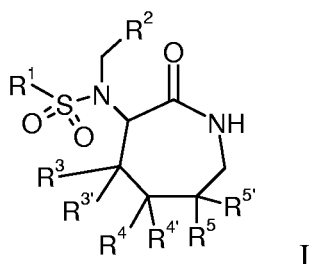


Case 23268FLUORO SUBSTITUTED 2-OXO AZEPAN DERIVATIVES

The invention relates to compounds of general formula



wherein

- R^1 is lower alkyl substituted by halogen, or is aryl or heteroaryl, unsubstituted or substituted by halogen;
- R^2 is heterocycloalkyl, aryl or heteroaryl, which are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyloxy, lower alkyl substituted by halogen, O-lower alkyl substituted by halogen or are substituted by $C(O)-NR''_2$, $(CR_2)_m-C(O)-R'$, heteroaryl or $S(O)_2$ -lower alkyl;
- $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ are independently from each other hydrogen or fluoro, wherein at least one of $R^4/R^{4'}$ or $R^5/R^{5'}$ is always fluoro;
- R' is aryl or hydroxy;
- R'' is hydrogen, cycloalkyl or is heterocycloalkyl;
- R is hydrogen or lower alkyl;
- m is 0, 1, 2 or 3;

and to pharmaceutically suitable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl,

isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above, and which is attached via an oxygen atom.

5 The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, for example phenyl or naphthyl. The preferred aryl group is phenyl.

10 The term "heteroaryl" denotes a monovalent aromatic carbocyclic radical, containing at least one heteroatom, selected from the group consisting of N, O or S, for example pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, tetrazolyl, [1,2,4]triazolyl, [1,2,4]oxadiazolyl, oxazolyl, or isoxazolyl. Preferred heteroaryl groups are pyridyl, thienyl, triazinyl, furyl or
15 thiazolyl.

The term "heterocycloalkyl" denotes a non aromatic hydrocarbon radical containing at least one heteroatom, selected from the group consisting of N, O or S, for example oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl. Preferred heterocycloalkyl
20 groups are morpholinyl, piperidinyl or pyrrolidinyl.

The term "cycloalkyl" denotes a saturated carbocyclic ring, containing 3 – 7 carbon atoms.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid,
25 phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

It has been found that the compounds of general formula I are γ -secretase inhibitors and the related compounds may be useful in the treatment of Alzheimer's disease or common cancers including but not limited to cervical carcinomas and breast
30 carcinomas and malignancies of the hematopoietic system.

Alzheimer's disease (AD) is the most common cause of dementia in later life. Pathologically AD is characterized by the deposition in the brain of amyloid in extracellular plaques and intracellular neurofibrillary tangles. The amyloid plaques are mainly composed of amyloid peptides (Abeta peptides) which originate from the β -
5 Amyloid Precursor Protein (APP) by a series of proteolytic cleavage steps. Several forms of APP have been identified of which the most abundant are proteins of 695, 751 and 770 amino acids length. They all arise from a single gene through differential splicing. The Abeta peptides are derived from the same domain of the APP but differ at their N- and C-termini, the main species are of 40 and 42 amino-acid length.

10 Abeta peptides are produced from APP through the sequential action of 2 proteolytic enzymes termed β - and γ -secretase. β -Secretase cleaves first in the extracellular domain of APP just outside of the trans-membrane domain (TM) to produce a C-terminal fragment of APP containing the TM- and cytoplasmatic domain (CTF β). CTF β is the substrate for γ -secretase which cleaves at several adjacent positions
15 within the TM to produce the A β peptides and the cytoplasmic fragment. The majority of Abeta peptides is of 40 amino acids length (A β 40), a minor species carries 2 additional amino acids at its C-terminus. The latter is supposed to be the more pathogenic amyloid peptide.

The β -secretase is a typical aspartyl protease. The γ -secretase is a proteolytic activity
20 consisting of several proteins, its exact composition is incompletely understood. However, the presenilins are essential components of this activity and may represent a new group of atypical aspartyl proteases which cleave within the TM of their substrates and which are themselves polytopic membrane proteins. Other essential components of γ -secretase may be presenilin, nicastrin and the products of the aph1 and pen-2 genes.
25 Proven substrates for γ -secretase are the APP and the proteins of the Notch receptor family, however, γ -secretase has a loose substrate specificity and may cleave further membrane proteins unrelated to APP and Notch. It was demonstrated by genetic means, i.e., ablation of either the presenilin 1 and 2 genes or the nicastrin gene, that γ -secretase is absolutely required for Notch signaling. This was subsequently confirmed by treatment
30 with specific γ -secretase inhibitors.

Notch receptors are not only essential in embryonal development but also play a critical role in several tissues of the adult organism which continue to undergo proliferation and differentiation, e.g., hematopoietic cells and epithelia of the gut and

skin. The signaling of Notch receptors occurs through an ordered sequence of events: binding to a ligand of the Delta or Jagged group, cleavage of the extracellular domain by an ADAM protease (TACE) and subsequent cleavage by the γ -secretase within the Notch transmembrane domain. The latter cleavage results in the liberation of the cytoplasmic domain which then translocates to the nucleus where it acts with other proteins as a regulator of a specific group of genes.

A role for Notch in human oncogenesis was most clearly established for T-cell Acute Lymphoblastic Leukemia (T-ALL). Some rare cases of T-ALL show a (7:9) chromosomal translocation which leads to a constitutive activation of Notch1. Recently it was reported that ca. 50% of all T-ALL cases have point mutation in the Notch1 receptor which also cause over-activation. It was shown that growth of some cell lines derived from such leukemias were sensitive to treatment with γ -secretase inhibitors which confirmed an essential role for Notch1 signaling.

A broader role for Notch in oncogenesis is discussed in several recent paper which describe that its signaling is required for maintaining the neoplastic phenotype in ras-transformed cells. Deregulation of the ras-signaling pathway is found in a number of common cancers including cervical carcinomas and breast carcinomas.

The γ -secretase activity is absolutely required for the production of Abeta peptides. This has been shown both by genetic means, i.e., ablation of the presenilin genes and by low-molecular-weight inhibitory compounds. Since according to the amyloid hypothesis of AD the production and deposition of Abeta is the ultimate cause for the disease, it is thought that selective and potent inhibitors of γ -secretase will be useful for the prevention and treatment of AD.

Thus, the compounds of this invention will be useful treating AD or common cancers by blocking the activity of γ -secretase and reducing or preventing the formation of the various amyloidogenic Abeta peptides and furthermore, by blocking the Notch signaling pathways they can interfere with cancer pathogenesis.

Numerous documents describe the current knowledge on γ -secretase inhibition, for example the following publications:

- The EMBO Journal (2004), 23, 483-488,
- Biochemistry (2004), 43 (30), 9774-9789,
- Nature Reviews/Neuroscience, Vol. 3, April 2002/281,
- Biochemical Society Transactions (2002), Vol. 30. part 4,
- Current Topics in Medicinal Chemistry, 2002, 2, 371-383,
- Current Medicinal Chemistry, 2002, Vol. 9, No. 11, 1087-1106,

- Drug Development Research, 56, 211-227, 2002,
Drug Discovery Today, Vol. 6, No. 9, May 2001, 459-462,
FEBS Letters, 483, (2000), 6-10,
Science, Vol. 297, 353-356, July 2002,
- 5 Journ. of Medicinal Chemistry, Vol. 44, No. 13, 2001, 2039-2060,
Nature Cell Biology 2, 461-462, 2000,
Nature 398, 518-522, 1999,
Nature Cell Biology 3, 1129-1132, 2001,
PNAS 98, 7487-7491, 2001,
- 10 Cancer Cell 1, 75-87, 2002,
Science 306, 269-271, 2004,
Mol Cell Biol 23, 655-664, 2003,
Nature Medicine 8, 979-986, 2002 and
Oncogene 22, 6598-6608, 2003.
- 15 Objects of the present invention are the compounds of formula I per se, the use of
compounds of formulas I and their pharmaceutically acceptable salts for the manufacture
of medicaments for the treatment of diseases, related to the γ -secretase inhibition, their
manufacture, medicaments based on a compound in accordance with the invention and
their production as well as the use of compounds of formula I in the control or
- 20 prevention of Alzheimer's disease or common cancers including but not limited to
cervical carcinomas and breast carcinomas. .
A further object of the invention are all forms of optically pure enantiomers, recemates or
diastereomeric mixtures for compounds of formula I.
- 25 The most preferred compounds of formula I are those, wherein
 $R^4/R^{4'}$ are both fluoro and R^1 is phenyl, substituted by halogen.
Preferred compounds from this group are further those, wherein R^2 is phenyl, substituted
by halogen and/or $C(O)-N(R'')_2$, for example the following compounds
4-[(4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl}-
30 N-cyclopropyl-benzamide or
4-[(4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl}-
3-fluoro-N-pyrrolidin-1-yl-benzamide.
- Further preferred compounds from this group are those, wherein R^2 is phenyl,
35 substituted by halogen and lower alkoxy, for example the compound
4-chloro-N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-

benzenesulfonamide.

Preferred compounds from this group are those, wherein R^2 is phenyl, substituted by halogen and heteroaryl, for example the following compound

4-chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-[2-fluoro-4-(2H-[1,2,4]triazol-3-yl)-benzyl]-benzenesulfonamide.

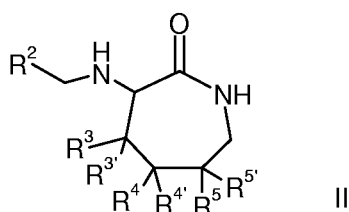
Preferred compounds from this group are further those, wherein R^2 is phenyl, substituted $(CR_2)_mC(O)-R'$, for example the following compounds

3-(4-{{(4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino}-methyl}-phenyl)-propionic acid or
3-(4-{{(4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino}-methyl}-phenyl)-3-methyl-butyric acid.

Preferred compounds are further those, wherein R^1 is heteroaryl, substituted by halogen or R^1 is lower alkyl substituted by halogen.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which processes comprise

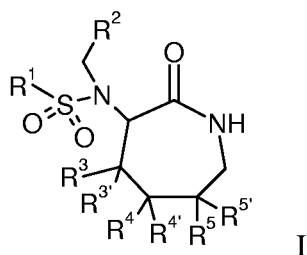
a) reacting a compound of formula



with a compound of formula



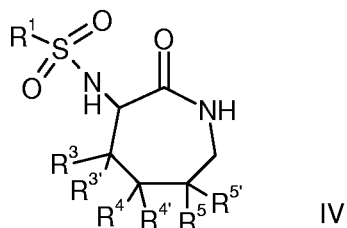
to a compound of formula



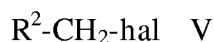
wherein R^1 , R^2 , $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ have the meaning as described above,

or

b) reacting a compound of formula

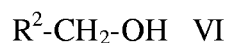


with a compound of formula



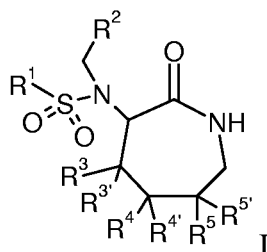
5 in the presence of a base

or with a compound of formula



in the presence of Ph_3P and DIAD

to a compound of formula



10

wherein R^1 , R^2 , $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ have the meaning as described above, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The detailed processes for preparing of compounds of formula I are described in schemes
 15 1 and 2 and in Examples 1 – 18. The starting materials of formulae VII, VIII, IX, X and XI are known compounds or may be prepared by methods well-known in the art.

The following abbreviations have been used:

DIAD – diethylazodicarboxylate

DMAP – 4-dimethylaminopyridine

20 EDC – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

TATU – 1,1,3,3-tetramethyl-2-(1H-1,2,3-triazolo[5,4-b]pyridine-1-yl)-uronium

tetrafluoroborate

TPTU – *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N,N,N',N'*-tetramethyluronium

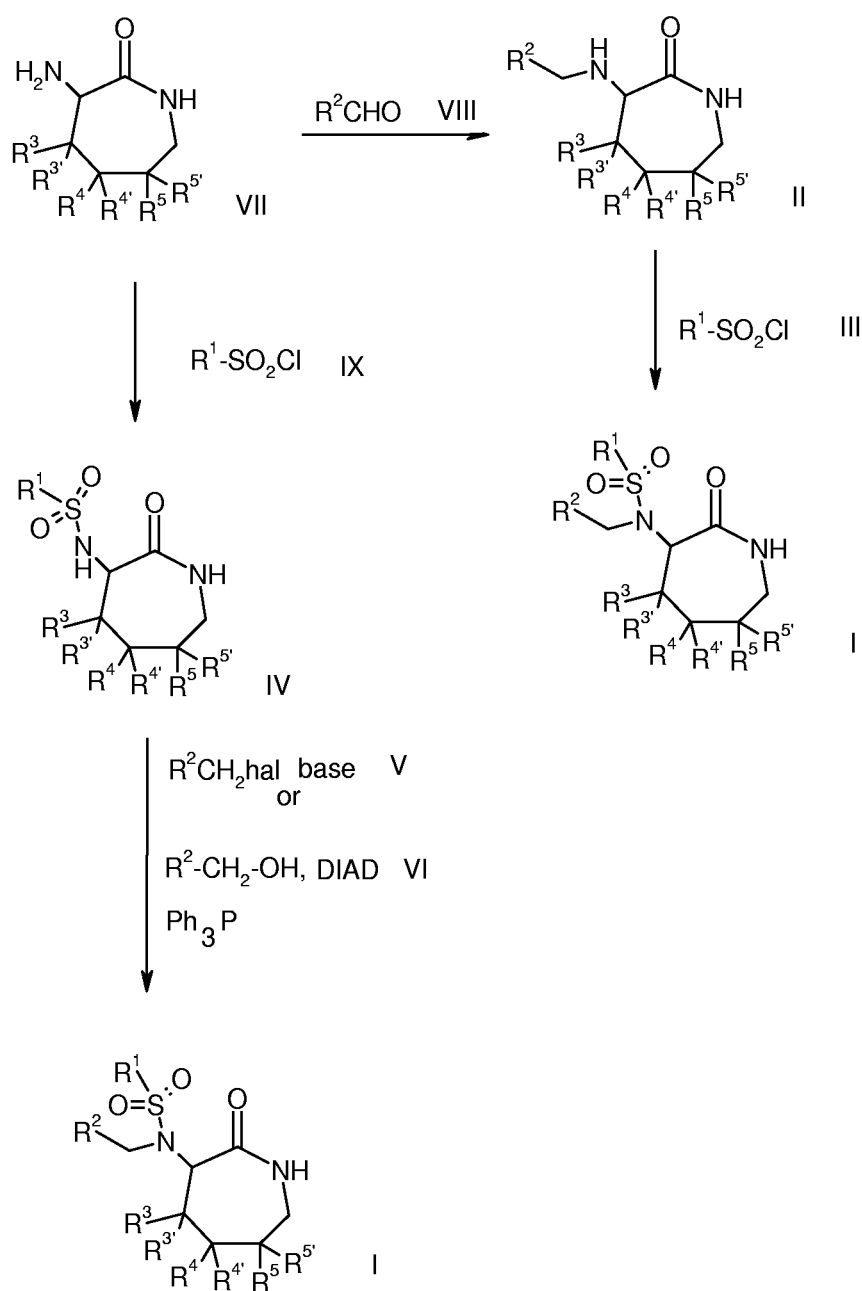
tetrafluoroborate

DMB – 2,4-dimethoxybenzyl

5 DAST – diethylaminosulfur trifluoride

DMF – *N,N*-dimethylformamide

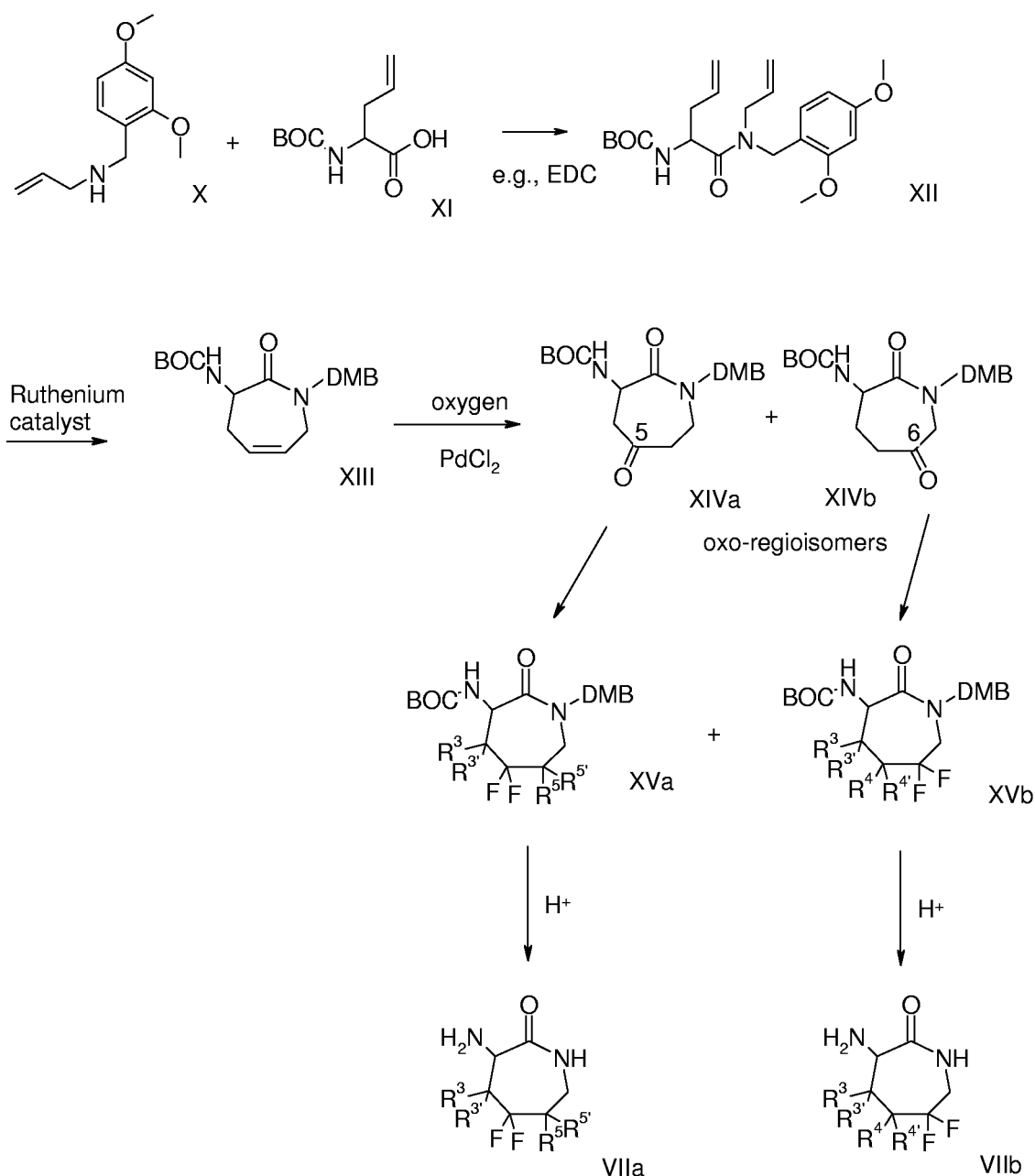
Deoxofluor – [bis(2-methoxy-ethyl)amino]sulfur trifluoride

Scheme 1

wherein R^1 , R^2 , $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ have the meaning as described above and Ph_3P is triphenylphosphine.

- An amino-azepan-2-one of formula VII is treated with an aldehyde and a suitable reducing reagent such as sodium triacetoxyborohydride or sodium cyanoborohydride to yield an amine compound of formula II. A solution of this amine in dichloromethane can be reacted with one equivalent of an aromatic sulfonyl chloride in the presence of a base such as Hünig's base or triethylamine and catalytic DMAP to yield after column chromatography a pure compound of formula I. Alternatively, the compound of formula VII can be reacted first with the sulfonyl chloride resulting in sulfonamide compounds of formula IV which are amenable to further derivatization using for example a Mitsunobu protocol whereby an alcohol R_2CH_2OH , triphenylphosphine and diisopropyl or diethyl azodicarboxylate are reacted at low temperature under an inert atmosphere in a dry solvent such as tetrahydrofuran. The reaction mixture is allowed to warm up and further stirred at room temperature for several hours to furnish after column chromatography compounds of formula I. Intermediates of formula IV can also be used in a reaction where a halide R^2CH_2hal in the presence of excess potassium carbonate, catalytic potassium iodide in dry DMF solvent and at an elevated temperature are reacted. The reaction mixture is then filtered, acidified and purified using column chromatography to give compounds of formula I.
- Fluoro ring-substituted 3-amino-azepan-2-ones of formula VII can be prepared by various methods described in the literature and specifically by one approach outlined in Scheme 2.

Scheme 2



- An amine of formula X (which is accessible by reacting the substituted benzaldehyde with allylamines under reductive conditions) can be coupled to an amino acid derivative of formula XI using standard peptide coupling reagents such as EDC or TATU to afford in high yields, bis-allyl derivatives of formula XII. Ring closure metathesis of compounds of formula XII can be achieved using ruthenium based catalysts as those described by Grubbs. The 2nd generation Grubbs catalyst was most efficient to prepare compounds of formula XIII. The resultant alkenes of formula XIII can be oxidized to the 5,6-oxo regioisomers of formula XIV via palladium complexes in a saturated oxygen environment. The regioisomeric mixture of ketones with formula XIV are not easily separated by chromatography. This mixture can be further transformed to geminal

difluorinated compounds of formula XV using commercial reagents such as DAST or Deoxofluor. Compounds of formula XV can be adequately separated by silica gel chromatography. Protecting group removal under acidolytic conditions will furnish fluoro ring-substituted 3-amino-azepan-2-ones of formula VII.

- 5 The detailed description can be found in Examples A – K and 1-18.

If compounds of Formula I are basic, they may be converted to a corresponding acid addition salt.

- The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric
10 acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether,
15 ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

- The acid addition salts of compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a
20 suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention may inhibit the γ -secretase.

- 25 The compounds were investigated in accordance with the test given hereinafter.

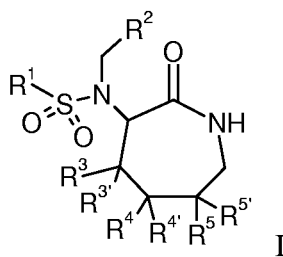
Description of γ -secretase assay

- The activity of test compounds can be evaluated in assays which measure the proteolytic cleavage of suitable substrates by γ -secretase activity. These can be cellular assays where e.g., a substrate of the γ -secretase is fused in its cytoplasmic domain to a
30 transcription factor. Cells are transfected with this fusion gene and a reporter gene, e.g., firefly luciferase, which expression is enhanced by the transcription factor. Cleavage of the fused substrate by γ -secretase will lead to expression of the reporter gene which can be

monitored in appropriate assays. The γ -secretase activity can also be determined in cell-free in vitro assays where e.g., a cell lysate containing the γ -secretase complex is incubated with a suitable APP-derived substrate which is cleaved to the Abeta peptides. The amount of produced peptides can be determined with specific ELISA assays. Cell lines of neuronal origin secrete Abeta peptides which can be measured with the specific ELISA assay. Treatment with compounds which inhibit γ -secretase leads to a reduction of secreted Abeta thus providing a measure of inhibition.

The in vitro assay of γ -secretase activity uses a HEK293 membrane fraction as a source of γ -secretase and a recombinant APP substrate. Latter consist of the C-terminal 100 amino acids of human APP fused to a 6xHistidin tail for purification which is expressed in E.coli in a regulatable expression vector, e.g. pEt15. This recombinant protein corresponds to the truncated APP fragment which results after γ -secretase cleavage of the extracellular domain and which constitutes the γ -secretase substrate. The assay principle is described in Li YM et al, PNAS 97(11), 6138-6143 (2000). Hek293 cells are mechanically disrupted and the microsomal fraction is isolated by differential centrifugation. The membranes are solubilized in detergent (0.25 % CHAPSO) and incubated with the APP substrate. The Abeta peptides which are produced by γ -secretase cleavage of the substrate are detected by specific ELISA assays as described (Brockhaus M et al, Neuroreport 9(7), 1481-1486 (1998)).

The preferred compounds show a $IC_{50} < 10$ nM. In the list below are described some data to the γ -secretase inhibition:



R ¹	R ²	R ³ /R ^{3'}	R ⁴ /R ^{4'}	R ⁵ /R ^{5'}	IC ₅₀ nM	Example
		H/H	F/F	H/H	4	1 (R)
		H/H	F/F	H/H	19	2 (R)

		H/H	F/F	H/H	29	3 (R)
		H/H	F/F	H/H	2	4 (R)
		H/H	F/F	H/H	17	5 (R)
		H/H	F/F	H/H	41	6 (R)
		H/H	F/F	H/H	7	7 (R)
		H/H	F/F	H/H	17	8 (R)
		H/H	F/F	H/H	45	9 (R)
		H/H	F/F	H/H	20	10 (R)
		H/H	F/F	H/H	460	11 (R)
		H/H	F/F	H/H	6	12 (R)
		H/H	H/H	F/F	297	13 (R)
		H/H	F/F	H/H	5	14 (R)
		H/H	F/F	H/H	10	15 (R)
		H/H	F/F	H/H	150	16 (R)
		H/H	F/F	H/H	110	17 (R)
		H/H	F/F	H/H	1000	18 (R)

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the inhibition of the γ -secretase, such as of Alzheimer's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt

thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

	<u>Item</u>	<u>Ingredients</u>	<u>mg/tablet</u>			
			5 mg	25 mg	100 mg	500 mg
5						
	1.	Compound of formula I	5	25	100	500
	2.	Lactose Anhydrous DTG	125	105	30	150
	3.	Sta-Rx 1500	6	6	6	30
	4.	Microcrystalline Cellulose	30	30	30	150
10	5.	Magnesium Stearate	1	1	1	1
		Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50 °C.
- 15 3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

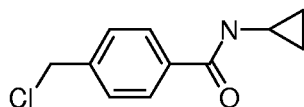
	<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
			5 mg	25 mg	100 mg	500 mg
20	1.	Compound of formula I	5	25	100	500
	2.	Hydrous Lactose	159	123	148	---
	3.	Corn Starch	25	35	40	70
	4.	Talc	10	15	10	25
	5.	Magnesium Stearate	1	2	2	5
25		Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example A

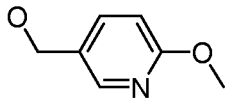
4-Chloromethyl-N-cyclopropyl-benzamide



- 4-Chloromethyl-benzoyl chloride (2.82 g, 15 mmol) and cyclopropylamine (1.26 ml, 18 mmol) were reacted in CH₂Cl₂ (30 ml) and in the presence of Hünig's base (3.1 ml, 18 mmol) for 1 h. A precipitate was formed which was resolubilized by adding ethyl acetate. The reaction mixture was washed with a 5 % KHSO₄/10 % K₂SO₄ solution, NaCl sat. solution and dried (Na₂SO₄). The organic phase was filtered and concentrated under reduced pressure to yield a semi-solid which was triturated in hexanes: solid 3.1 g (95 %);
- ¹H NMR (CDCl₃) δ 0.60-0.64 (m, 2H), 0.85-0.90 (m, 2H), 2.89-2.92 (m, 1H), 4.60 (s, 2H), 6.20 (br, 1H), 7.44 (d, 2H), 7.71-7.74 (m, 2H); MS: m/e = 210.2 (MH⁺)

Example B

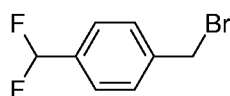
15 (6-Methoxy-pyridin-3-yl)-methanol



- To lithium aluminium hydride (0.68 g, 18 mmol) suspended in dry THF (10 ml) was added dropwise a solution of methyl 6-methoxynicotinate (1 g, 6 mmol) in dry THF (5 ml). The reaction mixture was stirred for 2 h at r.t. then cooled (ice-bath) and quenched with water (2 ml) followed by the further addition of 1 N NaOH (6 ml) and water (2 ml). The cold-bath was removed and the mixture stirred for 30 min at r.t., filtered and concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (3x). The combined organic extracts were washed with water, brine, dried (MgSO₄), filtered and concentrated under reduced pressure to give a crude oil which was purified over silica gel (ethyl acetate/n-heptane 1:1): colorless oil 0.45 g (51 %);
- ¹H NMR (CDCl₃) δ 1.69 (t, 1H), 3.94 (s, 3H), 4.62 (d, 2H), 6.75 (d, 1H), 7.62 (dd, 1H), 8.13 (d, 1H); MS: m/e = 139.0 (M⁺)

30 Example C

1-Bromomethyl-4-difluoromethyl-benzene

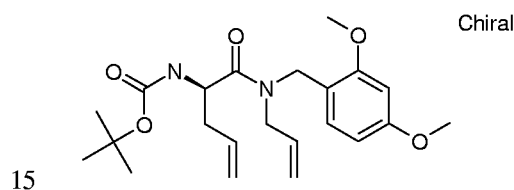


To a solution of 4-bromomethyl-benzaldehyde (1.0 g, 5.2 mmol) in CH_2Cl_2 (60 ml) was added [bis(2-methoxy-ethyl)amino]sulfurtrifluoride (50 % solution in toluene, 14 ml) and the light yellow reaction mixture was stirred for 4 hours at 40 °C under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and the oil residue was added dropwise to an ice-cold NaHCO_3 solution (half sat'd, 50 ml). The resultant mixture was extracted with ethyl acetate (3x) and the combined organic extracts were washed with NaHCO_3 aq., brine, dried ($\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$), filtered and concentrated under reduce pressure to yield a yellow oil: 1.03 g, 85 %;

MS: $m/e = 220.0$ (M), 141.0 (M-Br); ^1H NMR (400 MHz, CDCl_3) δ ppm 4.50 (s, 2H), 6.64 (t, $J_{\text{HF}}=51$ Hz, 1H), 7.49 (s, 4H).

Example D

{(R)-1-[Allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-but-3-enyl}-carbamic acid *tert*-butyl ester

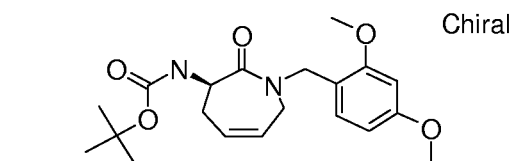


(R)-N-Boc-allylglycine (2.3 g, 9.9 mmol) was dissolved in dimethylformamide (20 ml) and activated with the coupling reagent TATU (3.5 g, 10.9 mmol) and Hünig's base (3.8 ml, 21.9 mmol) for 2 min. Allyl-(2,4-dimethoxy-benzyl)-amine (2.1 g, 9.9 mmol) dissolved in dimethylformamide (20 ml) was added to the chilled (ice-water bath) reaction mixture and the stirring was continued overnight. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with saturated NaHCO_3 solution, 1 M KHSO_4 solution, brine, dried ($\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$), filtered and concentrated under reduce pressure and purified over silica gel (ethyl acetate/n-heptane 1:4): colorless gum 2.6 g (62 %);

25 MS: $m/e = 405.5$ (MH^+).

Example E

[(R)-1-(2,4-Dimethoxy-benzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-yl]-carbamic acid *tert*-butyl ester



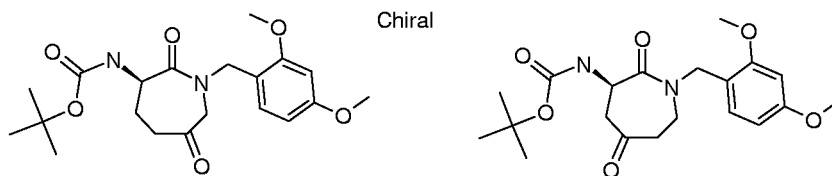
(R)-1-[Allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-but-3-enyl}-carbamic acid *tert*-butyl ester (2.6 g, 6.4 mmol) was dissolved in CH_2Cl_2 (200 ml), [1,3-bis-(2,4,6-

trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)-
 (tricyclohexylphosphine)ruthenium] Grubbs II catalyst (0.55 g, 0.64 mmol) was added
 and the reaction mixture was refluxed for 1.5 hours. The reaction mixture was
 concentrated under reduced pressure dissolved in ethyl acetate and washed with NaHCO₃
 5 solution, 1 M KHSO₄ solution, brine, dried (MgSO₄·2H₂O), filtered, concentrated under
 reduce pressure and purified over silica gel (ethyl acetate/n-heptane 1:4->1:2): dark
 brown solid 1.93 g (80 %);
 MS: m/e = 377.4 (MH⁺), 277.3 (M-Boc).

10

Example F

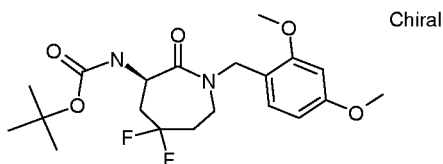
Mixture [(R)-1-(2,4-Dimethoxy-benzyl)-2,6-dioxo-azepan-3-yl]-carbamic acid *tert*-
 butyl ester; compound with [(R)-1-(2,4-dimethoxy-benzyl)-2,5-dioxo-azepan-3-yl]-
 carbamic acid *tert*-butyl ester



- 15 [(R)-1-(2,4-Dimethoxy-benzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-yl]-carbamic acid
tert-butyl ester (5.4 g, 14.3 mmol) was dissolved in DMF/water (10:1 v/v) and then
 Pd(II)Cl₂ (1 g, 5.7 mmol) and Cu(I)Cl (7.2 g, 72.4 mmol) were added. The reaction
 mixture was evacuated and saturated with O₂ and then heated at 50 °C for 48 h. Further
 additions of Pd(II)Cl₂ (3x 0.4 equiv.) were used during the reaction. The reaction mixture
 20 was diluted with water (400 ml) and filtered over Celite. The filtrate was extracted with
 ethyl acetate (5x) and the combined organic extracts were washed with NaHCO₃ solution,
 1 M KHSO₄ solution, brine, dried (MgSO₄·2H₂O), filtered, concentrated under reduce
 pressure and purified over silica gel (ethyl acetate/n-heptane 1:2->1:1) to yield a mixture
 of [(R)-1-(2,4-dimethoxy-benzyl)-2,6-dioxo-azepan-3-yl]-carbamic acid *tert*-butyl ester
 25 and [(R)-1-(2,4-dimethoxy-benzyl)-2,5-dioxo-azepan-3-yl]-carbamic acid *tert*-butyl
 ester in a 1:2 ratio: white solid 3.8 g (67 %);
 MS: m/e = 392.9 (MH⁺).

Example G

- 30 [(R)-1-(2,4-Dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-
 butyl ester



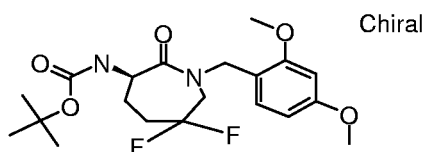
[Bis(2-methoxy-ethyl)amino]sulfur trifluoride (3.5 g, 15.8 mmol) was dissolved in dry toluene (30 ml) and cooled (ice bath) under an argon atmosphere. Boron trifluoride ethyl etherate (0.16 g, 1.13 mmol) was added dropwise and the mixture was stirred for 30 min at 5 °C. A 1:2 mixture of [(R)-1-(2,4-dimethoxy-benzyl)-2,6-dioxo-azepan-3-yl]-carbamic acid *tert*-butyl ester and [(R)-1-(2,4-dimethoxy-benzyl)-2,5-dioxo-azepan-3-yl]-carbamic acid *tert*-butyl ester (4.44 g, 11.3 mmol) dissolved in toluene (15 ml) was then added dropwise, the cold-bath was removed and the reaction mixture was slowly warmed to 50 °C and further stirred for 5 h at this elevated temperature. The reaction mixture was poured into an ice-cold, half-saturated NaHCO₃ solution and extracted with ethyl acetate (3x). The combined organic extracts were washed water, brine, dried (MgSO₄·2H₂O), filtered, concentrated under reduce pressure and purified over silica gel (ethyl acetate/n-heptane 1:4->1:3) to yield [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester: foam 1.32 g (25 %); R_f 0.4 (hexane/ethyl acetate, 1:1 v/v);

MS: m/e = 415.1 (MH⁺), at 437.1(MNa⁺)

¹H NMR (400 MHz, CDCl₃) δ ppm 1.45 (s, 9 H) 1.54 - 1.69 (m, 1 H) 1.75 - 1.98 (m, 1 H) 2.00 - 2.16 (m, 1 H) 2.49 - 2.65 (m, 1 H) 3.34 - 3.44 (m, 1 H) 3.47 - 3.60 (m, 1 H) 3.80 (s, 3 H) 3.81 (s, 3 H) 4.49 (d, J=14.2 Hz, 1 H) 4.52 - 4.56 (m, 1 H) 4.69 (d, J=14.5 Hz, 1 H) 5.97 (d, J=5.4 Hz, 1 H) 6.42 - 6.48 (m, 2 H) 7.19 (d, J=8.9 Hz, 1 H)

Example H

[(R)-1-(2,4-Dimethoxy-benzyl)-6,6-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester



25

The compound was isolated in 6.5 % yield as a by-product in the synthesis of the other regio-isomer [(R)-1-(2,4-dimethoxy-benzyl)-6,6-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester.

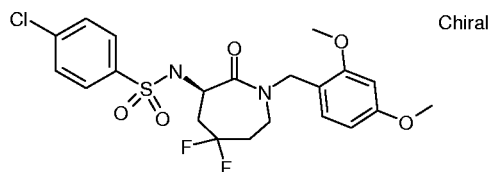
R_f 0.45 (hexane/ ethyl acetate, 1:1 v/v); MS: m/e = 415.3 (MH⁺), at 432.2(MNH₄⁺)

¹H NMR (400 MHz, CDCl₃) δ ppm 1.41 (s, 9 H) 1.54 - 1.56 (m, 1 H) 2.1 - 2.3 (m, 3 H) 3.6 - 3.8 (m, 2 H) 3.80 (s, 3 H) 3.82 (s, 3 H) 4.21 (d, J=14 Hz, 1 H) 4.38 (dd, J=6/8 Hz 1 H) 5.0 (d, J=14 Hz, 1 H) 6.05 (b, 1 H) 6.45 - 6.48 (m, 2 H) 7.3 (d, J=8 Hz, 1 H)

30

Example I

4-Chloro-*N*-[(*R*)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-benzenesulfonamide

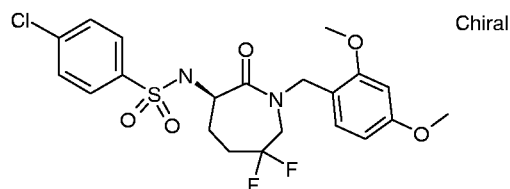


- 5 (*R*)-1-(2,4-Dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester (0.77 g, 1.86 mmol) was dissolved in 4 M HCl/1,4-dioxan (20 ml) and allowed to react for 1 h. The reaction mixture was concentrated under reduced pressure and concentrated once from acetonitrile. To the resultant hydrochloride salt was added CH₂Cl₂ (30 ml) followed by the dropwise addition of Hünig's base (1 ml, 5.6 mmol). A
- 10 solution of 4-chlorobenzenesulfonyl chloride (0.59 g, 2.8 mmol) in CH₂Cl₂ (4 ml) was added and the reaction mixture (pH 8) was stirred for a further 1.5 h. The reaction mixture was diluted with CH₂Cl₂ and washed with NaHCO₃ solution, 1 M KHSO₄ solution, brine, dried (MgSO₄·2H₂O), filtered, concentrated under reduce pressure and purified over silica gel (ethyl acetate/*n*-heptane 1:2): white crystals 0.74 g (78 %);
- 15 MS: *m/e* = 487.1 (MH⁺);

¹H NMR (400 MHz, CDCl₃) δ ppm 1.46 - 1.65 (m, 1 H) 1.87 - 2.11 (m, 2 H) 2.51 - 2.62 (m, 1 H) 3.27 - 3.32 (m, 2 H) 3.77 (s, 3 H) 3.81 (s, 3 H) 3.96 - 4.04 (m, 1 H) 4.38 (d, *J*=14.2 Hz, 1 H) 4.62 (d, *J*=14.5 Hz, 1 H) 6.33 (d, *J*=5.6 Hz, 1 H) 6.41 - 6.46 (m, 2 H) 6.91 - 6.95 (m, 1 H) 7.45 - 7.50 (m, 2 H) 7.78 - 7.83 (m, 2 H)

20 Example J

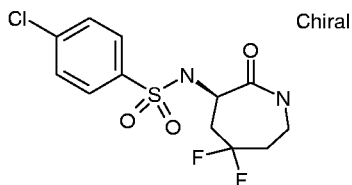
4-Chloro-*N*-[(*R*)-1-(2,4-dimethoxy-benzyl)-6,6-difluoro-2-oxo-azepan-3-yl]-benzenesulfonamide



- The title compound, MS: *m/e* = 487.2 (MH⁺), was prepared analogous to example I
- 25 starting from [(*R*)-1-(2,4-dimethoxy-benzyl)-6,6-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester.

Example K

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide



A cocktail containing 40 % trifluoroacetic acid, 1 % trifluoromethanesulfonic acid in CH_2Cl_2 (20ml) was added to 4-chloro-*N*-[(*R*)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-benzenesulfonamide (0.5 g, 1.0 mmol). After 30 min the reaction

5 mixture was concentrated and the residue was dissolved in ethyl acetate and washed with water, NaHCO_3 solution, 1 M KHSO_4 solution, brine, dried ($\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$), filtered, concentrated under reduce pressure and purified over silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5 v/v): white solid 0.74 g (78 %);

MS: $m/e = 337.1$ (MH^+);

10

Example 1

4-[[4-Chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-*N*-cyclopropyl-benzamide

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide (0.05 g, 0.15 mmol), 4-chloromethyl-*N*-cyclopropyl-benzamide (0.05 g, 0.22 mmol), K_2CO_3 (0.20 g, 1.5 mmol), KI (0.005 g, 0.03 mmol) were added to dry DMF (2.5 ml) and the resultant reaction mixture was stirred for 3.5 h at 65 °C under an argon atmosphere. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate and washed with 5 % KHSO_4 / 10 % K_2SO_4 (2x), water, brine, dried (MgSO_4), filtered,

20 concentrated under reduced pressure and purified over silica gel (ethyl acetate /*n*-heptane 3:2 v/v) and the purified product was lyophilized: white lyophilisate 60 mg;

MS: $m/e = 512.3$ (MH^+), 534.2 (MNH_4^+)

^1H NMR (400 MHz, CDCl_3) δ ppm 0.57 - 0.69 (m, 2 H) 0.79 - 0.94 (m, 2 H) 1.78 - 1.95 (m, 1 H) 1.98 - 2.14 (m, 1 H) 2.19 - 2.32 (m, 2 H) 2.88 - 2.94 (m, $J=7.1, 7.1, 7.0, 3.8$ Hz, 1 H) 3.16 - 3.25 (m, $J=13.2, 7.9, 5.2, 2.5, 2.5$ Hz, 1 H) 3.37 - 3.47 (m, 1 H) 4.52 (d, $J=17.2$ Hz, 1 H) 4.77 - 4.95 (m, 2 H) 5.78 (dd, $J=7.7, 5.2$ Hz, 1 H) 6.11 - 6.24 (m, 1 H) 7.40 - 7.46 (m, 3 H) 7.65 - 7.74 (m, 3 H)

25

Example 2

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-*N*-(4-isoxazol-5-yl-benzyl)-benzenesulfonamide

30

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 5-(4-bromomethyl-phenyl)-isoxazole analogous to Example 1 to afford 4-chloro-

N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(4-isoxazol-5-yl-benzyl)-benzenesulfonamide: MS: m/e = 496.0 (MH⁺), 513.2 (MNH₄⁺).

Example 3

5 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(6-methoxy-pyridin-3-ylmethyl)-benzenesulfonamide

a) 4-Chloro-N-[(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-N-(6-methoxy-pyridin-3-ylmethyl)-benzenesulfonamide

4-Chloro-N-[(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-benzenesulfonamide (0.04 g, 0.07 mmol), (6-methoxy-pyridin-3-yl)-methanol (0.014 g, 0.10 mmol), triphenyl phosphine (0.04 g, 0.13 mmol) were dissolved in dry THF (3 ml) at 0-5 °C (ice-water bath) under an argon atmosphere followed by the dropwise addition of diisopropyl azodicarboxylate (28 mg, 0.13 mmol) in dry THF (0.5 ml). The reaction mixture was further stirred for 1 h at r.t. and then concentrated under reduced pressure.

15 The crude yellow oil was purified over silica gel (ethyl acetate/n-heptane 1:2): colorless gum 23 mg (52 %); MS: m/e = 610.3 (MH⁺).

b) 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(6-methoxy-pyridin-3-ylmethyl)-benzenesulfonamide

20 benzenesulfonamide

A mixture containing trifluoroacetic acid/ trifluoromethanesulfonic acid (10:1 v/v, 4 ml) was added to 4-chloro-N-[1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-N-(6-methoxy-pyridin-3-ylmethyl)-benzenesulfonamide (21 mg, 0.03 mmol). After 1 h the reaction mixture was concentrated under reduced pressure and the residue taken up in ethyl acetate and washed with 5 % KHSO₄/ 10 % K₂SO₄ (2x), water, brine, dried (MgSO₄), filtered, concentrated under reduced pressure and purified over silica gel (ethyl acetate /n-heptane 3:2 v/v) and the purified product was lyophilized: white lyophilisate 15.3 mg;

MS: m/e = 460.1 (MH⁺).

30 Example 4

4-Chloro-N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide

4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 1-bromomethyl-2,3-difluoro-4-methoxy-benzene analogous to Example 1 to afford 4-chloro-N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-

35

3-yl)-benzenesulfonamide:

MS: $m/e = 495.1$ (MH^+), 512.1 (MNH_4^+).

Example 5

5 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(2-fluoro-4-methoxy-benzyl)-benzenesulfonamide

4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was reacted with (2-fluoro-4-methoxy-phenyl)-methanol analogous to Example 3a to afford 4-chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(2-fluoro-4-methoxy-benzyl)-

10 benzenesulfonamide:

MS: $m/e = 477.1$ (MH^+), 494.3 (MNH_4^+).

Example 6

4-[[[4-Chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl]-amino]-methyl]-3-fluoro-benzoic acid

a) 4-[[[4-Chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester

4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 4-bromomethyl-3-fluoro-benzoic acid methyl ester analogous to Example 1 to afford 4-[[[4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester: MS: $m/e = 504.9$ (MH^+), 522.1 (MNH_4^+).

b) 4-[[[4-Chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid

25 4-[[[4-Chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester (130 mg, 0.26 mmol) was dissolved in THF/MeOH (5 ml) and treated with 1 N NaOH (1.2 ml) for 1.5 h. The reaction mixture was concentrated under reduced pressure diluted using water and extracted with diethyl ether. The aqueous phase was acidified using a 5 % $KHSO_4$ /10 % K_2SO_4 mixture and
30 extracted with ethyl acetate (3x). The combined organic fractions were washed with brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure (103 mg). Crude product (50 mg) was purified using preparative RP(C_{18}) chromatography: lyophilisate 22 mg;

MS: $m/e = 489.0$ (MH^-).

Example 7

4-[[[4-Chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl]-amino]-methyl}-
3-fluoro-N-pyrrolidin-1-yl-benzamide

- 4-[[[4-Chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl]-amino]-methyl}-
5 3-fluoro-benzoic acid (50 mg, 0.10 mmol) was dissolved in DMF (1 ml) and activated
with the coupling reagent TPTU (33 mg, 0.11 mmol) and Hünig's base (0.03 ml,
0.26mmol) for 2 min. 1-Aminopyrrolidine hydrochloride (0.013 g, 0.22 mmol) and
further Hünig's base (0.03 ml, 0.26mmol) were added. After 1 h the reaction mixture was
concentrated under reduced pressure and the residue taken up in ethyl acetate and
10 washed with 5 % KHSO₄/ 10 % K₂SO₄ (2x) , water, brine, dried (MgSO₄), filtered,
concentrated under reduced pressure and purified over silica gel (ethyl acetate -> ethyl
acetate/5 % MeOH) and the purified product was lyophilized: white lyophilisate 32 mg;
MS: m/e = 559.3 (MH⁺), 581.2 (MNa⁺).

15 Example 8

4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(4-methanesulfonylbenzyl)-
benzenesulfonamide

- 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated
using 4-methylsulphonylbenzyl bromide analogous to Example 1 to afford 4-chloro-N-
20 ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-(4-methanesulfonylbenzyl)-
benzenesulfonamide: MS: m/e = 507.2 (MH⁺), 524.1(MNH₄⁺).

Example 9

- 4-Chloro-N-(4-difluoromethoxy-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-
25 benzenesulfonamide

- 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated
using 4-(difluoromethoxy)benzyl bromide analogous to Example 1 to afford 4-chloro-N-
(4-difluoromethoxy-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-
30 benzenesulfonamide:
MS: m/e = 495.1 (MH⁺), 512.1(MNH₄⁺).

Example 10

- 4-Chloro-N-(4-difluoromethyl-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-
35 benzenesulfonamide

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 1-bromomethyl-4-difluoromethyl-benzene analogous to Example 1 to afford 4-chloro-*N*-(4-difluoromethyl-benzyl)-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide:

- 5 MS: $m/e = 479.1$ (MH^+), 496.0 (MNH_4^+).

Example 11

N-(1-Benzoyl-piperidin-4-ylmethyl)-4-chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide

- 10 a) 4-[[(4-Chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-piperidine-1-carboxylic acid tert-butyl ester

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 4-(toluene-4-sulfonyloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester analogous to Example 1 to afford 4-[[(4-chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-

- 15 oxo-azepan-3-yl)-amino]-methyl]-piperidine-1-carboxylic acid tert-butyl ester:

MS: $m/e = 536.3$ (MH^+), 553.2 (MNH_4^+).

b) 4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-*N*-piperidin-4-ylmethyl-benzenesulfonamide

- 20 4-[[(4-Chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-piperidine-1-carboxylic acid tert-butyl ester (0.105 g, 0.2 mmol) was dissolved in a mixture of trifluoroacetic acid and dichloromethane (1:1) and stirred overnight. After extraction with aqueous sodium bicarbonate solution the organic layer was dried ($MgSO_4$) and evaporated to yield 80 mg (94 %) of 4-chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-*N*-piperidin-4-ylmethyl-benzenesulfonamide;

25 MS: $m/e = 436.2$ (MH^+).

c) *N*-(1-Benzoyl-piperidin-4-ylmethyl)-4-chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide

- 30 4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-*N*-piperidin-4-ylmethyl-benzenesulfonamide (0.04 g, 0.09 mmol) and triethylamine (19 mg, 0.18 mmol) were dissolved in dichloromethane (1.5 ml). Then benzoyl chloride (0.018 g, 0.13 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue
- 35 was purified over silica gel (heptane/ethyl acetate 1:1) to yield 29 mg (58 %) of the title

compound;

MS: $m/e = 540.3$ (MH^+), 557.1 (MNH_4^+).

Example 12

5 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-[2-fluoro-4-(2H-[1,2,4]triazol-3-yl)-benzyl]-benzenesulfonamide

a) 4-Chloro-N-(4-cyano-2-fluoro-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide

4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated
10 using 4-bromomethyl-3-fluoro-benzonitrile analogous to Example 1 to afford 4-chloro-N-(4-cyano-2-fluoro-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide: MS: $m/e = 472.2$ (MH^+).

b) 4-[(4-Chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl}-3-fluoro-benzimidic acid ethyl ester hydrochloride

4-Chloro-N-(4-cyano-2-fluoro-benzyl)-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide (0.23 g, 0.49 mmol) was suspended in dry ethanol (10 ml) and cooled to 0 °C. Dry HCl gas was gently bubbled over 30 min into this suspension. The light red reaction mixture was stirred at room temperature for 20 h. A clear yellow
20 solution resulted which was concentrated under reduced pressure and the crude was used directly in the next step: 0.28 g; MS: $m/e = 516.2$ (MH^+).

c) 4-Chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-[2-fluoro-4-(2H-[1,2,4]triazol-3-yl)-benzyl]-benzenesulfonamide

25 The crude hydrochloride salt (0.27 g, ca. 0.49 mmol) and formyl hydrazine (90 % grade, 36 mg, 0.54 mmol) were dissolved in pyridine (7.3 ml) and stirred for 3 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and xylenes (12.1 ml) were added and the reaction mixture was heated at 145 °C for 30 min. The reaction mixture was concentrated under reduced pressure and the crude yellow solid was
30 purified over silica gel ($CH_2Cl_2/MeOH$ 95:5) and the purified product was lyophilized: white lyophilisate 75 mg;
MS: $m/e = 514.2$ (MH^+), 531.0 (MNH_4^+).

Example 13

35 4-[(4-Chloro-benzenesulfonyl)-((R)-6,6-difluoro-2-oxo-azepan-3-yl)-amino]-methyl}-N-cyclopropyl-benzamide

4-Chloro-*N*-[(*R*)-1-(2,4-dimethoxy-benzyl)-6,6-difluoro-2-oxo-azepan-3-yl]-benzenesulfonamide was subjected to dimethoxybenzyl protecting group removal analogous to Example K and further alkylated using chloromethyl-*N*-cyclopropyl-benzamide analogous to the protocol in Example 1 to yield 4-[(4-chloro-benzenesulfonyl)-((*R*)-6,6-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-*N*-cyclopropyl-benzamide.

MS: $m/e = 512.1$ (MH^+);

1H NMR (400 MHz, $CDCl_3$) δ ppm 0.56 - 0.68 (m, 2 H) 0.81 - 0.91 (m, 2 H) 1.72 - 1.87 (m, 2 H) 1.95 - 2.14 (m, 1 H) 2.17 - 2.27 (m, 1 H) 2.91 (qd, $J=7.1, 3.8$ Hz, 1 H) 3.31 - 3.50 (m, 1 H) 3.54 - 3.67 (m, 1 H) 4.51 - 4.62 (m, 1 H) 4.82 - 4.94 (m, 2 H) 5.51 - 5.62 (m, 1 H) 6.16 (s, 1 H) 7.41 - 7.52 (m, 3 H) 7.65 - 7.72 (m, 3 H)

Example 14

3-(4-[(4-Chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-propionic acid

a) 3-(4-[(4-Chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-propionic acid methyl ester

4-Chloro-*N*-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 3-(4-bromomethyl-phenyl)-propionic acid methyl ester analogous to Example 1 to afford 3-(4-[(4-chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-propionic acid methyl ester:

MS: $m/e = 515.1$ (MH^+), 532.1 (MNH_4^+).

b) 3-(4-[(4-Chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-propionic acid

3-(4-[(4-chloro-benzenesulfonyl)-((*R*)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-propionic acid methyl ester (65 mg, 0.13 mmol) was dissolved in methanol (0.5 ml) and treated with 2 N LiOH in water (0.25 ml, 0.5 mmol) overnight at 40° C. The reaction mixture was distributed between 4 N HCl and ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (50 mg) was purified using column chromatography (dichloromethane/methanol 90:10) to yield 45 mg (71 %);

MS: $m/e = 499.0$ (MH^+).

Example 15

3-(4-[[(4-Chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-3-methyl-butyric acid

This compound was prepared analogous to Example 14 using 3-(4-bromomethyl-phenyl)-3-methyl-butyric acid methyl ester in step 14a) to afford 3-(4-[[(4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-3-methyl-butyric acid:

MS: $m/e = 527.1$ (MH^+).

Example 16

3,3,3-Trifluoro-propane-1-sulfonic acid ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-(6-methoxy-pyridin-3-ylmethyl)-amide

a) 3,3,3-Trifluoro-propane-1-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-amide

[(R)-1-(2,4-Dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester (0.85 g, 1.85 mmol) was dissolved in 38 ml dichloromethane. 4 M HCl/1,4-dioxan (20 ml) were added dropwise and the mixture was allowed to react for 1 h. The reaction mixture was concentrated under reduced pressure and concentrated once from acetonitrile. To 291 mg of the resultant hydrochloride salt was added CH_2Cl_2 (20 ml) followed by the dropwise addition of Hünig's base (0.36 ml, 2.1 mmol). A solution of 3,3,3-trifluoropropane-1-sulfonyl chloride (0.19 g, 0.9 mmol) in CH_2Cl_2 (5 ml) was added and the reaction mixture (pH 8) was stirred for a further 1.5 h. The reaction mixture was purified over silica gel (heptane-ethylacetate, 95:5 – 0:100): white solid 0.30 g (77 %);

MS: $m/e = 473.1$ ($M-H^+$).

b) 3,3,3-Trifluoro-propane-1-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-(6-methoxy-pyridin-3-ylmethyl)-amide

3,3,3-Trifluoro-propane-1-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-amide (0.15 g, 0.31 mmol), (6-methoxy-pyridin-3-yl)-methanol (0.06 g, 0.38 mmol), triphenyl phosphine (0.17 g, 0.62 mmol) were dissolved in dry THF (15 ml) at 0-5 °C (ice-water bath) under an argon atmosphere followed by the dropwise addition of diisopropyl azodicarboxylate (0.12 ml, 0.62 mmol) in dry THF (1.5 ml). The reaction mixture was further stirred for 1 h at r.t. and then concentrated under reduced pressure. The crude oil was purified over silica gel (first: heptane-ethylacetate, 97:3 –

0:100; second: dichloromethane-methanol, 98:2 – 90:10): white solid 214 mg (81 %);
MS: $m/e = 654.2$ ($M + CH_3COO^-$).

5 c) 3,3,3-Trifluoro-propane-1-sulfonic acid ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-(6-methoxy-pyridin-3-ylmethyl)-amide

A mixture containing trifluoroacetic acid/ trifluoromethanesulfonic acid (5:2 v/v, 0.76 ml) was added to 3,3,3-trifluoro-propane-1-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-(6-methoxy-pyridin-3-ylmethyl)-amide (0.2 g, 0.24 mmol) in dichloromethane (10 ml). After 2 h the reaction mixture was concentrated
10 under reduced pressure and the residue taken up in ethyl acetate and washed with water, saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified over silica gel (heptane-ethyl acetate, 9:1 – 0:1): white solid 72 mg (69 %);
MS: $m/e = 446.2$ (MH^+).

15 Example 17

5-Chloro-thiophene-2-sulfonic acid ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-(6-methoxy-pyridin-3-ylmethyl)-amide

20 a) 5-Chloro-thiophene-2-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-amide

[(R)-1-(2,4-Dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester (0.85 g, 1.85 mmol) was dissolved in 38 ml dichloromethane. 4 M HCl/1,4-dioxan
(20 ml) were added dropwise and the mixture was allowed to react for 1 h. The reaction mixture was concentrated under reduced pressure and concentrated once from
25 acetonitrile. To 291 mg of the resultant hydrochloride salt was added CH_2Cl_2 (20 ml) followed by the dropwise addition of Hünig's base (0.36 ml, 2.1 mmol). A solution of 5-chlorothiophene-2-sulfonyl chloride (0.21 g, 0.9 mmol) in CH_2Cl_2 (5 ml) was added and the reaction mixture (pH 8) was stirred for a further 1.5 h. The reaction mixture was purified over silica gel (heptane-ethylacetate, 95:5 – 0:100): white solid 0.40 g (97 %);
30 MS: $m/e = 493.1$ ($M-H^-$).

b) 5-Chloro-thiophene-2-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-(6-methoxy-pyridin-3-ylmethyl)-amide

5-Chloro-thiophene-2-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-amide (0.20 g, 0.40 mmol), (6-methoxy-pyridin-3-yl)-methanol (0.07 g, 0.48 mmol), triphenyl phosphine (0.22 g, 0.80 mmol) were dissolved in dry THF (15 ml)
35 at 0-5°C (ice-water bath) under an argon atmosphere followed by the dropwise addition

of diisopropyl azodicarboxylate (0.16 ml, 0.80 mmol) in dry THF (1.5 ml). The reaction mixture was further stirred for 1 h at r.t. and then concentrated under reduced pressure. The crude oil was purified over silica gel (first: heptane-ethylacetate, 97:3 – 0:100; second: dichloromethane-methanol, 98:2 – 90:10): white solid 0.19 g (53 %);

5 MS: $m/e = 674.2$ ($M + CH_3COO^-$).

c) 5-Chloro-thiophene-2-sulfonic acid ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-(6-methoxy-pyridin-3-ylmethyl)-amide

A mixture containing trifluoroacetic acid/ trifluoromethanesulfonic acid (5:2 v/v, 0.62 ml) was added to 5-chloro-thiophene-2-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-(6-methoxy-pyridin-3-ylmethyl)-amide (0.17 g, 0.19 mmol) in dichloromethane (10 ml). After 2 h the reaction mixture was concentrated under reduced pressure and the residue taken up in ethyl acetate and washed with water, saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified over silica gel (heptane-ethylacetate, 9:1 – 0:1): white solid 69 mg (77 %);

15 MS: $m/e = 466.1$ (MH^+).

Example 18

20 5-Chloro-pyridine-2-sulfonic acid (4-difluoromethoxy-benzyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amide

a) 5-Chloro-pyridine-2-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-amide

[(R)-1-(2,4-Dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-carbamic acid *tert*-butyl ester (0.46 g, 1.0 mmol) was dissolved in 20 ml dichloromethane. 4 M HCl/1,4-dioxan (20 ml) were added dropwise and the mixture was allowed to react for 1 h. The reaction mixture was concentrated under reduced pressure and concentrated once from acetonitrile. To the resultant hydrochloride salt was added CH_2Cl_2 (15 ml) followed by the dropwise addition of Hünig's base (0.44 ml, 2.5 mmol). A solution of 5-chloropyridine-2-sulfonyl chloride (0.33 g, 1.1 mmol) in CH_2Cl_2 (5 ml) was added and the reaction mixture (pH 8) was stirred for a further 1.5 h. The reaction mixture was purified over silica gel (heptane-ethylacetate, 95:5 – 0:100): white solid 0.37 g (76 %);

30 MS: $m/e = 490.2$ (MH^+).

35

b) 5-Chloro-pyridine-2-sulfonic acid ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amide

A mixture containing trifluoroacetic acid/ trifluoromethanesulfonic acid (5:2 v/v, 2.44 ml) was added to 5-chloro-pyridine-2-sulfonic acid [(R)-1-(2,4-dimethoxy-benzyl)-5,5-difluoro-2-oxo-azepan-3-yl]-amide (0.37 g, 0.76 mmol) in dichloromethane (20 ml).

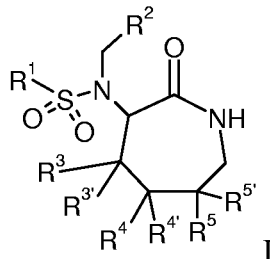
After 2 h the reaction mixture was concentrated under reduced pressure and the residue
5 taken up in ethyl acetate and washed with water, saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified over silica gel (heptane-ethylacetate, 1:1 – 0:1); white solid 0.22 g (84 %); MS: $m/e = 340.0$ (MH^+).

10 c) 5-Chloro-pyridine-2-sulfonic acid (4-difluoromethoxy-benzyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amide

5-Chloro-pyridine-2-sulfonic acid ((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amide (0.21 g, 0.61 mmol), 4-(difluoromethoxy)benzyl bromide (0.23 g, 0.91 mmol), K_2CO_3 (0.85 g, 6.08 mmol), KI (0.02 g, 0.12 mmol) were added to dry DMF (10 ml) and the resultant
15 reaction mixture was stirred for 1.5 h at 65 °C and for additional 3 h at room temperature under an argon atmosphere. The solvent was removed under reduced pressure and the residue was purified over silica gel (first: ethyl acetate /n-heptane 1:2 v/v; second: dichloromethane/ MeOH, 100:0 – 95:5); brownish oil, 0.23 g ;
MS: $m/e = 496.1$ (MH^+).

Claims

1. Compounds of the general formula



5 wherein

R^1 is lower alkyl substituted by halogen, or is aryl or heteroaryl, unsubstituted or substituted by halogen;

R^2 is heterocycloalkyl, aryl or heteroaryl, which are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyloxy,
 10 lower alkyl substituted by halogen, O-lower alkyl substituted by halogen or are substituted by $C(O)-NR''_2$, $(CR_2)_m-C(O)-R'$, heteroaryl or $S(O)_2$ -lower alkyl;

$R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ are independently from each other hydrogen or fluoro, wherein at least one of $R^4/R^{4'}$ or $R^5/R^{5'}$ is always fluoro;

R' is aryl or hydroxy;

15 R'' is hydrogen, cycloalkyl or is heterocycloalkyl;

R is hydrogen or lower alkyl;

m is 0, 1, 2 or 3;

and to pharmaceutically suitable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof.

20 2. Compounds of formula I as described in claim 1, wherein $R^4/R^{4'}$ are both fluoro and R^1 is phenyl, substituted by halogen.

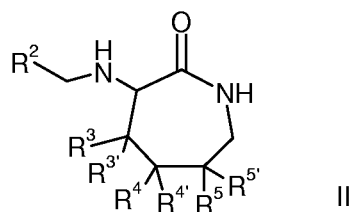
3. Compounds of formula I according to claim 2, wherein R^2 is phenyl, substituted by halogen and/or $C(O)-N(R'')_2$.

4. Compounds of formula I according to claim 3, which compounds are
 25 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-

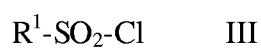
methyl}-N-cyclopropyl-benzamide or
4-[[[(4-chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl)-amino]-
methyl]-3-fluoro-N-pyrrolidin-1-yl-benzamide.

- 5 5. Compounds of formula I as described in claim 2, wherein R² is phenyl,
substituted by halogen and lower alkoxy.
6. Compounds of formula I according to claim 5, which compounds are
4-chloro-N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-5,5-difluoro-2-oxo-
azepan-3-yl)-benzenesulfonamide.
- 10 7. Compounds of formula I as described in claim 2, wherein R² is phenyl,
substituted by halogen and heteroaryl.
8. Compounds of formula I according to claim 7, which compound is
4-chloro-N-((R)-5,5-difluoro-2-oxo-azepan-3-yl)-N-[2-fluoro-4-(2H-
[1,2,4]triazol-3-yl)-benzyl]-benzenesulfonamide.
- 15 9. Compounds of formula I as described in claim 2, wherein R² is phenyl,
substituted (CR₂)_mC(O)-R'.
10. Compounds of formula I according to claim 9, which compounds are
3-(4-[[[(4-chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl)-
amino]-methyl]-phenyl)-propionic acid or
3-(4-[[[(4-chloro-benzenesulfonyl)-(R)-5,5-difluoro-2-oxo-azepan-3-yl)-
20 amino]-methyl]-phenyl)-3-methyl-butyric acid.
11. Compounds of formula I as described in claim 1, wherein R¹ is heteroaryl,
substituted by halogen.
- 25 12. Compounds of formula I as described in claim 1, wherein R¹ is lower alkyl
substituted by halogen.
13. A process for preparing a compound of formula I as defined in claim
1, which process comprises

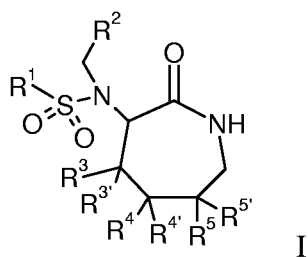
a) reacting a compound of formula



5 with a compound of formula

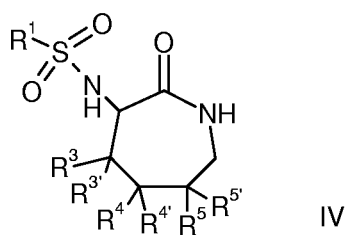


to a compound of formula

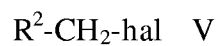


wherein R^1 , R^2 , $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ have the meaning as described in claim 1, or

10 b) reacting a compound of formula



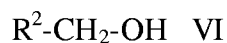
with a compound of formula



in the presence of a base

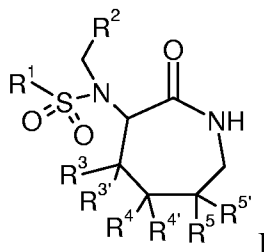
15 or with a compound of formula

- 35 -



in the presence of Ph_3P

to a compound of formula



5 wherein R^1 , R^2 , $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ have the meaning as described in claim 1, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

14. A compound according to claim 1, whenever prepared by a process as claimed in
10 claim 13 or by an equivalent method.

15. A medicament containing one or more compounds as claimed in claim 1 and pharmaceutically acceptable excipients.

16. A medicament according to claim 15 for the treatment of Alzheimer's disease or common cancers.

15 17. The use of a compound according to claim 1 for the manufacture of medicaments for the treatment of Alzheimer's disease or common cancers.

18. The invention as hereinbefore described.
