 as defined under formula I and R^5 is an alkyl group such as methyl or ethyl.

Compounds of the general formula XI (when R^3 is an amino group) are obtained by hydrogenation of compounds of the general formula X (when R^3 is nitro) in the presence of a catalyst such as palladium on carbon. Compounds of the general formula XIV are obtained by treatment of compounds of the general formula XI (when R^3 is an amino group) with an acid such as hydrochloric acid in methanol followed by treatment with a base such as triethylamine or potassium carbonate in methanol followed by protection of the aniline moiety (XIV) gives compounds of the general formula XV.

Compound of the general formula XVII may be prepared as shown in Scheme 5.

Scheme 5

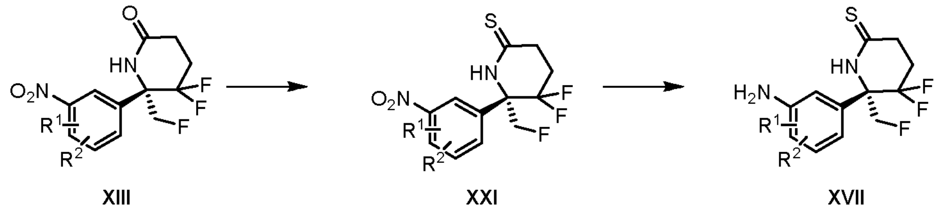


where R^1 and R^2 as defined under formula I

Treatment of compounds of the general formula XV with a reagent such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) followed by deprotection gives compounds of the general formula XVII.

Compound of the general formula XVII may be prepared as shown in Scheme 6.

Scheme 6

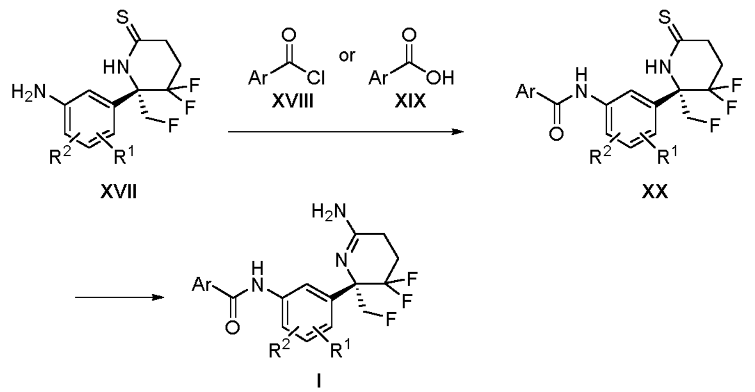


where R^1 and R^2 as defined under formula I

Treatment of compounds of the general formula XIII with a reagent such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) gives compounds of the general formula XXI. Compounds of the general formula XVII can be obtained by reduction of compounds of the general formula XXI with a reductant such as sodium dithionite or with hydrogen in the precense of a catalyst such as palladium on carbon.

Compounds of the general formula I may be prepared as shown in Scheme 7.

Scheme 7

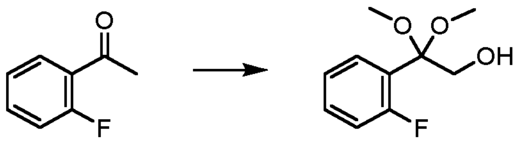


where R^1, R^2 and Ar are as defined under formula I.

Compounds of the general formula XX may be prepared by reacting compounds of the general formula XVII with a carboxylic acid chloride of general formula XVIII or by reaction with a carboxylic acid of general formula XIX using procedures known to chemists skilled in the art. Treatment of compounds of the general formula XX with ammonia gives compounds of the general formula I. In some cases, the addition of an oxidizing reagent such as tert-butyl hydroperoxide might be necessary to facilitate the reaction.

PREPARATION OF INTERMEDIATES

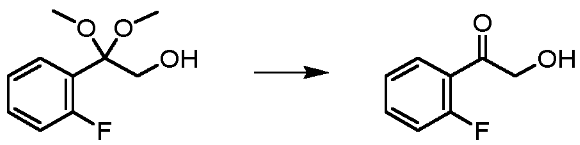
INTERMEDIATE: 2-(2-fluorophenyl)-2,2-dimethoxyethan-1-ol



To a mixture of potassium hydroxide (91.4 g, 1.63 mol) in methanol (1 L) was added a solution of 1-(2-fluorophenyl)ethan-1-one (50 g, 362 mmol) in methanol (300 mL) in a dropwise manner at 0°C. Then bis(acetoxy)iodobenzene (175 g, 543 mmol) was added in portions. After stirring at 0°C for 4 hours, the reaction was quenched with the addition of water (500 mL). The mixture was concentrated to remove methanol and the aqueous phase was extracted with ethyl acetate (700 mL, three times), the combined organic phases were washed with brine (300 mL), dried over Na_2SO_4 and concentrated. The crude product was used in the next step directly without further purification.

2-(2,3-difluorophenyl)-2,2-dimethoxyethan-1-ol was prepared in a similar way from 1-(2,3-difluoro-phenyl)ethan-1-one.

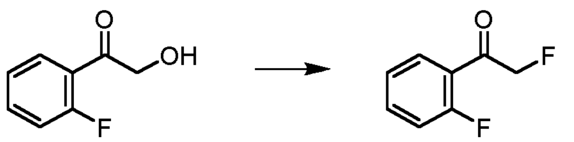
INTERMEDIATE: 1-(2-fluorophenyl)-2-hydroxyethan-1-one



2-(2-Fluorophenyl)-2,2-dimethoxyethan-1-ol (crude, 362 mmol) was dissolved in THF (450 mL) and water (150 mL). Then p-toluene sulfonic acid (125 g, 726 mmol) was added portionwise at room temperature. After the addition, the mixture was stirred under reflux for 5 hours. Water (150 mL) and sat. $NaHCO_3$ was added to quench the reaction, the mixture was extracted with ethyl acetate (500 mL, three times). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the residue was purified by column chromatography with petroleum ether: ethyl acetate = 20: 1 to give 1-(2-fluorophenyl)-2-hydroxyethan-1-one (42 g, 76% yield, two steps).

1-(2,3-difluorophenyl)-2-hydroxyethan-1-one was prepared in a similar way from 2-(2,3-difluoro-phenyl)-2,2-dimethoxyethan-1-ol.

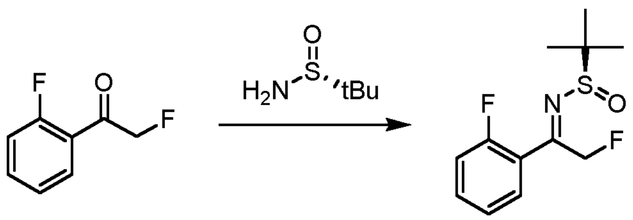
INTERMEDIATE: 2-fluoro-1-(2-fluorophenyl)ethan-1-one



To a solution of 1-(2-fluorophenyl)-2-hydroxyethan-1-one (10 g, 64.88 mmol) in dichloromethane (200 mL) was added $Et_3N(HF)_3$ (10.46 g, 227.8 mmol) and $CF_3(CF_2)_3SO_2F$ (29.4 g, 97.32 mmol) dropwise at 0°C, the solution was stirred at room temperature for 12 hours. TLC (petroleum ether: ethyl acetate = 10:1) showed no starting material. The mixture was poured into a saturated solution of $NaHCO_3$ and ice, extracted with dichloromethane (200 mL three times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 1:0-10:1) to afford 2-fluoro-1-(2-fluorophenyl)ethan-1-one (6 g, yield: 59%).

1-(2,3-difluorophenyl)-2-fluoroethan-1-one was prepared in a similar way from 1-(2,3-difluorophenyl)-2-hydroxyethan-1-one.

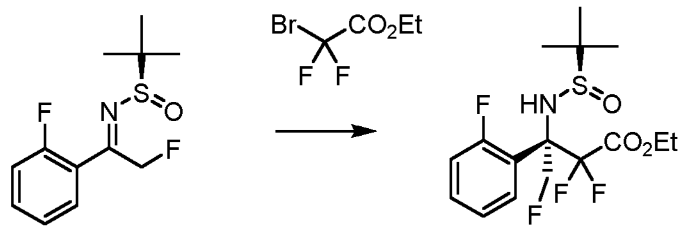
INTERMEDIATE: (*R*)-*N*-(2-fluoro-1-(2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide



To a solution of 2-fluoro-1-(2-fluorophenyl)ethan-1-one (6 g, 38.43 mmol) and $Ti(OEt)_4$ (17.53 g, 76.86 mmol) in THF (100 mL) was added (*R*)-2-methylpropane-2-sulfinamide (5.59 g, 46.12 mmol), the solution was stirred at 70°C for 12 h. TLC (petroleum ether: ethyl acetate = 10:1) showed no starting material. The mixture was quenched with water (200 mL), then filtered and extracted with ethyl acetate (200 mL, four times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 1:0 - 10:1) to afford (*R*)-*N*-(2-fluoro-1-(2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (6.9 g, yield: 69%).

(*R*)-*N*-(1-(2,3-difluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide was prepared in a similar way from 1-(2,3-difluorophenyl)-2-fluoroethan-1-one.

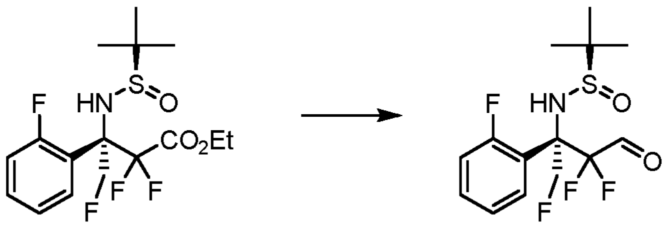
INTERMEDIATE: ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-2,2,4-trifluoro-3-(2-fluorophenyl)-butanoate



To a solution of (*R*)-*N*-(2-fluoro-1-(2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (10 g, 38.6 mmol), tris(triphenylphosphine)rhodium(I) chloride (1.01 g, 1.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (15.7 g, 77.1 mmol) in anhydrous THF (200 mL) was added dropwise Et_2Zn (77.1 mL, 1M in hexane, 77.1 mmol) at -78°C, the solution was stirred at 0°C for 1 hour under N_2. TLC (petroleum ether: ethyl acetate = 10:1) showed no (*R*)-*N*-(2-fluoro-1-(2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide. The mixture was quenched with water (100 mL), filtered and extracted with ethyl acetate (200 mL, three times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 20:1 - 5:1) to afford ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-2,2,4-trifluoro-3-(2-fluorophenyl)butanoate (13 g, yield: 88%) as a yellow oil. ^1H NMR ($CDCl_3$, 400MHz): δ 7.59-7.57 (m, 1H), 7.44-7.42 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.14-7.10 (m, 1H), 5.52-5.37 (m, 1H), 5.24-5.10 (m, 2H), 4.35 (q, J = 7.6 Hz, 2H), 1.36-1.23 (m, 12H).

Ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(2,3-difluorophenyl)-2,2,4-trifluorobutanoate was prepared in a similar way from (*R*)-*N*-(1-(2,3-difluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide.

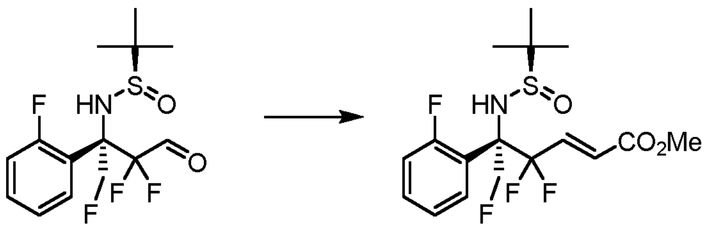
INTERMEDIATE: (*R*)-2-methyl-*N*-((*S*)-1,3,3-trifluoro-2-(2-fluorophenyl)-4-oxobutan-2-yl)propane-2-sulfinamide



To a solution of ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-2,2,4-trifluoro-3-(2-fluorophenyl)butanoate (12 g, 31.30 mmol) in anhydrous THF (200 mL) DIBAL-H (diisobutylaluminium hydride) (62.6 mL, 1 M in THF, 62.6 mmol) was added dropwise at -78°C. The solution was stirred at -78°C for 2 hours under N_2. The mixture was quenched with water (100 mL), filtered and extracted with ethyl acetate (200 mL, four times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure to afford crude (*R*)-2-methyl-*N*-((*S*)-1,3,3-trifluoro-2-(2-fluorophenyl)-4-oxobutan-2-yl)propane-2-sulfinamide (10.6 g) which was used in the next step without further purification.

(*R*)-*N*-((*S*)-2-(2,3-difluorophenyl)-1,3,3-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide was prepared in a similar way from ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(2,3-difluorophenyl)-2,2,4-trifluorobutanoate.

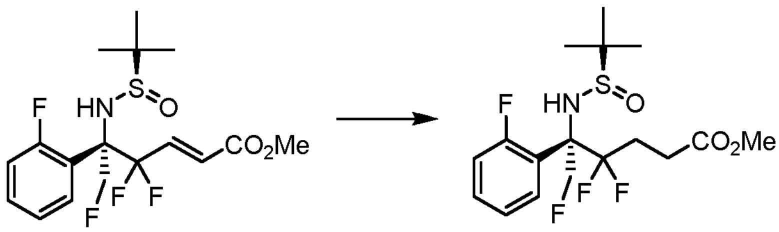
INTERMEDIATE: Methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-4,4,6-trifluoro-5-(2-fluorophenyl)hex-2-enoate



To a mixture of *N*,*N*-diisopropylethylamine (4.8 g, 37.49 mmol) and LiCl (1.6 g, 37.49 mmol) in acetonitrile (200mL) was added methyl 2-(dimethoxyphosphoryl)-acetate (7.9 g, 37.49 mmol), then (*R*)-2-methyl-*N*-((*S*)-1,3,3-trifluoro-2-(2-fluorophenyl)-4-oxobutan-2-yl)propane-2-sulfinamide (10.6 g, 31.24 mmol) was added to the mixture at 0°C. The mixture was allowed to warm to 25°C and stirred for 12 hours. TLC (petroleum ether: ethyl acetate = 3:1) showed no starting material. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate (500 mL, three times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 5:1 - 1:1) to afford methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-4,4,6-trifluoro-5-(2-fluorophenyl)hex-2-enoate (8 g, yield: 75%, two steps).

Methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-5-(2,3-difluorophenyl)-4,4,6-trifluorohex-2-enoate-sulfinamide was prepared in a similar way from (*R*)-*N*-((*S*)-2-(2,3-difluorophenyl)-1,3,3-trifluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide.

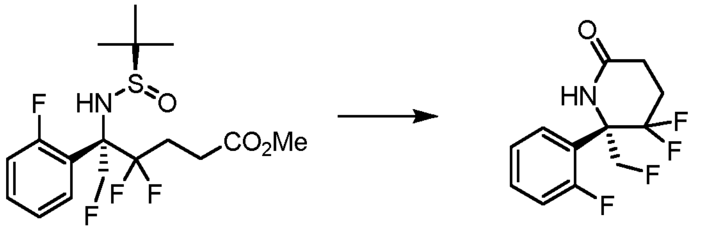
INTERMEDIATE: Methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-4,4,6-trifluoro-5-(2-fluorophenyl)-hexanoate



To a solution of methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-4,4,6-trifluoro-5-(2-fluorophenyl)hex-2-enoate (8 g, 20.23 mmol) in ethyl acetate (1000 mL) was added Pd/C (5 g, 10%). The mixture was stirred at 30°C under 50 psi of H_2 for 12 h. LCMS showed no starting material. The mixture was filtered and concentrated under reduced pressure to afford crude methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-4,4,6-trifluoro-5-(2-fluorophenyl)hexanoate (8.04 g) which was used in the next step without further purification.

Methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-5-(2,3-difluorophenyl)-4,4,6-trifluorohexanoate was prepared in a similar way from methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-5-(2,3-difluorophenyl)-4,4,6-trifluorohex-2-enoate sulfinamide.

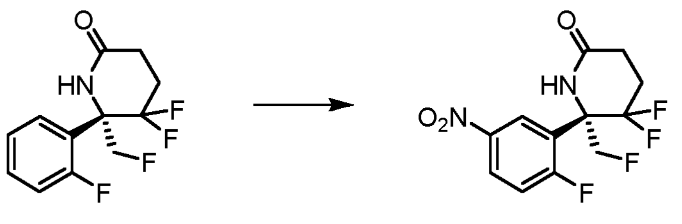
INTERMEDIATE: (*S*)-5,5-difluoro-6-(fluoromethyl)-6-(2-fluorophenyl)piperidin-2-one



To a solution of methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-4,4,6-trifluoro-5-(2-fluorophenyl)-hexanoate (8.0 g, 20.13 mol) in methanol (200 mL) was added HCl/methanol (100 mL), the solution was stirred at 20°C for 2 h. TLC (petroleum ether: ethyl acetate = 3:1) showed no starting material. The solvent was removed under reduce pressure, the residue was dissolved in xylene (200 mL), then to the solution was added Et_3N (5 mL). The solution was stirred at 110°C for 12 h under N_2. The solvent was removed under reduce pressure. The mixture was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 3:1 - 0:1) to afford (*S*)-5,5-difluoro-6-(fluoromethyl)-6-(2-fluorophenyl)piperidin-2-one (4.1 g, 77% yield over two steps). ^1H NMR ($CDCl_3$, 400MHz): δ 7.55-7.53 (m, 1H), 7.48-7.46 (m, 1H), 7.31-7.29 (m, 1H), 7.20-7.17 (m, 1H), 6.49 (s, 1H), 5.25-5.22 (m, 1H), 5.13-5.11 (m, 1H), 2.75-2.71 (m, 2H), 2.36-2.28 (m, 2H).

(*S*)-6-(2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidin-2-one was prepared in a similar way from Methyl (*S*)-5-(((*R*)-tert-butylsulfinyl)amino)-5-(2,3-difluorophenyl)-4,4,6-trifluorohexanoate.

INTERMEDIATE: (*S*)-5,5-difluoro-6-(2-fluoro-5-nitrophenyl)-6-(fluoromethyl)piperidin-2-one

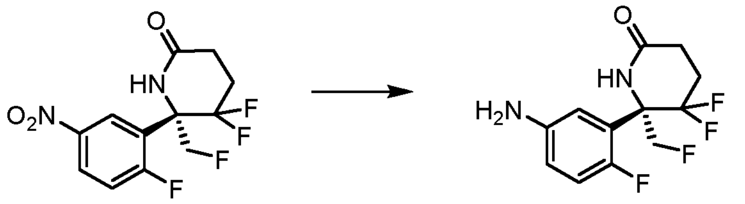


(*S*)-5,5-difluoro-6-(fluoromethyl)-6-(2-fluorophenyl)piperidin-2-one (3.5 g, 13.4 mmol) was dissolved in TFA (23 mL). The solution was cooled to 0°C and concentrated H_2SO_4 (5.5mL) was added. Finally, 65% HNO_3 (1.0 mL, 14.7 mmol) was added dropwise over 5 min. The solution was stirred at 0°C for 10 min. LCMS showed no starting material. The solution was poured onto 50 g ice and basified to pH>11 using 5N NaOH. The suspension was extracted with ethyl acetate (200 mL), the combined organic layers were washed with a solution of saturated aqueous NH_4Cl (50 mL) and water (100 mL), then dried over Na_2SO_4 and concentrated under reduce pressure to afford : (*S*)-5,5-difluoro-6-(2-fluoro-

5-nitrophenyl)-6-(fluoromethyl)piperidin-2-one (4 g, 98% yield). ^{1}H NMR (DMSO-*d*6, 400MHz): δ 8.73 (s, 1H), 8.41-8.34 (m, 2H), 7.64-7.59 (m, 1H), 5.35-5.20 (m, 1H), 4.92-4.78 (m, 1H), 2.57-2.50 (m, 2H), 2.34-2.30 (m, 2H).

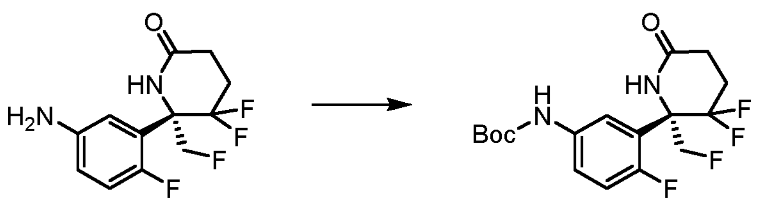
(*S*)-6-(2,3-difluoro-5-nitrophenyl)-5,5-difluoro-6-(fluoromethyl)piperidin-2-one was prepared in a similar way from (*S*)-6-(2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidin-2-one.

INTERMEDIATE: (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidin-2-one



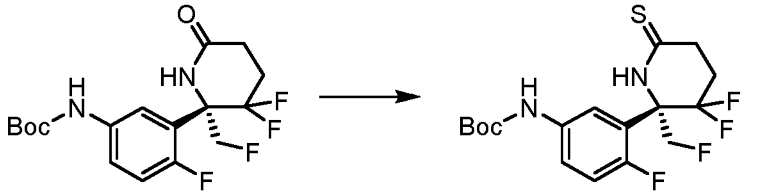
A solution of (*S*)-5,5-difluoro-6-(2-fluoro-5-nitrophenyl)-6-(fluoromethyl)piperidin-2-one (4 g, 13.06 mmol) in ethyl acetate (200 mL) was added Pd/C (2 g, 10%), the mixture was stirred at 30°C for 12 h under 50 psi of H_2. LCMS showed no starting material. The mixture was filtered and concentrated under reduced pressure to afford crude (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-fluoromethyl)piperidin-2-one (3.6 g) which was used in the next step without further purification.

INTERMEDIATE: *tert*-butyl (*S*)-(3-(3,3-difluoro-2-(fluoromethyl)-6-oxopiperidin-2-yl)-4-fluorophenyl)carbamate



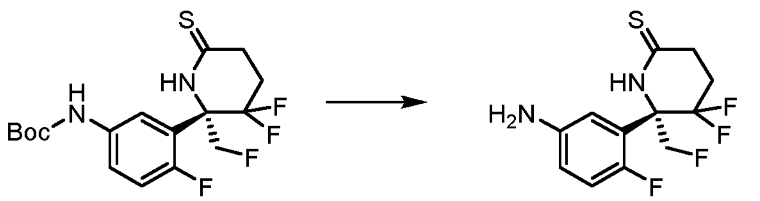
To a solution of (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidin-2-one (3.6 g, 13.03 mmol) in anhydrous dichloromethane (100 mL) and saturated aqueous $NaHCO_3$ (72 mL) was added Boc_2O (8.53 g, 39.09 mmol), the solution was stirred at 20°C for 12 hours. The mixture was quenched with water (50 mL) and extracted with dichloromethane (100 mL, three times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1 - 10:1) to afford *tert*-butyl (*S*)-(3-(3,3-difluoro-2-(fluoromethyl)-6-oxopiperidin-2-yl)-4-fluorophenyl)carbamate (4.9 g, 94% yield over two steps). ^{1}H NMR (DMSO-*d*6, 400MHz): δ 9.51 (s, 1H), 8.37 (s, 1H), 7.66-7.65 (m, 1H), 7.53 (s, 1H), 7.16-7.11 (m, 1H), 5.22 (dd, *J* = 48.0, 9.2 Hz, 1H), 4.69 (dd, *J* = 48.0, 9.2 Hz, 1H), 2.50-2.16 (m, 4H), 1.46 (s, 9H).

INTERMEDIATE: *tert*-butyl (*S*)-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluoro-phenyl)carbamate



To a solution of *tert*-butyl (*S*)-(3-(3,3-difluoro-2-(fluoromethyl)-6-oxopiperidin-2-yl)-4-fluorophenyl)-carbamate (2.3 g, 6.11 mmol) in anhydrous toluene (50 mL) was added Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) (1.36 g, 3.36 mmol), the solution was stirred at 90°C for 12 h under N_2. TLC (petroleum ether: ethyl acetate = 3:1) showed no starting materials. The solution was extracted with ethyl acetate (50 mL three times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 10:1 - 3:1) to afford *tert*-butyl (*S*)-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)-carbamate (2.15 g, yield: 90%).

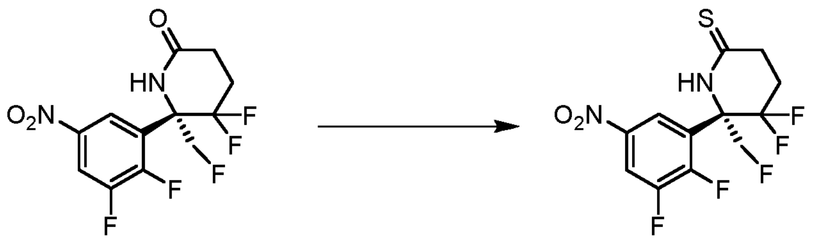
INTERMEDIATE: (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione



To a solution of *tert*-butyl (*S*)-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluoro-phenyl)carbamate (5.5 g, 14.02 mmol) in dichloromethane (100 mL) was added HCl/methanol (50 mL), the solution was stirred at 20°C for 2 hours. TLC (petroleum ether: ethyl acetate = 2:1) showed no starting material. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (50 mL), the solution was basified to pH=7-8 using saturated aqueous $NaHCO_3$, the solution was extracted with dichloromethane (100 mL, three times), the combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced. The residue was dispersed in dichloromethane (20 mL), then filtered, the filtrate was dried under reduced pressure to give (*S*)-6-(5-

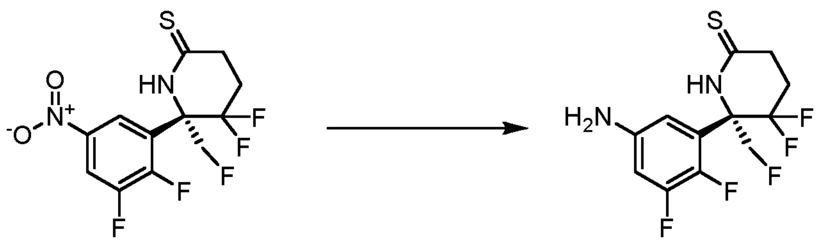
amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione (1.74 g) as a white solid, ^{1}H NMR (DMSO-*d*6, 400 MHZ): *δ* 10.69 (s, 1H), 6.92-6.87 (m, 1H), 6.60-6.58 (m, 1H), 6.51-6.49 (m, 1H), 5.35-5.33 (m, 1H), 5.23-5.18 (m, 2H), 4.72 (dd, *J* = 48.0, 10.0 Hz, 1H), 3.29-2.92 (m, 2H), 2.24-2.19 (m, 2H), $[\alpha]^{20}{}_{,D}$ = -192 (c = 0.1 g/100 mL, EtOH).

INTERMEDIATE: (*S*)-6-(2,3-difluoro-5-nitrophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione



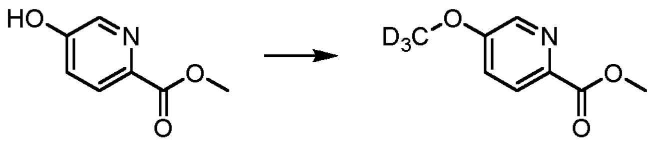
Lawesson's Reagent (0.81 g, 2.0 mmol) was added to (*S*)-6-(2,3-difluoro-5-nitrophenyl)-5,5-difluoro-6-(fluoromethyl)piperidin-2-one (0.59 g, 1.82 mmol) in toluene (25 ml). The reaction mixture was stirred at 110°C overnight. The reaction mixture was cooled to room temperature and poured into sat. $NaHCO_3$ (aq). The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified via flash chromatography on silica gel (etyl acetate/heptane) to give (*S*)-6-(2,3-difluoro-5-nitrophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione (0.58g 65% purity, 61% yield).

INTERMEDIATE: (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione



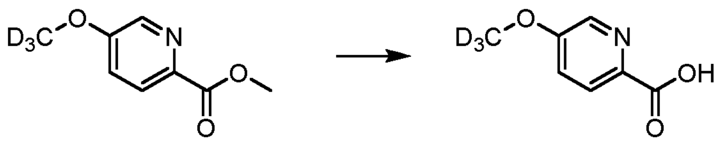
Sodium dithionite (1.16 g, 6.65 mmol) and potassium carbonate (0.459 g, 3.32 mmol) were dissolved in water (5.00 g, 5 ml, 278 mmol). The reaction mixture was cooled to 0°C. (*S*)-6-(2,3-difluoro-5-nitrophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione (0.58 g, 1.11 mmol, 65% purity) in ethanol (5 ml,) was added dropwise. The reaction mixture was stirred at room temperature for 30 minutes. Water was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in ethyl acetate and filtered through a plug of silica gel and concentrated in vacuo. The crude material was purified via flash chromatography on silica gel (ethyl acetate/heptane) to give (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione (105mg, 35%)

INTERMEDIATE: methyl 5-(methoxy-d_3)picolinate



Methyl 5-hydroxypicolinate (2.88 g, 18.8 mmol) was dissolved in dimethylformamide (108 ml) under argon. Potassium carbonate (7.20 g, 52.1 mmol) was added and the orange suspension was stirred for 45 minutes at room temperature. Iodomethane-d_3 (1.41 ml, 22.6 mmol) was added. The reaction mixture was stirred for 2 hours. Water was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo and purified by column chromatography on silica gel (heptane: ethyl acetate) to give methyl 5-(methoxy-d_3)picolinate.

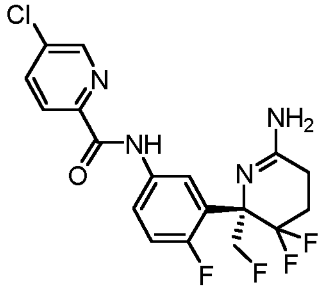
INTERMEDIATE: 5-(methoxy-d_3)picolinic acid



Methyl 5-(methoxy-d_3)picolinate (200mg, 1.175 mmol) was dissolved in water (1.5 ml) and 1,4-dioxane (3 ml). Lithium hydroxide (70.4 mg, 2.94 mmol) was added and the reaction mixture was stirred for 1 hour. The reaction mixture was evaporated to about 2 ml and extracted with diethylether. The organic phase was extracted with 1M NaOH and the combined aqueous phases were acidified to pH 2 with 6N HCl (aq). The mixture was cooled on an icebath and a precipitate was formed. The precipitate was colected to give 5-(methoxy-d_3)picolinic acid.

PREPARATION OF THE COMPOUNDS OF THE INVENTION

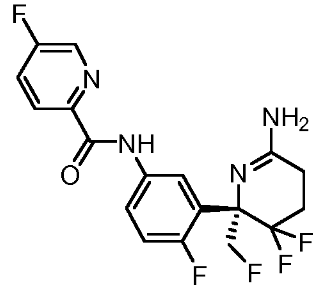
Example 1 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-chloropicolinamide (compound 1)



To a solution 5-chloropicolinic acid (0.243 g, 1.540 mmol) in DMF (12 mL), HATU (1-[bis(dimethyl-amino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (0.86 g, 2.3 mmol) was added, the solution was stirred 5 minutes. Then (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-fluoromethyl)piperidine-2-thione (0.3 g, 1.026 mmol) and DIPEA (*N*,*N*-diisopropylethylamine) (0.90 mL, 5.1 mmol) were added. The mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride was added and the mixture was extrated with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The mixture was purified by column chromatography on silica gel (heptane: ethyl acetate) to afford (*S*)-5-chloro-*N*-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide, which was dissolved in 7M ammonia in methanol (12 mL). The mixture was stirred at 50°C overnight, concentrated under reduce pressure and purified by column chromatography on silica gel (heptane: ethyl acetate) to afford (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-chloropicolinamide (0.23 g, 55% yield). ^{1}H NMR (600 MHz, DMSO-*d*6) δ 10.75 (s, 1H), 8.80 (dd, J = 2.4, 0.6 Hz, 1H), 8.21 (dd, J = 8.4, 2.4 Hz, 1H), 8.16 (dd, J = 8.4, 0.6 Hz, 1H), 7.89 (ddd, J = 11.7, 6.6, 3.8 Hz, 1H), 7.86 (dd, J = 6.6, 2.4 Hz, 1H), 7.16 (dd, J = 11.7, 8.8 Hz, 1H), 6.10 (s, 2H), 5.02 – 4.88 (m, 1H), 4.79 (dd, J = 45.9, 8.8 Hz, 1H), 2.53 – 2.50 (m, 2H), 2.18 – 1.97 (m, 2H). LC-MS (m/z) 415 (MH^+); t_R = 0.52 minutes (Method A)

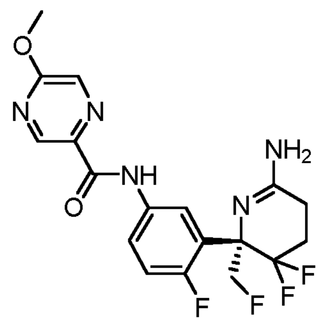
The following compounds were prepared in a way similar to example 1:

Example 2 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-fluoropicolinamide (compound 2)



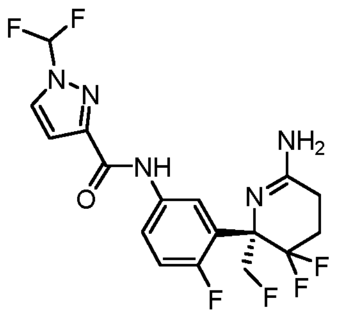
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-fluoropicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.85 (s, 1H), 8.76 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 8.6, 4.4 Hz, 1H), 8.15 (m, 1H), 8.00 (td, *J* = 8.7, 2.8 Hz, 2H), 7.33 (dd, *J* = 11.8, 9.1 Hz, 1H), 5.15 (ddd, *J* = 54.9, 46.5, 9.2 Hz, 2H), 2.58 – 2.46 (m, 2H), 2.46 – 2.23 (m, 2H). LC-MS (m/z) 399.2 (MH^+); t_R = 0.49 minutes (Method B)

Example 3 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide (compound 3)



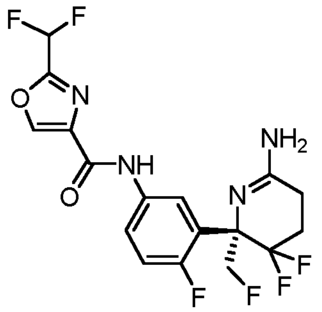
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-methoxypyrazine-2-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.71 (s, 1H), 8.91 (d, *J* = 1.3 Hz, 1H), 8.43 (d, *J* = 1.3 Hz, 1H), 8.06 (m, 1H), 7.98 (m, 1H), 7.29 (dd, *J* = 11.6, 9.1 Hz, 1H), 5.11 (ddd, *J* = 94.4, 46.2, 8.7 Hz, 2H), 4.03 (s, 3H), 2.55 – 2.48 (m, 2H), 2.42 – 2.19 (m, 2H). LC-MS (m/z) 412 (MH^+); t_R = 0.47 minutes (Method A)

Example 4 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1H-pyrazole-3-carboxamide (compound 4)



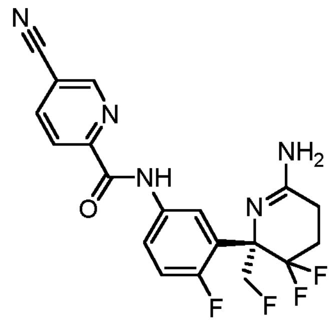
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 1-(difluoromethyl)-1H-pyrazole-3-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.46 (s, 1H), 8.42 (d, *J* = 2.7 Hz, 1H), 8.04 – 7.76 (m, 3H), 7.15 (dd, *J* = 11.7, 8.6 Hz, 1H), 7.02 (d, *J* = 2.7 Hz, 1H), 6.16 (s, 2H), 5.06 – 4.72 (m, 2H), 2.54 – 2.49 (m, 2H), 2.20 – 1.98 (m, 2H). LC-MS (m/z) 420 (MH^+); t_R = 0.46 minutes (Method A)

Example 5 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-2-(difluoromethyl)oxazole-4-carboxamide (compound 5)



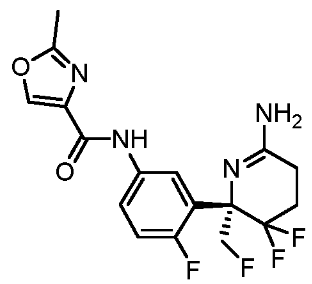
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 2-(difluoromethyl)oxazole-4-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.54 (s, 1H), 9.04 (s, 1H), 7.93 (s, 1H), 7.86 (d, *J* = 4.8 Hz, 1H), 7.47 – 7.21 (m, 2H), 5.04 (dd, *J* = 94.5, 46.0 Hz, 2H), 2.55 – 2.49 (m, 2H), 2.24 (dd, *J* = 68.4, 4.9 Hz, 2H). LC-MS (m/z) 421 (MH^+); t_R = 0.46 minutes (Method A)

Example 6 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-cyanopicolinamide (compound 6)



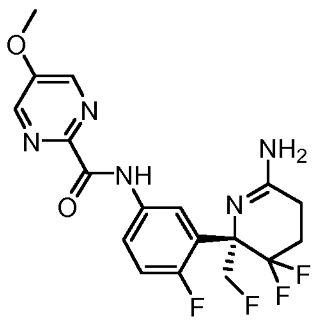
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-cyanopicolinic acid. [1]H NMR (600 MHz, DMSO) δ 10.95 (s, 1H), 9.21 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.59 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.29 (dd, *J* = 8.2, 0.8 Hz, 1H), 8.03 – 7.90 (m, 2H), 7.23 (s, 1H), 4.97 (dd, *J* = 94.5, 45.1 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.29 – 2.03 (m, 2H). LC-MS (m/z) 406 (MH^+); t_R = 0.47 minutes (Method A)

Example 7 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-2-methyloxazole-4-carboxamide (compound 7)



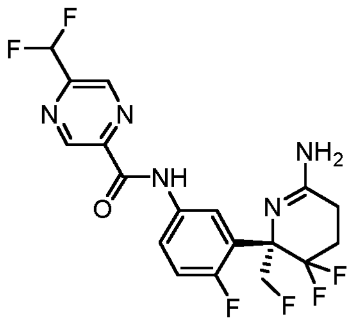
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 2-methyloxazole-4-carboxylic acid. [1]H NMR (600 MHz, DMSO) of the trifluroracetic acid salt δ 10.97 (s, 1H), 10.38 (s, 1H), 9.71 (s, 1H), 9.16 (s, 1H), 8.68 (s, 1H), 8.09 (m, 1H), 7.94 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.32 (dt, *J* = 12.1, 9.0 Hz, 1H), 5.37 – 4.99 (m, 2H), 3.10 – 2.96 (m, 2H), 2.53 (s, 3H), 2.49 – 2.31 (m, 2H).LC-MS (m/z) 385 (MH^+); t_R = 0.43 minutes (Method A)

Example 8 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-methoxypyrimidine-2-carboxamide (compound 8)



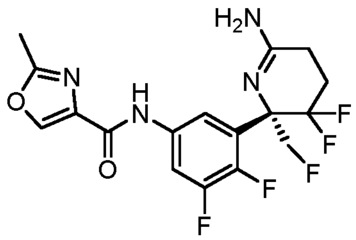
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-methoxypyrimidine-2-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) of the trifluroracetic acid salt δ 10.89 (s, 1H), 10.81 (s, 1H), 9.67 (s, 1H), 8.91 (s, 1H), 8.74 (s, 2H), 8.16 (ddd, *J* = 8.9, 4.0, 2.7 Hz, 1H), 7.99 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.36 (dd, *J* = 12.1, 9.0 Hz, 1H), 5.21 (ddd, *J* = 55.4, 45.9, 10.0 Hz, 2H), 4.04 (s, 3H), 3.11 – 2.97 (m, 2H), 2.50 – 2.31 (m, 2H). LC-MS (m/z) 412 (MH^+); t_R = 0.42 minutes (Method A)

Example 9 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide (compound 9)



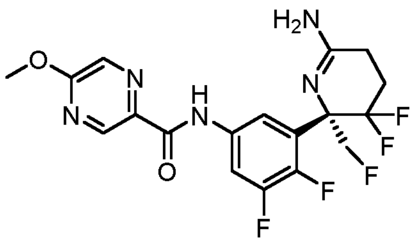
Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-(difluoromethyl)pyrazine-2-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) of the trifluroracetic acid salt δ 11.14 (s, 1H), 11.00 (s, 1H), 9.72 (s, 1H), 9.42 (d, *J* = 1.2 Hz, 1H), 9.18 (s, 1H), 9.11 (s, 1H), 8.19 (ddd, *J* = 8.9, 3.9, 2.7 Hz, 1H), 8.06 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.40 (dd, *J* = 12.0, 9.0 Hz, 1H), 7.28 (t, *J* = 53.9 Hz, 1H), 5.21 (ddd, *J* = 55.5, 46.0, 10.0 Hz, 2H), 3.12 – 2.97 (m, 2H), 2.51 – 2.32 (m, 2H). LC-MS (m/z) 432 (MH^+); t_R = 0.48 minutes (Method A)

Example 10 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-2-methyloxazole-4-carboxamide (compound 10)



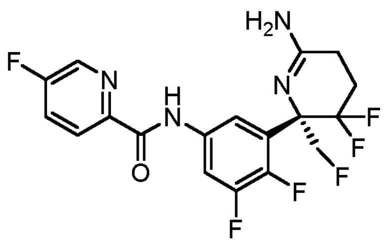
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 2-methyloxazole-4-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.44 (s, 1H), 8.67 (s, 1H), 7.96 (ddd, *J* = 12.2, 6.6, 2.6 Hz, 1H), 7.69 – 7.65 (m, 1H), 6.17 (s, 2H), 4.87 (td, *J* = 46.0, 8.9 Hz, 2H), 2.55 – 2.49 (m, 2H), 2.52 (s, 3H), 2.19 – 1.96 (m, 2H). LC-MS (m/z) 403 (MH^+); t_R = 0.46 minutes (Method A)

Example 11 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-methoxypyrazine-2-carboxamide (compound 11)



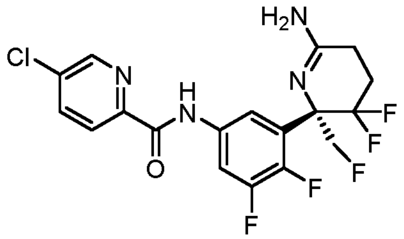
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-methoxypyrazine-2-carboxylic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.77 (s, 1H), 8.89 (d, *J* = 1.2 Hz, 1H), 8.42 (d, *J* = 1.2 Hz, 1H), 8.03 (ddd, *J* = 12.0, 6.6, 2.4 Hz, 1H), 7.79 – 7.71 (m, 1H), 6.18 (s, 2H), 5.03 – 4.70 (m, 2H), 4.02 (s, 3H), 2.55 – 2.49 (m, 2H), 2.23 – 1.95 (m, 2H). LC-MS (m/z) 430 (MH^+); t_R = 0.52 minutes (Method A)

Example 12 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-fluoropicolinamide (compound 12)



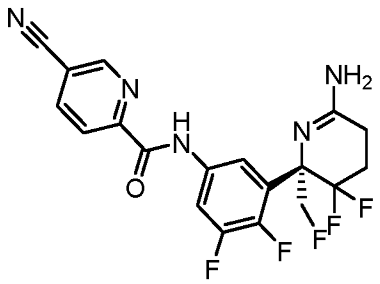
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-fluoropicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.89 (s, 1H), 8.74 (d, *J* = 2.8 Hz, 1H), 8.24 (dd, *J* = 8.7, 4.6 Hz, 1H), 8.06 (m, 1H), 7.99 (td, *J* = 8.7, 2.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 6.23 (s, 2H), 4.98 – 4.81 (m, 2H), 2.52 – 2.50 (m, 2H), 2.22 – 1.97 (m, 2H). LC-MS (m/z) 417 (MH$^+$); t_R = 0.52 minutes (Method A)

Example 13 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-chloropicolinamide (compound 13)



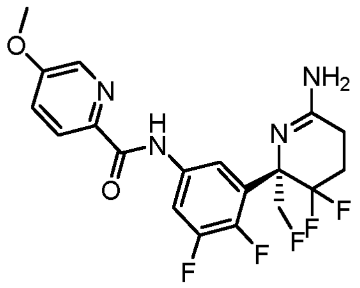
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-chloropicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.96 (s, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.22 – 8.14 (m, 2H), 8.12 – 8.04 (m, 1H), 7.75 (s, 1H), 6.38 (s, 2H), 5.04 – 4.80 (m, 2H), 2.56 – 2.49 (m, 2H), 2.11 (m, 2H). LC-MS (m/z) 433 (MH$^+$); t_R = 0.55 minutes (Method A)

Example 14 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-cyanopicolinamide (compound 14)



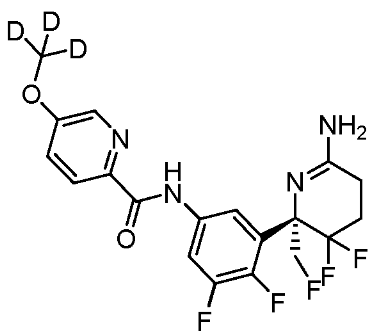
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-cyanopicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 11.10 (s, 1H), 9.22 (d, *J* = 1.9 Hz, 1H), 8.60 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.30 (dd, *J* = 13.0, 4.9 Hz, 1H), 8.06 (ddd, *J* = 12.0, 6.6, 2.5 Hz, 1H), 7.80 – 7.76 (m, 1H), 6.18 (s, 2H), 5.00 – 4.77 (m, 2H), 2.51 (dd, *J* = 3.5, 1.7 Hz, 2H), 2.20 – 1.99 (m, 2H). LC-MS (m/z) 424 (MH$^+$); t_R = 0.49 minutes (Method B)

Example 15 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-methoxypicolinamide (compound 15)



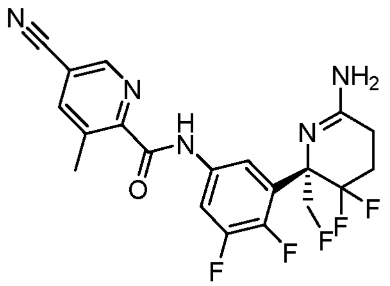
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-methoxypicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.72 (s, 1H), 8.40 (d, *J* = 2.8 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 8.05 (ddd, *J* = 12.2, 6.6, 2.4 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.63 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.15 (s, 2H), 4.99 – 4.77 (m, 2H), 3.94 (s, 3H), 2.55 – 2.47 (m, 2H), 2.20 – 1.98 (m, 2H). LC-MS (m/z) 429 (MH^+); t_R = 0.51 minutes (Method B)

Example 16 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-(methoxy-d_3)picolinamide (compound 16)



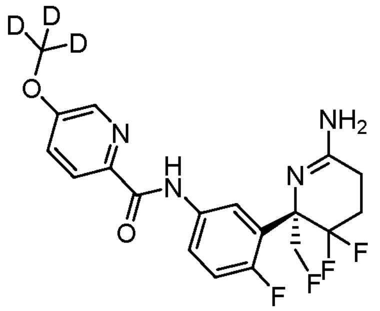
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-(methoxy-d_3)picolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.72 (s, 1H), 8.40 (d, *J* = 2.8 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 8.05 (ddd, *J* = 12.2, 6.6, 2.6 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.62 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.17 (s, 2H), 5.00 – 4.75 (m, 2H), 2.20 – 2.00 (m, 2H). LC-MS (m/z) 432.1 (MH^+); t_R = 0.54 (Method B)

Example 17 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide (compound 17)



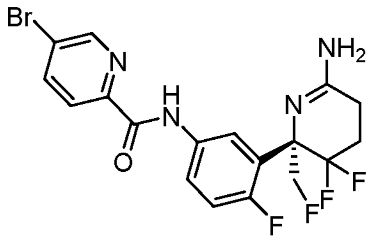
Prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-cyano-3-methylpicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.98 (s, 1H), 9.00 (dd, *J* = 1.9, 0.6 Hz, 1H), 8.42 (dd, *J* = 1.9, 0.7 Hz, 1H), 8.12 – 7.99 (m, 1H), 7.57 (s, 1H), 6.19 (s, 2H), 4.88 (ddd, *J* = 54.2, 46.8, 8.0 Hz, 2H), 2.55 (s, 3H), 2.24 – 1.99 (m, 2H). LC-MS (m/z) 438.1 (MH^+); t_R = 0.55 (Method B)

Example 18 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(methoxy-d_3)picolinamide (compound 18)



Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-(methoxy-d_3)picolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.52 (s, 1H), 8.39 (d, *J* = 2.9 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.84 (dd, *J* = 6.9, 2.7 Hz, 1H), 7.61 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.14 (dd, *J* = 11.8, 8.8 Hz, 1H), 6.11 (s, 2H), 5.02 – 4.88 (m, 1H), 4.79 (dd, *J* = 46.0, 8.9 Hz, 1H), 2.18 – 1.96 (m, 2H). LC-MS (m/z) 414.1 (MH^+); t_R = 0.49 (Method B)

Example 19 (*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-bromopicolinamide (compound 19)



Prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-bromopicolinic acid. ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 8.87 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.33 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.08 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.90 (ddd, *J* = 8.7, 4.0, 2.9 Hz, 1H), 7.86 (dd, *J* = 6.9, 2.7 Hz, 1H), 7.15 (dd, *J* = 11.8, 8.8 Hz, 1H), 6.10 (s, 2H), 4.95 (ddd, *J* = 48.4, 8.8, 2.5 Hz, 1H), 4.79 (dd, *J* = 46.0, 8.9 Hz, 1H), 2.52 – 2.48 (m, 2H), 2.18 – 1.95 (m, 2H). LC-MS (m/z) 459.1 (MH^+); t_R = 0.53 (Method B)

Stereochemistry

Crystals were obtained by recrystallization of (*S*)-5-bromo-*N*-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide from a mixture of heptane and ethyl acetate. The structure of (*S*)-5-bromo-*N*-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide was elucidated by X-ray crystallography of said crystals. The structure shows the absolute configuration of (*S*)-5-bromo-*N*-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide. (*S*)-5-Bromo-*N*-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide was prepared as described in example 1 starting from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and 5-bromopicolinic acid.

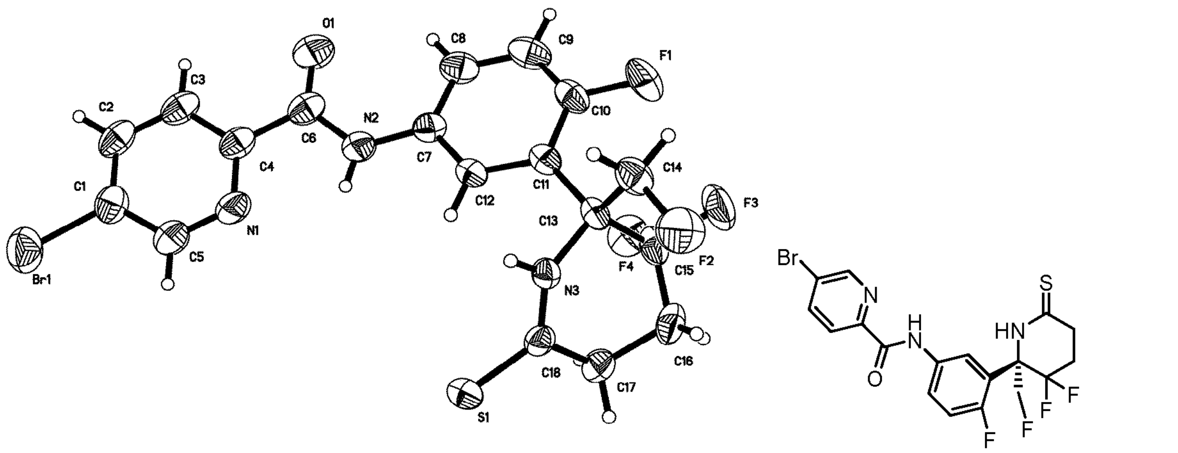


Figure 1: X-ray structure of (*S*)-5-bromo-*N*-(3-(2-(difluoromethyl)-3,3-difluoro-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide

The absolute configurations of the exemplified compounds of the present invention can thus be rationalized. (*S*)-5-Bromo-*N*-(3-(3,3-difluoro-2-(fluoromethyl)-6-thioxopiperidin-2-yl)-4-fluorophenyl)picolinamide was prepared from (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione which is staring material for exemplified compounds 1-9 and exemplified compound 18 of the present invention. The remaining exemplified compounds of the present invention were prepared from (*S*)-6-(5-amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione. (*S*)-6-(5-Amino-2,3-difluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione was prepared by the same method as (*S*)-6-(5-amino-2-fluorophenyl)-5,5-difluoro-6-(fluoromethyl)piperidine-2-thione and must thus have the same absolute and relative stereochemistry.

Pharmacological Testing

BACE1 binding assay

The binding assay was performed as SPA-based assay using a biotinylated form of human BACE1 recombinantly expressed and subsequently purified from Freestyle HEK293 cells. The binding assay was run in a 50 mM sodium acetate buffer, pH 4.5 containing 50 mM NaCl and 0.03% Tween-20 in white clear bottom 384 plates (Corning #3653). 10 nM (final concentration) radioligand ([^{3}H]-*N*-((1S,2*R*)-1-benzyl-3-cyclopropylamino-2-hydroxy-propyl)-5-(methanesulfonyl-methyl-amino)-*N*-((*R*)-1-phenyl-ethyl)-isophthalamide) (TRQ11569 purchased from GE Healthcare) was mixed with test compound at a given concentration, 6 nM (final concentration) human BACE1 and 25 µg Streptavidin coated PVT core SPA beads (RPNQ0007, GE Healthcare Life Sciences) in a total volume of 40 µl. Several concentrations of each test compound were tested in the assay for IC_{50} determination. The plates were incubated for one hour at room temperature and counted in a Wallac Trilux counter. Total and non-specific binding were determined using buffer and 1 µM (final concentration) of the high affinity BACE1 reference inhibitor (S)-6-[3-chloro-5-(5-prop-1-ynyl-pyridin-3-yl)-thiophen-2-yl]-2-imino-3,6-dimethyl-tetrahydro-pyrimidin-4-one, respectively. For each test compound, a IC_{50} value (the concentration mediating 50% inhibition of the specific binding of the radioligand) was determined from concentration-response curve and used to calculate the K_i from the equation $K_i = IC_{50}/(1+L/K_d)$, where L and K_d are the final concentration of the radioligand used in the assay and the dissociation constant of the radioligand, respectively. The K_d of the radioligand was determined from saturation binding experiments.

Table 1: binding affinity of selected compounds

Compound No	BACE1 Ki (nM)
1	5.7
2	22
3	13
4	25
5	15
6	20
7	32
8	29
9	30
10	55
11	14
12	84
13	22
14	23
15	9
16	21
17	16
18	25
19	11

BACE1 efficacy assay

The efficacy assay was performed as a FRET-based assay using a commercially available BACE1 kit (Life Technologies, P2985). 2 µl test compound at 10 µM (final concentration) and 15 µl BACE1 enzyme from the kit (final concentration 3 nM) were preincubated for 15 minutes at room temperature before addition of 15 µl of substrate from the kit (250 nM final concentration) and incubated for additional 90 minutes at room temperature. The assay plate was subsequently read in a Pherastar (Ex540/Em590). The enzyme activity observed in presence of test compound were normalized to the enzyme activity observed in presence of buffer and 10 µM (final concentration) of the high affinity BACE1 reference inhibitor (S)-6-[3-Chloro-5-(5-prop-1-ynyl-pyridin-3-yl)-thiophen-2-yl]-2-imino-3,6-dimethyl-tetra-hydropyrimidin-4-one, respectively. The efficacy of the test compounds was evaluated at 10 µM (final concentration) and defined as the percent inhibition of the enzyme activity using the equation %inhibition = 100% - normalized enzyme activity in percent.

Table 2: BACE1 activity of selected compounds

Compound No	BACE1 inhibition at 10µM (%)
1	104
2	104
3	104
4	104
5	102
6	103
7	96
9	103
10	102

11	103
12	101
13	103
14	103
15	106
16	106
17	111
18	109

Assessment of Aβ peptide levels in rat brain and plasma following BACE1 inhibition.

Animals.

All rat care and experimental procedures were approved by Lundbeck Veterinary Staff, according to Danish legislature. The rats were maintained in a barrier facility with a 12/12-h light/dark cycle and ad libitum food and water access.

Treatment of naïve Rats.

Young adult Male Sprague Dawley rats of approximately 250g weight were purchased from Charles River and received 0-30 mg/kg of vehicle (10% HP betaCD + 1M $MeSO_4$, pH 2.5) or test compounds (dissolved in vehicle) only by oral gavage (p.o). The compounds are dosed at a volume of 5ml/kg. Cohorts of 5-10 animals were established for each treatment condition.

The animals undergoing treatment were closely monitored by veterinary staff for any signs of toxicity. Monitoring parameters included body weight, physical appearance, changes in coat appearance, occurrence of unprovoked behavior, and blunted or exaggerated responses to external stimuli.

Tissue collection.

At T =180 minutes after initial dosing the animals were stunned and decapitated with a guillotine. Trunk-blood was sampled in EDTA coated tubes after decapitation of the animal. The blood was centrifuged at 2200G at 4°C for 15 minutes and the plasma was collected and frozen at -80°C. The blood was aliquoted for Aβ ELISA and DMPK analysis. Immediately following sacrifice, the brain was extracted and split into 2 halves. The right hemibrains were snap frozen on dry ice and stored at -80°C. The left half was dissected; with the front forebrain taken for Aβ ELISA and the remainder used for DMPK analysis. These samples were also snap frozen on dry ice and stored at -80°C until use for analysis.

Tissue processing.

The cortex samples were thawed slightly on wet ice before they were homogenized with a small volume dispersing instrument (T10 basic ULTRA-TURRAX®) which was set at speed 5 for approximately 5-7 sec. The tissue was processed in a 10 times volume of the weight, for example 100mg of tissue was homogenized in 1000µL of Homogenization buffer. Homogenization buffer: 50ml Milli Q water + 50nM NaCl + 0.2% Diethylamin (DEA) + 1 tablet of Complete Protease inhibitor cocktail + 1nM 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride irreversible serine protease inhibitor (AEBSF).

After homogenization 450 µL aliquots of the samples are collected into a 1.5ml Eppendorf tube and placed on wet ice, 0.5% NP-40 (50ul) was added to all samples and then they were incubated on ice for 30 min. After which all samples were sonicated using an Ultrasonic homogenizer with 20 kHz homogeneous sound (SONOPLUS HD2070, Bandelin Electronic) 10 pulse set at 12-13 % power to extract all the Aβ species. The samples were then centrifuged (Ole Dich 157 MPRF Micro centrifuge) at 20000G for 20 minutes at 4°C. After centrifugation 285µL of the supernatant was pipetted into 600µL microtubes tubes and neutralized with 15µL of 1M Tris-HCL buffer.

ELISA protocol.

WAKO 294-62501 Human/Rat Abeta amyloid (40) kit was used for all ELISA analyses. 30 µL plasma samples or 30 µL of the cortex supernatants generated as described above were placed in 600 µL microtubes tubes on wet ice. To this 30 µL of 8M Urea (AppliChem A1049, 9025) are added to generate a 2-fold dilution. Both plasma and cortex supernatants are incubated on ice for 30 min. Standard rows were prepared from the standard peptide stock provided in the kit and standard diluent containing 1.6M Urea (200 µL 8M Urea + 800 µL of standard diluent) and 0.8M Urea (400µL 8M Urea + 3600µL Standard diluent). A serial 2-fold dilution of Aβ40 from 100 pmol/ml to 0 pmol/L was prepared for the assay.

After incubation with urea, all samples were further diluted by addition of 5 times standard diluent from the Kit. This was done by adding 240 µL Standard Diluent to 60 µL sample/urea mixture, which was then mixed well. 100 µL of each diluted sample was pipetted into designated wells of the ELISA plate in duplicates. The plate was then covered and incubated overnight at 4°C. The following day, the ELISA kit was brought to room temperature before use. The incubated plate was washed 5 times with the 20x washing solution diluted in Milli Q water. 100 µL HRP-conjugate was applied to each well, and the plate was covered and incubates at 4°C for 1 hr. The wash was repeated again for 5 times. 100 µL 3,3',5,5'-Tetramethylbenzidine (TMB) solution was applied to each well and the plate was covered and incubated in the dark at room temperature for 30 minutes. 100 µL STOP-solution was next applied to each well, and the plate was read at 450 nm wavelength in a spectrophotometer (Labsystems Multiscan Ascent) within 30 min of adding the STOP-solution to the wells.

Concentration of Aβ peptide in the samples was determined based on a standard curve generated from standards containing known concentrations of synthetic Aβ40. Those skilled in the art will appreciate that diethylamine (DEA) and urea extractions will release soluble Aβ, and insoluble Aβ respectively. Since the ELISA kit is validated and widely used, it is accepted that as long as the treatment conditions and assay conditions are the same for each compound tested, then the assay should yield consistent robust data for the compounds tested and produce minimal discrepancies.

Data analysis

To determine the concentration of Aβ40 in the samples, the interpolated values of the samples loaded on plates are multiplied by 20 to account for the dilutions made when the volumes of DEA, urea and neutralization solution were added up. Values are calculated as percentage change in Aβ40 compared to vehicle treated animals.

Bioanalysis of brain and plasma samples

TC was determined in plasma and brain homogenate using UltraPerformance LC® (UPLC®) chromatography followed by tandem-MS (MS/MS) detection.

Apparatus:

Tecan Genesis RSP 200; Biomek NXP, Beckman Coulter; Sigma 4K15 centrifuge; Acquity UPLC, Waters; Sciex API4000 TQ, Applied Biosystems; MS software: Analyst version 1.4.1

Chemicals

Acetonitrile, HPLC-grade, Fluka, No. 34967N; Methanol, HPLC-grade, Sigma-Aldrich, Lot 9003S; Formic acid, HPLC-grade, Riedel-de Haën, Lot 51660; Purified water, Millipore Synergy UV

Sample preparation

Brain homogenate was prepared by homogenizing the brain 1:4 (v/v) with water:2-propanol:DMSO (50:30:20 v/v/v) followed by centrifugation and collection of the supernatant. Calibration standards and QC samples were prepared using a Hamilton robot. 150 µL of ISTD in acetonitrile (1 ng/mL ISTD) was added to 25 µL of calibration standards, QC samples and test samples (plasma and brain homogenate) using a Biomek robot. After centrifugation (6200 g, 4 °C, 20 min) 100 µL supernatant from each sample was transferred to a new plate and mixed with 100 µL water with 0.1 % formic acid using a Biomek robot (method file InVivo transfer). After a quick centrifugation (6200 g, 4 °C, 5 min) the samples were placed in the auto-sampler.

UPLC-MS/MS analysis

MS/MS detection was done with an Applied Biosystems Sciex API 4000 instrument in positive-ion electrospray ionisation mode. TC and ISTD were detected at a parent > daughter mass to charge ratio (m/z). Nitrogen was used for the nebulizer and collision gases. The peak area correlated linearly with the plasma and brain concentration of the analytes in the range of 1.00 – 1000 ng/mL plasma and 5.00 – 5000 ng/g brain (corrected for dilution). If the plasma/brain sample drug concentration was above 1000 ng/mL or 5000 ng/g, the sample was diluted appropriately in blank plasma/blank brain homogenate before analysis.

Chromatographic system

Analytical columns:

Waters Acquity UPLC HSS C18 SB (pH 2-8) 1.8 µm, 2.1x30mm.

Mobile phase A: 0.1 % aq. formic acid or 0.1 % aq. ammonium hydroxide

Mobile phase B: Acetonitrile with 0.1 % aq. formic acid or 0.1 % aq. ammonium hydroxide.

Weak wash: Methanol

Strong wash: Acetonitrile/Isopropanol/formic acid (50/50/2 v/v/v)

Flow: 0.6 mL/min

Run time: 3 min.

To waste: 0-0.5 min

Temperature: 40°C

Gradient:

Time (min)	% A	% B
0	98	2
0.01	98	2

1.5	5	95
2	5	95
2.2	98	2
3	98	2

Compounds 11 and 15 were administered at doses of 10 mg/kg p.o. and brain and plasma samples were collected at 3 hours post dose and the following exposures were measured as described above.

Table 3: Results for compound 11

	Dose (mg/kg)	Exp (ng/g)	Brain/Plasma ratio	Aβ40 reduction (%)
Brain Rat Plasma Rat	10	1758 1118	1.8	43 31
Brain Rat Plasma Rat	30	4210 3290	1.3	50 37

Table 4: Results for compound 15

	Dose (mg/kg)	Exp (ng/g)	Brain/Plasma ratio	Aβ40 reduction (%)
Brain Rat Plasma Rat	10			33 34
Brain Rat Plasma Rat	30			43 34

As shown in tables 3 and 4, compounds of the present invention are able to penetrate the blood brain barrier and show efficacy in the CNS.

MDCK-MDR1 assay

The permeability of the test compounds was assessed in MDCK-MDR1 cells that were cultured to confluency (4-6 days) in a 96 transwell plate. Test compounds were diluted with the transport buffer (HBSS + 1% BSA) to a concentration of 0.5 µM and applied to the apical or basolateral side of the cell monolayer. Permeation of the test compounds from A to B direction or B to A direction was determined in triplicate over a 60-minute incubation time at 37°C and 5% CO2 with a relative humidity of 95%. Test compounds were quantified by LC-MS/MS analysis based on the peaks area ratios of analyte/IS in both the receiver and donor wells of the transwell plate.

The apparent permeability coefficient Papp (cm/s) was calculated using the equation:

Papp = (dCr/dt) x Vr / (A x C0)

Where dCr/dt is the cumulative concentration of compound in the receiver chamber as a function of time (µM/s); Vr is the solution volume in the receiver chamber (0.05 mL on the apical side; 0.25 mL on the basolateral side); A is the surface area for the transport, i.e. 0.0804 cm^2 for the area of the monolayer; C0 is the initial concentration in the donor chamber (µM).

Compounds are classified Pgp substrates when efflux ratio (Papp BA / Papp AB) is ≥ 2.

Table 5: BACE1 activity of selected compounds

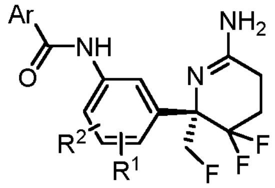
Compound	MDCK- MDR1 efflux ratio
1	1.75
2	2.6
3	2.84
4	13.81
5	7.31
6	2.07
7	4.59
8	23.42
9	1.76
10	3.57
11	0.77
12	1.11
13	1.11
14	1.81
15	1.09
16	1.1
17	2.21

19	1.59

As shown in tables 5, the majority of the exemplified compounds of the present invention have MDCK-MDR1 efflux ratios below 2 and are thus likely to be able to cross the blood brain barrier (E Kerns, L Di, Drug-like Properties: Concepts, Structure Design and Methods (2008) Elsevier).

CLAIMS

1. A compound of formula I



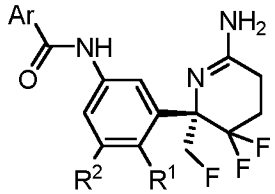
Formula I

wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl and isoxazolyl, and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy; and

R^1 and R^2 independently are hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein the compound is of formula Ia



Formula Ia;

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein R^1 and R^2 independently are F or H.

4. The compound according to claim 1, wherein Ar is optionally substituted with one or more F, Cl, CN, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl or C_1-C_3 alkoxy.

5. The compound according to anyone of claims 1-4, wherein Ar is optionally substituted pyridyl.

6. The compound according to anyone of claims 1-4, wherein Ar is optionally substituted pyrimidyl.

7. The compound according to anyone of claims 1-4, wherein Ar is optionally substituted pyrazinyl.

8. The compound according to anyone of claims 1-4, wherein Ar is optionally substituted oxazolyl.

9. The compound according to claim 1 selected from the group consisting of:

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-chloropicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-fluoropicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1H-pyrazole-3-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyanopicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-2-methyloxazole-4-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-methoxypyrazine-2-carboxamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-fluoropicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-chloropicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-cyanopicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-methoxypicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-(methoxy-d_3)picolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(methoxy-d_3)picolinamide(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-bromopicolinamide

(*S*)-*N*-(3-(6-amino-3,3-difluoro-2-(fluoromethyl)-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-bromopicolinamide

or a pharmaceutically acceptable salt thereof

10. A pharmaceutical composition comprising a compound according to anyone of claims 1-9 and a pharmaceutically acceptable carrier.

11. A method of treating a disease selected from Alzheimer’s disease (familial or sporadic), preclinical Alzheimer’s disease, prodromal Alzheimer’s disease, mild cognitive impairment, Down’s syndrome and cerebral amyloid angiopathy, the method comprising the administration of a therapeutically effective amount of a compound according to any of claims 1-9 to a patient in need thereof.

12. The use of a compound according to anyone of claims 1-9 in the manufacture of a medicament for the treatment of a disease selected from Alzheimer’s disease (familial or sporadic), preclinical Alzheimer’s disease, prodromal Alzheimer’s disease, mild cognitive impairment, Down’s syndrome and cerebral amyloid angiopathy.

13. A compound according to anyone of claims 1-9 for use in therapy.

14. A compound according to anyone of claims 1-9 for use in a method for the treatment of a disease selected from Alzheimer’s disease (familial or sporadic), preclinical Alzheimers’s disease, prodromal Alzheimer’s disease, mild cognitive impairment, Down’s syndrome and cerebral amyloid angiopathy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/076017

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D413/12 A61K31/444 A61K31/497 A61K31/4439
A61K31/506 A61P25/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/168164 A1 (HOFFMANN LA ROCHE [CH]; SIENA BIOTECH SPA [IT]; WOLTERING THOMAS [DE]) 13 December 2012 (2012-12-13) scheme F; page 5, lines 6-16; claims 1,7,10-12,17-27; example 2 -----	1-14
A	WO 2011/154431 A1 (JANSSEN PHARMACEUTICA NV [BE]; TRABANCO-SUAREZ ANDRES AVELINO [ES]) 15 December 2011 (2011-12-15) page 1, lines 6-15; claims 1,11,13,14; examples B15-B18 -----	1-14
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2016	08/02/2016

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HANS HILPERT ET AL: "[beta]-Secretase (BACE1) Inhibitors with High in Vivo Efficacy Suitable for Clinical Evaluation in Alzheimer's Disease", JOURNAL OF MEDICINAL CHEMISTRY, vol. 56, no. 10, 16 April 2013 (2013-04-16), pages 3980-3995, XP055113495, ISSN: 0022-2623, DOI: 10.1021/jm400225m the whole document -----	1-14
A	DANIEL OEHLRICH ET AL: "The evolution of amidine-based brain penetrant BACE1 inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 24, no. 9, 20 March 2014 (2014-03-20), pages 2033-2045, XP055233028, AMSTERDAM, NL ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2014.03.025 the whole document -----	1-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/076017

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