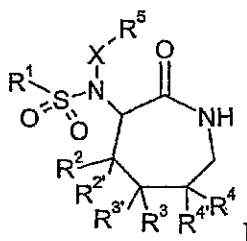


Case 22502

Sulfonamide derivatives

The invention relates to compounds of general formula



wherein

- 5 R^1 is aryl or heteroaryl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, lower alkyl substituted by halogen, -O-lower alkyl substituted by halogen, NO_2 or CN;

R^2 - R^4 and $R^{2'}$ - $R^{4'}$ are hydrogen, lower alkyl, phenyl or lower alkyl substituted by halogen;

- 10 R^5 is aryl or heteroaryl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, lower alkyloxy, CN, nitro, amino, hydroxy, lower alkyl substituted by hydroxy, lower alkyl substituted by halogen, or are substituted by
- 15 $-C(O)-NR''_2$,
 $-(CR_2)_m-C(O)-R'$,
 $-(CH_2)_m$ -heterocycloalkyl,
 $-(CH_2)_m$ -heteroaryl, unsubstituted or substituted by $-(CH_2)_m$ -lower alkoxy, lower alkyl, $-(CH_2)_m$ -O-benzyl or CH_2OH ,
 $-O-C(O)$ -lower alkyl,
- 20 $-O-C(O)-NR_2$,
 $-O-(CH_2)_m-C(O)OH$,
 $-O$ -lower alkynyl,
 $-O$ -lower alkyl substituted by halogen,
 $-O-(CH_2)_m$ -heterocyclyl,

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- O-(CH₂)_m-phenyl, unsubstituted or substituted by hydroxy,
 -O-(CH₂)_m-heteroaryl, unsubstituted or substituted by lower alkyl,
 -(CH₂)_m-NH-C(O)R',
 -(CH₂)_m-NH-S(O)₂-R',
 5 -S(O)₂-lower alkyl,
 -S(O)₂-heterocyclyl,
 -S(O)₂NH-cycloalkyl,
 or is cycloalkyl;
- R' is hydrogen, lower alkyl, lower alkinyloxy, hydroxy, cycloalkyl, heterocycloalkyl,
 10 which is unsubstituted or substituted by one or more substituents, selected from
 COOH, -C(O)O-lower alkyl -CH₂C(O)O-lower alkyl, halogen or lower alkyl, or is
 phenyl, benzyl, heteroaryl, -(CH₂)_m-lower alkoxy or -(CHR)_m-C(O)O-lower alkyl;
- R'' is hydrogen, cycloalkyl, which is unsubstituted or substituted by one or more
 substituents, selected from halogen, or is lower alkyl, lower alkyl substituted by
 15 halogen, lower alkyl substituted by hydroxy, -(CH₂)_m-heterocycloalkyl, -NR₂,
 heteroaryl, benzyl or
 -(CHR)_m-C(O)O-lower alkyl;
- R is hydrogen or lower alkyl;
- R⁶ is hydrogen or lower alkyl;
- 20 X is -CHR-;
- m is 0, 1, 2 or 3;

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

25 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.

30 As used herein, the term "lower alkynyl" denotes a straight- or branched-chain
 group containing from 2 to 7 carbon atoms, wherein at least one bond is a triple bond for
 example, ethynyl, propynyl, isopropynyl, n-butylnyl, i-butylnyl and the like.

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

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, and wherein the fused ring may contain one or two heteroatoms, for example phenyl, benzyl, naphthyl, biphenyl, indanyl, benzo[1,3]dioxolyl or benzofuranyl. The preferred aryl group is phenyl.

The term "heteroaryl" denotes a monovalent aromatic carbocyclic radical, 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 thiazolyl.

The term "heterocycloalkyl" denotes a non aromatic hydrocarbon radical, for example oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl. Preferred heterocycloalkyl 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, 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 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 (A β peptides) which originate from the β -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.

Abeta peptides are produced from APP through the sequential action of 2
5 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 cytoplasmic domain (CTF β). CTF β is the substrate for γ -secretase which cleaves at several adjacent positions within the TM to produce the A β peptides and the cytoplasmic fragment. The majority of
10 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 consisting of several proteins, its exact composition is incompletely understood.
15 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. Proven substrates for γ -secretase are the APP and the proteins of the Notch receptor
20 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 with specific γ -secretase inhibitors.

25 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
30 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:

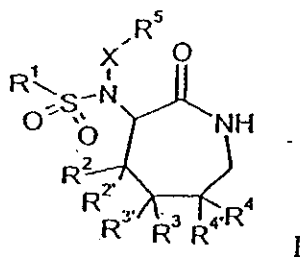
- The EMBO Journal (2204), 23, 483-488,
- Biochemistry (2004), 43 (30), 9774-9789,
- Nature Reviews/Neuroscience, Vol. 3, April 2002/281,
- Biochemical Society Transactions (2002), Vol. 30. part 4,
- Current Topics in Medicinal Chemistry, 2002, 2, 371-383,
- Current Medicinal Chemistry, 2002, Vol. 9, 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,
- 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,
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.

Disclosed herein 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 prevention of Alzheimer's disease or common cancers including but not limited to cervical carcinomas and breast carcinomas. .

Further disclosed herein are all forms of optically pure enantiomers, recemates or diastereomeric mixtures for compounds of formula I.

In a first aspect, there is provided compounds of the general formula



wherein

- R^1 is phenyl, thiophenyl or furanyl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, lower alkyl substituted by halogen, -O-lower alkyl substituted by halogen, NO_2 or CN ;
- R^2 - R^4 and R^2' - R^4' are hydrogen, lower alkyl, phenyl or lower alkyl substituted by halogen;

R^5 is phenyl, pyridinyl, benzo[1,3]dioxolyl or benzofuranyl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, lower alkyloxy, CN, nitro, amino, hydroxy, lower alkyl substituted by hydroxy, lower alkyl substituted by halogen, or are substituted by

- C(O)-NR''₂,
- (CR₂)_m-C(O)-R',
- (CH₂)_m-heterocycloalkyl,
- (CH₂)_m-heteroaryl, unsubstituted or substituted by -(CH₂)_m-lower alkoxy, lower alkyl, -(CH₂)_m-O-benzyl or CH₂OH,
- O-C(O)-lower alkyl,
- O-C(O)-NR₂,
- O-(CH₂)_m-C(O)OH,
- O-lower alkynyl,
- O-lower alkyl substituted by halogen,
- O-(CH₂)_m-heterocyclyl,
- O-(CH₂)_m-phenyl, unsubstituted or substituted by hydroxy,
- O-(CH₂)_m-heteroaryl, unsubstituted or substituted by lower alkyl,
- (CH₂)_m-NH-C(O)R',
- (CH₂)_m-NH-S(O)₂-R',
- S(O)₂-lower alkyl,
- S(O)₂-heterocyclyl,
- S(O)₂NH-cycloalkyl,

or is cycloalkyl;

R' is hydrogen, lower alkyl, lower alkynyloxy, hydroxy, cycloalkyl, heterocycloalkyl, which is unsubstituted or substituted by one or more substituents, selected from COOH, -C(O)O-lower alkyl -CH₂C(O)O-lower alkyl, halogen or lower alkyl, or is phenyl, benzyl, heteroaryl, -(CH₂)_m-lower alkoxy or -(CHR)_m-C(O)O-lower alkyl;

R'' is hydrogen, cycloalkyl, which is unsubstituted or substituted by one or more substituents, selected from halogen, or is lower alkyl, lower alkyl substituted by halogen, lower alkyl substituted by hydroxy, -(CH₂)_m-heterocycloalkyl, -NR₂, heteroaryl, benzyl or -(CHR)_m-C(O)O-lower alkyl;

R is hydrogen or lower alkyl;

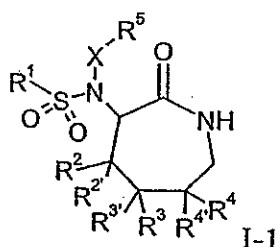
R^6 is hydrogen or lower alkyl;

X is $-\text{CHR}-$;

m is 0, 1, 2 or 3;

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

Disclosed herein are compounds, encompassed by the general formula



wherein

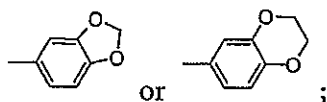
R^1 is aryl or heteroaryl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, CF_3 , OCF_3 , NO_2 or CN ;

R^2 - R^4 and $R^{2'}$ - $R^{4'}$ are hydrogen, lower alkyl or CF_3 ;

R^5 is cycloalkyl, aryl or heteroaryl, wherein cycloalkyl, aryl or heteroaryl are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, CHO , CN , hydroxy, lower alkyloxy, lower alkinyloxy, $-\text{OCF}_3$, OCHF_2 , OCH_2F , $-\text{OC}(\text{O})$ -lower alkyl, $-\text{OC}(\text{O})-\text{NR}'\text{R}''$, $-\text{O}-(\text{CH}_2)_n$ -heterocycloalkyl, $-\text{O}-(\text{CH}_2)_n$ -heteroaryl, which may be

- substituted by lower alkyl, or is $-O-(CH_2)_n\text{-aryl}$,
 $-(CH_2)_n\text{-C(O)NR'R''}$, $-(CH_2)_n\text{-C(O)O-lower alkyl}$, $-(CH_2)_n\text{-C(O)OH}$,
 $-(CH_2)_n\text{-C(O)O-lower alkynyl}$, $-C(O)\text{-heterocycloalkyl}$, optionally substituted by
COOH, or is $-C(O)\text{-cycloalkyl}$, $-C(O)\text{-aryl}$, $-NR'R''$, nitro,
5 $-S(O)_2\text{-lower alkyl}$, $-S(O)_2\text{-cycloalkyl}$, $-S(O)_2\text{-heterocycloalkyl}$, $-S(O)_2\text{-aryl}$,
 $-S(O)_2\text{-NR'R''}$,

or is



- R'/R'' are independently from each other hydrogen, lower alkyl, cycloalkyl,
10 heterocycloalkyl, heteroaryl, di-lower alkylamino, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}_2\text{F}$, $-C(O)\text{-lower alkyl}$, $-C(O)\text{O-lower alkyl}$ or $-C(O)\text{-cycloalkyl}$;

X is a bond, lower alkyl or lower alkenyl;

n is 0, 1, 2 or 3;

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

The most preferred compounds of formula I are those, wherein
 R^1 is phenyl, substituted by halogen and R^5 is phenyl, substituted by $-C(O)\text{-NR''}_2$, for
example the following compounds:

- 4-[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
20 4-[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-
benzamide,
rac-4-[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-
N-cyclopropyl-benzamide,
rac-4-[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-
25 cyclopropyl-benzamide,
4-[[(4-chloro-benzenesulfonyl)-(2-oxo-5-phenyl-azepan-3-yl)-amino]-methyl]-N-
cyclopropyl-benzamide,
5-[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-
pyridine-2-carboxylic acid cyclopropylamide,
30 N-cyclopropyl-4-[[((R)-2-oxo-azepan-3-yl)-(4-bromo-benzenesulfonyl)-amino]-
methyl]-benzamide,
4-[[(5-*tert*-butyl-2-oxo-azepan-3-yl)-(4-chloro-benzenesulfonyl)-amino]-methyl]-N-
cyclopropyl-benzamide,

- 4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
 4-[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
 5 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-fluoro-ethyl)-benzamide,
 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2,2,2-trifluoro-ethyl)-benzamide,
 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-((1R,2S)-2-fluoro-cyclopropyl)-benzamide,
 10 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-hydroxy-ethyl)-benzamide,
 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopentyl-benzamide,
 15 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-methyl-benzamide,
 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
 rac-N-benzyl-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
 20 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoylamino)-acetic acid methyl ester,
 rac-4-[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
 25 4-[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
 4-chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-2-fluoro-benzyl]-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide or
 4-chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-benzyl]-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide.
 30

Further preferred are compounds, wherein R¹ is phenyl, substituted by halogen or lower alkyl substituted by halogen and R⁵ is phenyl, substituted by halogen or lower alkyl substituted by halogen, or halogen and lower alkoxy or CH₂OH, for example the
 35 following compounds:

rac-4-chloro-N-(4-chloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,

- rac-4-chloro-N-(3-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
 rac-4-chloro-N-(4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
 rac-4-Chloro-N-(3,4-dichloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
 5 4-chloro-N-(3-fluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide,
 rac-4-bromo-N-(3-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
 4-chloro-N-(2-fluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide,
 10 4-chloro-N-(3-fluoro-4-methoxy-benzyl)-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide,
 N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-4-trifluoromethyl-benzenesulfonamide,
 15 Rac-4-chloro-N-(4-difluoromethyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
 4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(2-fluoro-4-methoxy-benzyl)-benzenesulfonamide,
 4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(2-fluoro-4-hydroxymethyl-benzyl)-benzenesulfonamide,
 20 4-chloro-N-(2-fluoro-4-methoxy-benzyl)-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide or
 4-chloro-N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.
- 25 Further preferred are compounds, wherein R¹ is phenyl, substituted by halogen and R⁵ is phenyl, substituted by -(CR₂)_m-C(O)-R' or -(CR₂)_m-C(O)-R' and halogen, for example the following compounds:
- 4-{[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl}-3-fluoro-benzoic acid methyl ester,
 30 4-{[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid ethyl ester,
 4-{1-[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-ethyl}-benzoic acid methyl ester,
 rac-4-{[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid
 35 methyl ester,

- 4-[[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester,
- Rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester,
- 5 4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid,
- 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid methyl ester,
- 10 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid,
- 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid,
- 15 3-(4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid,
- 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-20 3-fluoro-benzoic acid,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 25 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-3-methyl-butyric acid or
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-2,2-dimethyl-propionic acid.

30 Further preferred are compounds, wherein R^1 is phenyl, substituted by halogen and R^5 is phenyl, substituted by hydroxy, for example the following compounds:

rac- 4-chloro-N-(4-hydroxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide or
4-chloro-N-(4-hydroxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

35 Further preferred are compounds, wherein R^1 is heteroaryl, unsubstituted or

substituted by one or more substituents as described in formula I, for example the following compounds:

- rac-4-chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-N-[4-(2H-tetrazol-5-yl)-benzyl]-benzenesulfonamide,
5 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzyl]-benzenesulfonamide,
4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl]-benzenesulfonamide,
4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(4-isoxazol-5-yl-benzyl)-
10 benzenesulfonamide,
4-chloro-N-(4-isoxazol-5-yl-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide or
4-Chloro-N-[2-fluoro-4-(2H-[1,2,4]triazol-3-yl)-benzyl]-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

- 15 Further preferred are compounds, wherein R¹ is phenyl, substituted by halogen and R⁵ is phenyl, substituted by NH₂, for example the following compound:
N-(4-amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

- Further preferred are compounds, wherein R¹ is phenyl, substituted by halogen and R⁵ is phenyl, substituted by -(CH₂)_m-NH-C(O)R', for example the following
20 compounds:

rac-N-(4-{[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl}-phenyl)-acetamide or
Rac-N-(4-{[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-phenyl)-malonamic acid ethyl ester.

25

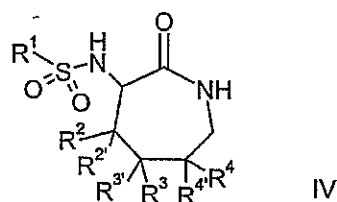
Preferred are further those compounds, wherein X is -CH₂-.

Further preferred are compounds, wherein R¹ is aryl and R⁵ is aryl.

- The disclosed compounds of formula I and their pharmaceutically acceptable
30 salts can be prepared by methods known in the art, or by processes described below.

In a second aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises

- a) reacting a compound of formula



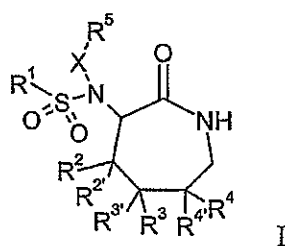
with a compound of formula

$R^5X\text{-hal}$ in the presence of a base, or

with a compound of formula

5 R^5XOH in the presence of diethylazodicarboxylate and triphenylphosphine

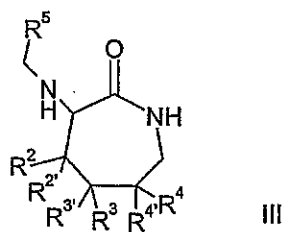
to a compound of formula



wherein $R^1 - R^5$ and X have the meaning as described above,

or

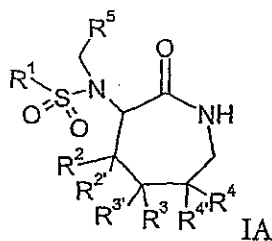
10 b) reacting a compound of formula



with a compound of formula

$R^1\text{-S(O)}_2\text{-Cl}$ in the presence of a base

to a compound of formula



wherein R¹ – R⁵ and X have the meaning as described above, and

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

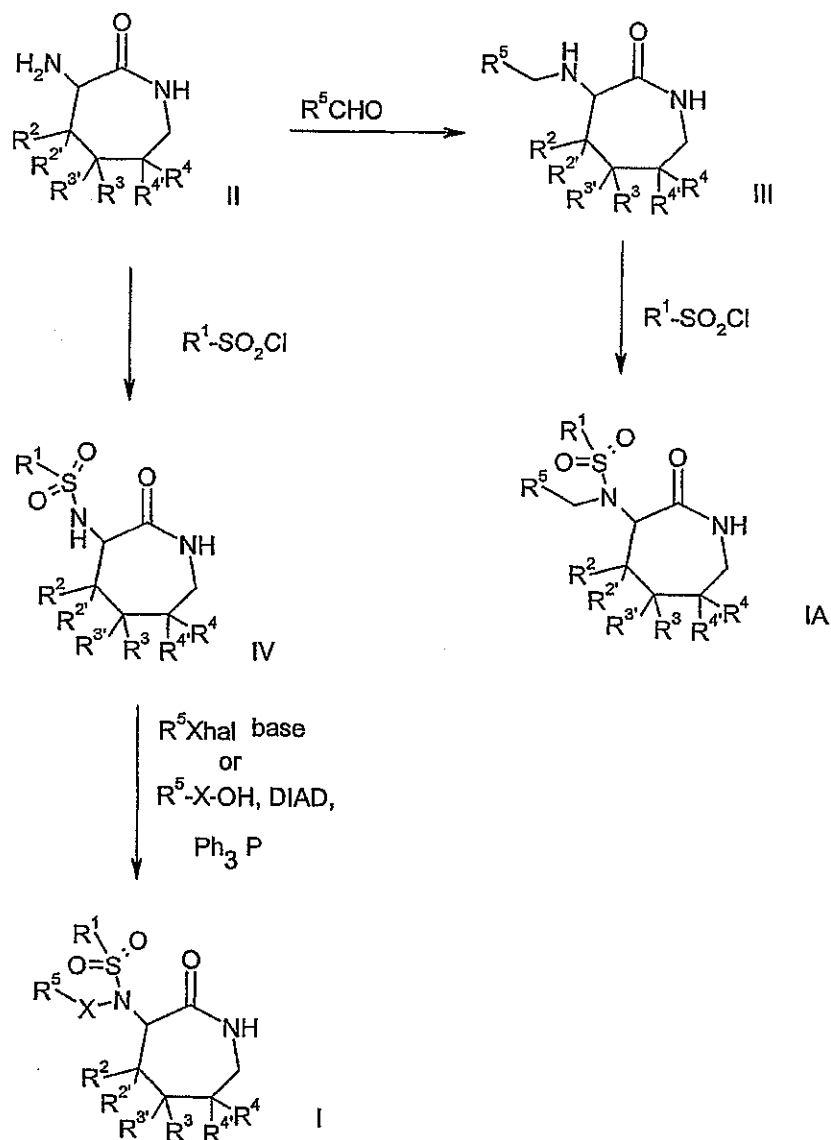
In a third aspect, there is provided a compound as defined above, whenever prepared by a process as defined above or by an equivalent method.

In a fourth aspect, there is provided a medicament containing one or more compounds as defined above and pharmaceutically acceptable excipients.

In a fifth aspect, there is provided a compound as defined above for the manufacture of medicaments for the treatment of Alzheimer's disease or common cancers.

The detailed processes for preparing of compounds of formula I are described in schemes 1 and 2 and in Examples 1 – 223. The starting materials of formulae II, VI, R¹-S(O)₂Cl, R⁵Xhal, R⁵X-OH or HOSO₃NH₂ are known compounds or may be prepared by methods well-known in the art.

Scheme 1



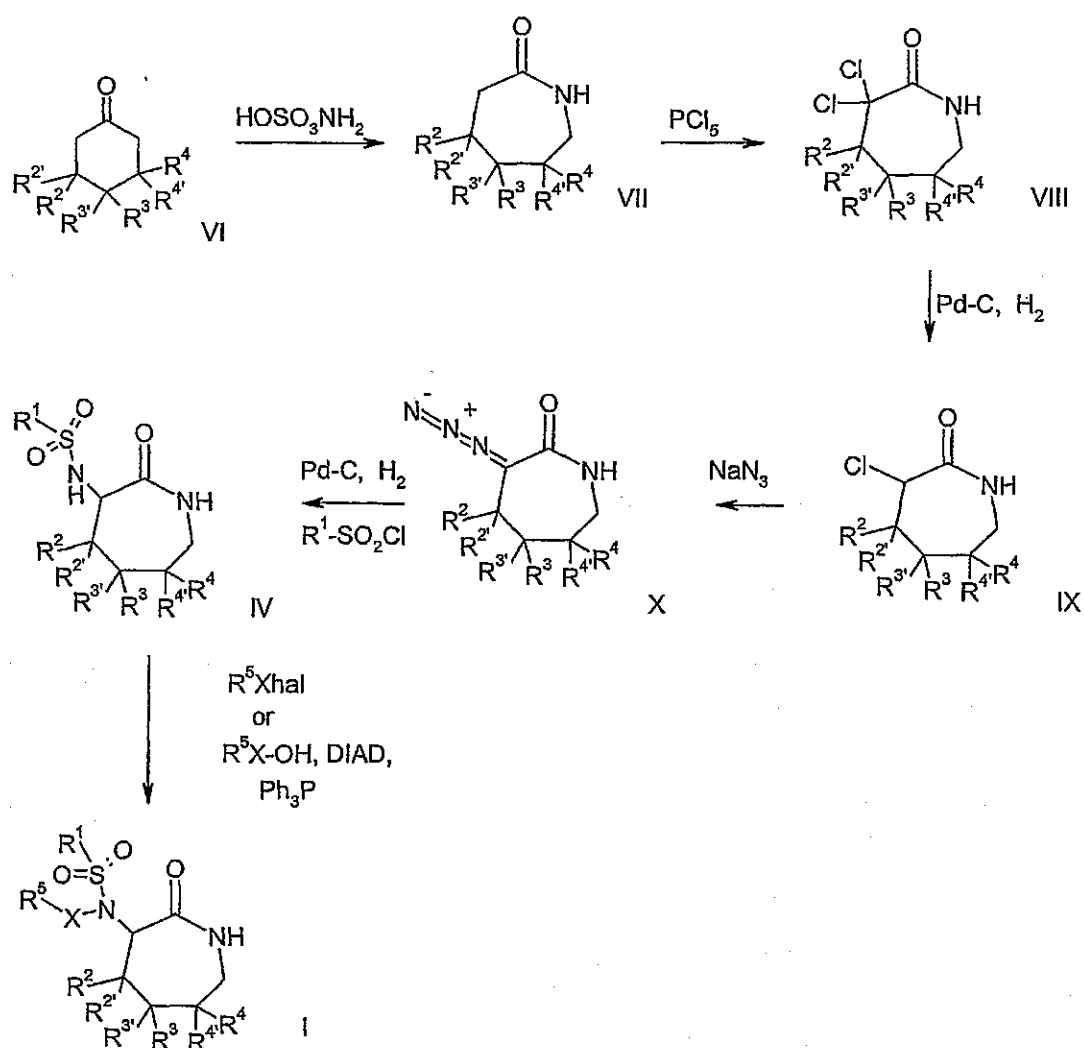
wherein $R^1 - R^5$ and X have the meaning as described above, DIAD is diethylazodicarboxylate and Ph_3P is triphenylphosphine.

- 5 An amino-azepan-2-one of formula II is treated with an aldehyde and a suitable reducing reagent such as sodium triacetoxyborohydride or sodium cyanoborohydride to yield an amine compound of formula III. 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
- 10 chromatography a pure compound of formula IA. Alternatively, the compound of formula II 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^5XOH , 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
 5 be used in a reaction where a halide R^5Xhal 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.

An unsubstituted amino-azepan-2-one (II) can for example be prepared from the
 10 corresponding lysine hydrochloride in toluene under refluxing conditions in the presence of a base such as hexamethyldisilazane. Ring-substituted 3-amino-azepan-2-ones can be prepared by numerous methods described in the literature and specifically by one approach outlined in Scheme 2.

Scheme 2



wherein $R^1 - R^5$ and X have the meaning as described above, DIAD is diethylazodicarboxylate and Ph_3P is triphenylphosphine.

A substituted cyclohexanone of formula VI can be reacted with hydroxylamine O-sulfonic acid in formic acid as solvent under refluxing conditions for several hours to
5 yield a ring expansion product of formula VII. Such cyclic amides can be chlorinated using phosphorous pentachloride in xylenes by slowly warming the reaction mixture to $90^\circ C$ in an exothermic reaction whereby the evolution of HCl gas is also observed. After careful quenching with water at lower temperature the organic phase is isolated in an appropriate organic solvent such as chloroform, which is dried and a crude compound of
10 formula VIII is isolated ready to be used in the next step. Monodechlorination of a compound of formula VIII can be achieved under conditions of controlled hydrogenation using palladium catalyst in acetic acid as solvent yielding compound of formula IX which can undergo substitution reaction with sodium azide as a nucleophile in preferably dry dimethylsulfoxide as solvent. Azides of compound formula X can be
15 isolated in pure form following chromatographic purification on silica gel. Hydrogenation of azides X to the amine tend to proceed quantitatively, however owing to the instability of the amine on storage, we preferred to derivatize in situ with an appropriate aryl sulfonyl chloride to yield stable sulfonamides of compound formula IV. These can be further subjected to a Mitsunobu protocol as described before to yield target
20 compounds of formula I.

The detailed description can be found in Examples 1-223.

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
25 an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric 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
30 like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between $0^\circ C$ and $50^\circ C$. 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
35 corresponding free bases by treatment with at least a stoichiometric equivalent of a

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
5 compounds of the present invention may inhibit the γ -secretase.

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

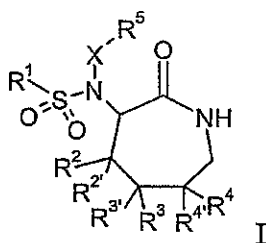
Description of γ -secretase assay

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
10 assays where e.g., a substrate of the γ -secretase is fused in its cytoplasmic domain to a 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-
15 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
20 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
25 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
30 incubated with the APP substrate. The Abeta peptides which are produced by γ -secretase

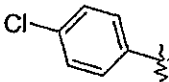
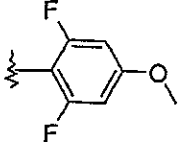
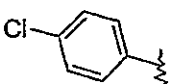
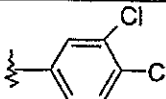
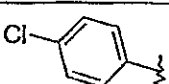
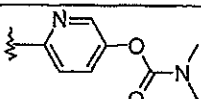
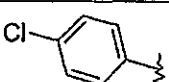
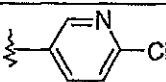
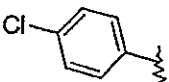
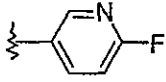
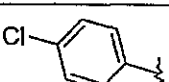
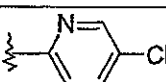
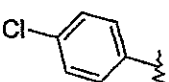
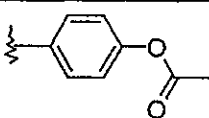
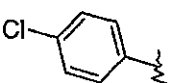
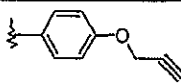
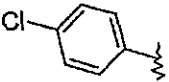
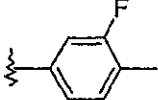
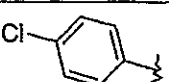
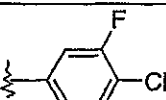
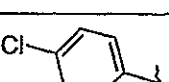
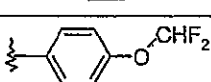
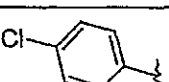
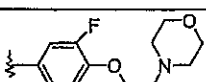
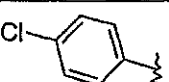
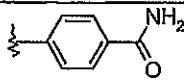
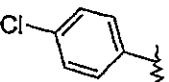
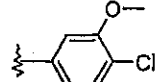
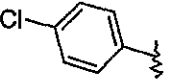
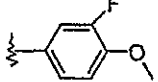
cleavage of the substrate are detected by specific ELISA assays as described (Brockhaus M et al, Neuroreport 9(7), 1481-1486 (1998).

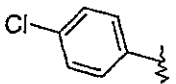
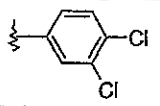
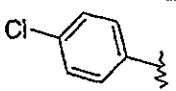
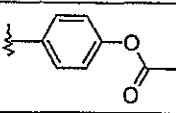
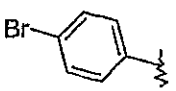
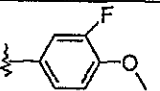
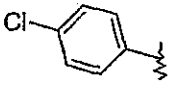
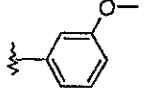
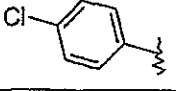
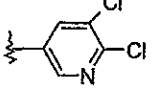
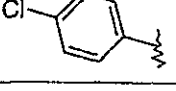
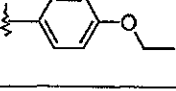
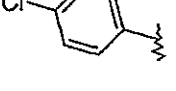
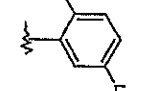
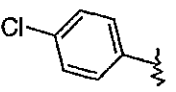
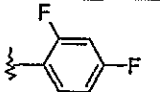
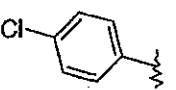
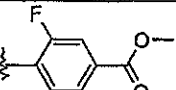
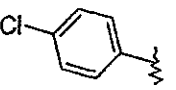
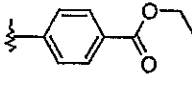
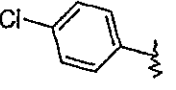
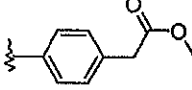
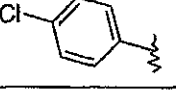
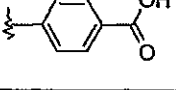
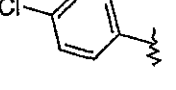
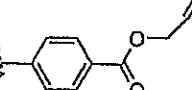
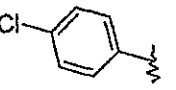
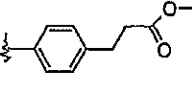
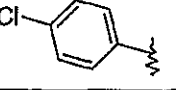
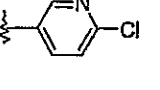
The preferred compounds show a $IC_{50} < 0.3 \mu M$. In the list below are described some data to the γ -secretase inhibition:

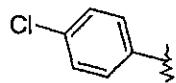
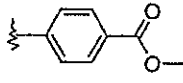
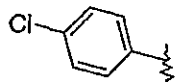
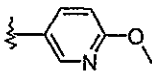
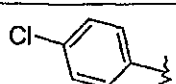
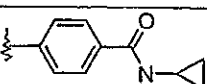
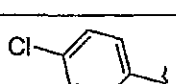
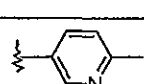
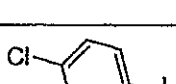
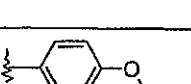
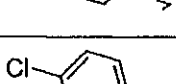
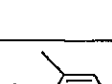
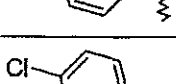
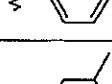
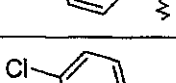
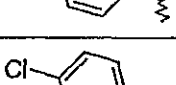
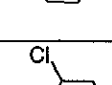
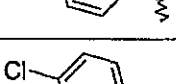
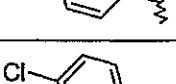
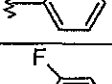
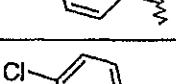
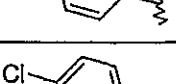
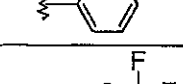
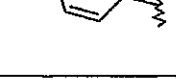
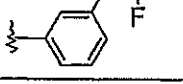
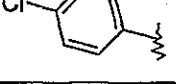
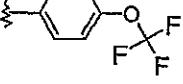


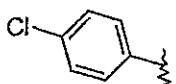
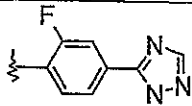
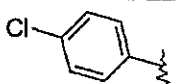
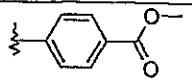
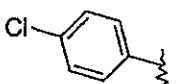
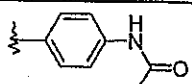
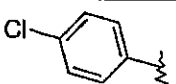
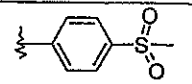
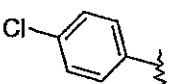
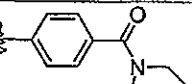
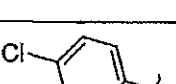
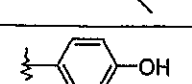
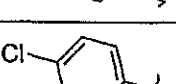
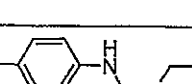
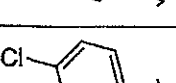
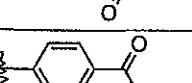
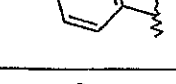
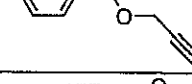
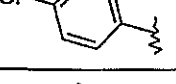
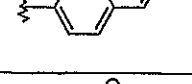
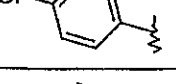
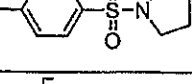
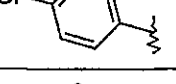
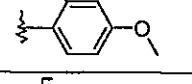
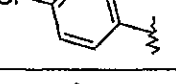
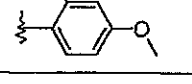
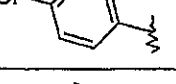
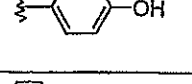
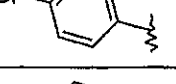
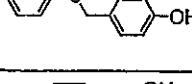
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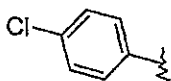
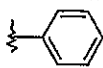
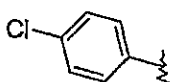
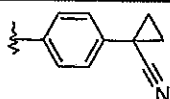
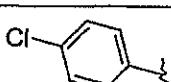
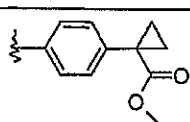
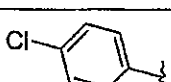
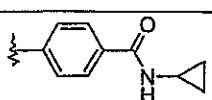
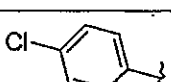
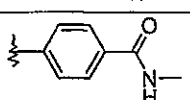
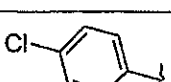
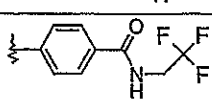
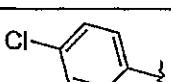
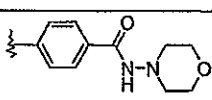
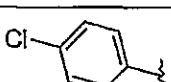
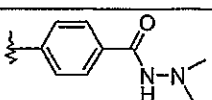
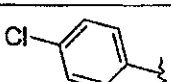
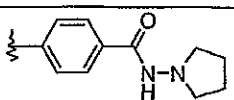
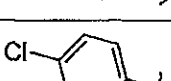
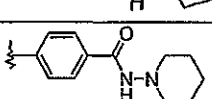
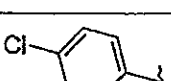
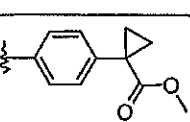
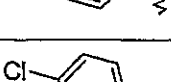
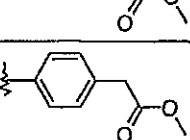
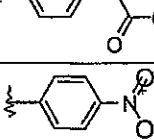
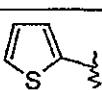
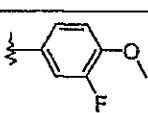
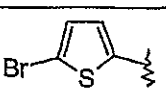
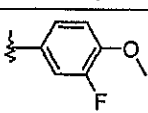
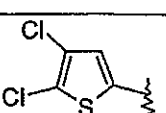
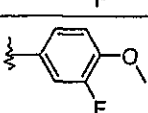
IC_{50} in vitro	R^1	R^2	R^3	R^4	R^5	X	Expl.
		H	H	H		CH ₂	1 rac
0.15		H	H	H		CH ₂	2 (R)
		H	H	H		CH ₂	3 (R)
0.26		H		H		CH ₂	4
		H	H	H		CH ₂	5 rac
		H	H	H		CH ₂	6 rac
0.20		H	H	H		CH ₂	7 rac
0.12		H	H	H		CH ₂	8 rac
		H	H	H		CH ₂	9 rac
0.15		H	H	H		CH ₂	10 rac

		H	H	H		CH ₂	11 (R)
0.08		H	H	H		CH ₂	12 rac
		H	H	H		CH ₂	13 rac
		H	H	H		CH ₂	14 rac
		H	H	H		CH ₂	15 rac
		H	H	H		CH ₂	16 rac
		H	H	H		CH ₂	17 rac
		H	H	H		CH ₂	18 rac
		H	H	H		CH ₂	19 rac
		H	H	H		CH ₂	20 rac
		H	H	H		CH ₂	21 rac
		H	H	H		CH ₂	22 rac
		H	H	H		CH ₂	23 rac
		H	H	H		CH ₂	24 rac
0.13		H	H	H		CH ₂	25 (R)

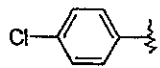
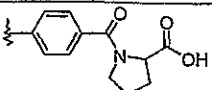
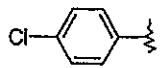
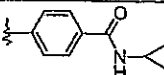
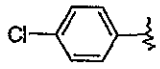
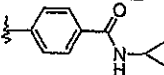
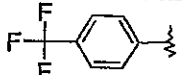
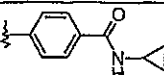
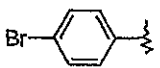
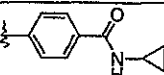
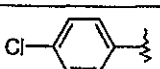
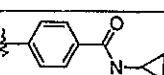
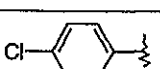
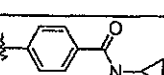
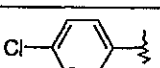
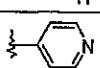
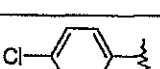
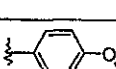
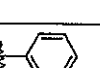
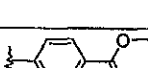
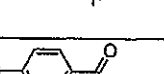
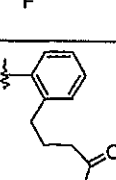
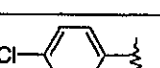
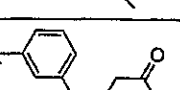
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		H	H	H		CH ₂	30 rac
		H	H	H		CH ₂	31 rac
		H	H	H		CH ₂	32 rac
		H	H	H		CH ₂	33 rac
0.14		H	H	H		CH ₂	34 (R)
0.09		H	H	H		CH ₂	35 (R)
		H	H	H		CH ₂	36 (R)
		H	H	H		CH ₂	37 (R,S)
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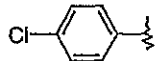
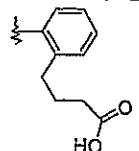
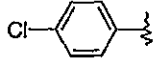
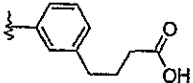
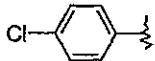
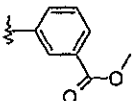
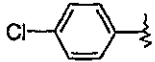
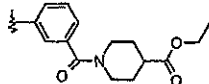
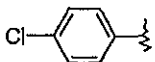
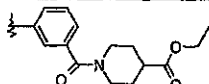
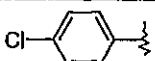
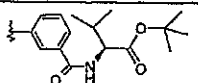
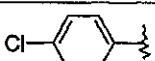
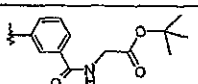
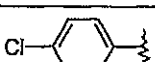
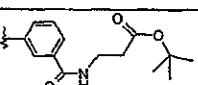
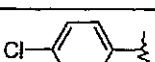
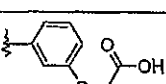
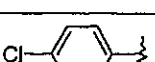
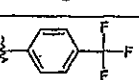
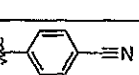
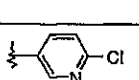
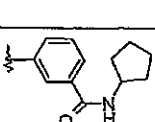
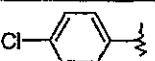
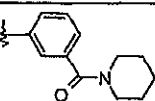
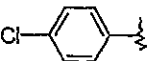
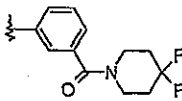
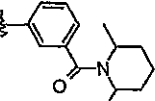
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		H		H		CH ₂	45 rac
		H	H	H		CH ₂	46 rac
		H	H	H		CH ₂	47 rac
		H	H	H		CH ₂	48 rac
		H	H	H		CH ₂	49 rac
		H	H	H		CH ₂	50 rac
		H	H	H		CH ₂	51 rac
		H	H	H		CH ₂	52 rac
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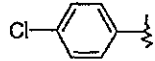
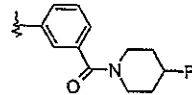
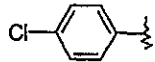
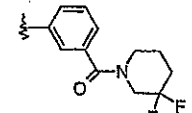
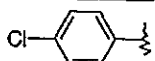
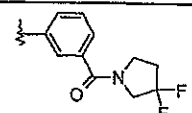
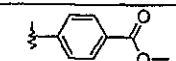
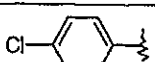
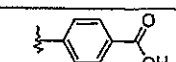
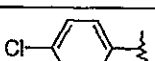
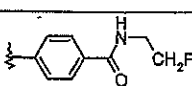
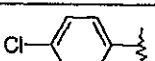
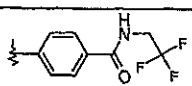
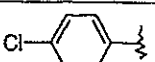
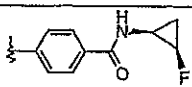
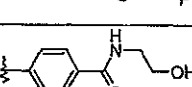
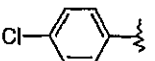
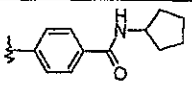
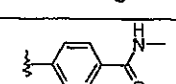
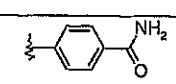
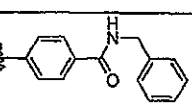
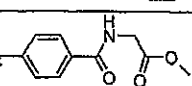
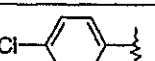
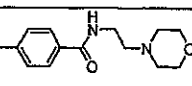
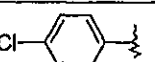
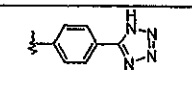
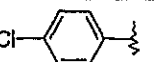
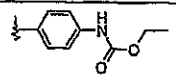
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		H	H	H		CH ₂	59 rac
		H	H	H		CH ₂	60 rac
0.28		H	H	H		CH ₂	61 rac
		H	H	H		CH ₂	62 rac
		H	H	H		CH ₂	63 rac
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		H	H	H		CH ₂	65 rac
		H	H	H		CH ₂	66 rac
		H	H	H		CH ₂	67 rac
0.12		H	H	H		CH ₂	68 R
0.06		H	H	H		CH ₂	69 R
		H	H	H		CH ₂	70 (R)
		H	H	H		CH ₂	71 rac

		H	H	H		CH ₂	72 rac
		H	H	H		CH ₂	73 rac
		H	H	H		CH ₂	74 rac
0.19		H	H	H		CH ₂	75 rac
		H	H	H		CH ₂	76 rac
		H	H	H		CH ₂	77 rac
		H	H	H		CH ₂	78 rac
		H	H	H		CH ₂	79 rac
		H	H	H		CH ₂	80 rac
		H	H	H		CH ₂	81 rac
		H	H	H		CH ₂	82 (R)
		H	H	H		CH ₂	83 (R)
		H	H	H		CH ₂	84 (R)
		H	H	H		CH ₂	85 rac
		H	H	H		CH ₂	86 rac
		H	H	H		CH ₂	87 rac

		H	H	H		CH ₂	88 rac
		H	H	H		CH ₂	89 rac
		H	H	H		CH ₂	90 rac
		H	H	H		CH ₂	91 rac
0.27		H	H	H		CH ₂	92 rac
		H	H	H		CH ₂	93 (R)
		H	H	H		CH ₂	94 (R)
		H	H	H		CH ₂	95 rac
		H	H	H		CH ₂	96 rac
		H	H	H		CH ₂	97 rac
		H	H	H		CH ₂	98 rac
		H	H	H		CH(CH ₃)	99 rac
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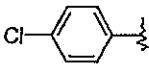
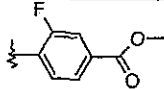
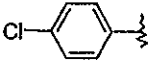
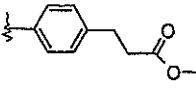
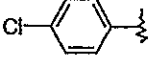
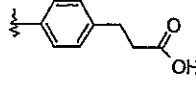
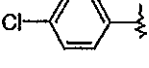
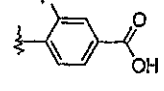
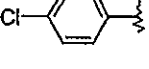
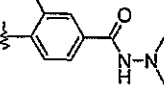
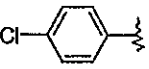
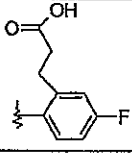
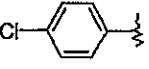
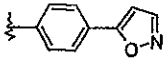
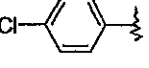
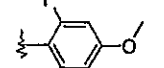
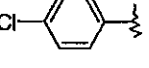
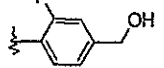
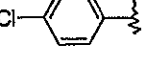
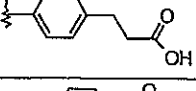
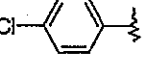
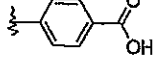
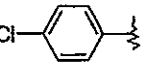
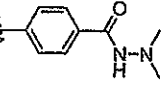
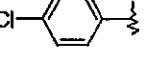
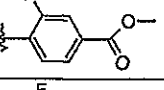
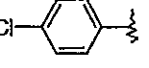
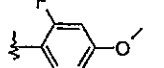
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0.29		H	H	H		CH ₂	107 (R)
		H		H		CH ₂	108
0.28		H	di- CH ₃	H		CH ₂	109
0.14		H	H	H		CH ₂	110 (R)
0.008		H		H		CH ₂	111
		H		H		CH ₂	112
		H		H		CH ₂	113
		H		H		CH ₂	114
0.03		H	CF ₃	H		CH ₂	115
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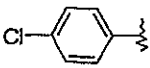
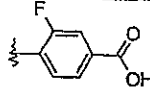
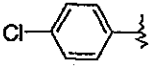
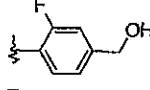
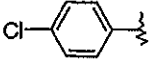
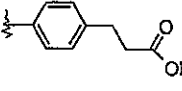
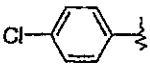
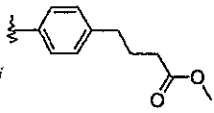
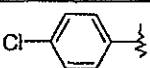
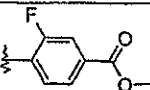
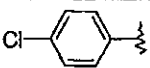
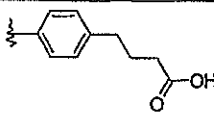
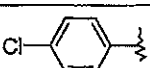
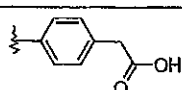
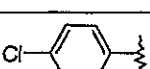
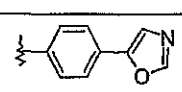
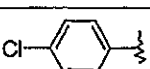
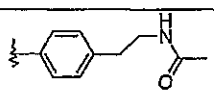
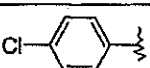
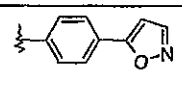
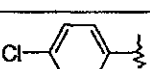
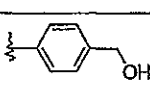
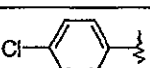
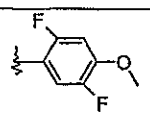
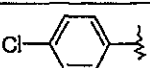
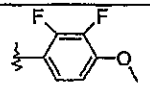
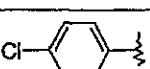
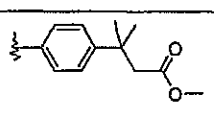
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		H	H	H		CH ₂	120
		H	H	H		CH ₂	121 rac
		H	H	H		CH ₂	122 rac
		H	H	H		CH ₂	123 rac
		H	H	H		CH ₂	124 (3S) (3RS)
		H	H	H		CH ₂	125 rac
		H	H	H		CH ₂	126 rac
		H	H	H		CH ₂	127 rac
		H	di- CH ₃	H		CH ₂	128 rac
		H	di- CH ₃	H		CH ₂	129 rac
		H	di- CH ₃	H		CH ₂	130 rac
		H	H	H		CH ₂	131 rac
		H	H	H		CH ₂	132 rac
		H	H	H		CH ₂	133 rac
		H	H	H		CH ₂	134 rac

		H	H	H		CH ₂	135 rac
		H	H	H		CH ₂	136 rac
		H	H	H		CH ₂	137 rac
0.01		H	di- CH ₃	H		CH ₂	138 rac
0.07		H	di- CH ₃	H		CH ₂	139
0.02		H	di- CH ₃	H		CH ₂	140 rac
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0.02		H	di- CH ₃	H		CH ₂	142 rac
0.04		H	di- CH ₃	H		CH ₂	143 rac
0.05		H	di- CH ₃	H		CH ₂	144 rac
0.01		H	di- CH ₃	H		CH ₂	145 rac
0.02		H	di- CH ₃	H		CH ₂	146 rac
0.02		H	di- CH ₃	H		CH ₂	147 rac
0.02		H	di- CH ₃	H		CH ₂	148 rac
0.15		H	di- CH ₃	H		CH ₂	149 rac
0.10		H	di- CH ₃	H		CH ₂	150 rac
		H	di- CH ₃	H		CH ₂	151 rac

0.02		H	di- CH ₃	H		CH ₂	152 rac
		H	H	H		CH ₂	153 rac
		H	H	H		CH ₂	154 rac
		H	H	H		CH ₂	155 rac
		H	H	H		CH ₂	156 rac
		H	H	H		CH ₂	157 rac
		H	H	H		CH ₂	158 rac
		H	H	H		CH ₂	159 rac
		H	H	H		CH ₂	160 rac
		H	H	H		CH ₂	161 rac
		H	H	H		CH ₂	162 rac
		H	H	H		CH ₂	163 rac
		H	H	H		CH ₂	164 rac
0.27		H	H	H		CH ₂	165 rac
0.23		H	H	H		CH ₂	166 (R)
		H	H	H		CH ₂	167 (R)
		H	H	H		CH ₂	168 (R)

		H	H	H		CH ₂	169 (R)
		H	H	H		CH ₂	170 rac
		H	H	H		CH ₂	171 rac
0.23		H	H	H		CH ₂	172 rac
		H	H	H		CH ₂	173 rac
		H	H	H		CH ₂	174 rac
		H	H	H		CH ₂	175 rac
		H	H	H		CH ₂	176 rac
		H	H	H		CH ₂	177
		H		H		CH ₂	178
		H		H		CH ₂	179
0.14		H		H		CH ₂	180
0.27		H		H		CH ₂	181
		H		H		CH ₂	182
0.01		H	di- CH ₃	H		CH ₂	183 (R)
		H	di- CH ₃	H		CH ₂	184 (S)

0.01		H	di- CH ₃	H		CH ₂	185 (R)
0.13		H	di- CH ₃	H		CH ₂	186 (R)
0.01		H	di- CH ₃	H		CH ₂	187 (R)
0.03		H	di- CH ₃	H		CH ₂	188 (R)
0.02		H	di- CH ₃	H		CH ₂	189 (R)
		H	di- CH ₃	H		CH ₂	190 (R)
0.06		H	di- CH ₃	H		CH ₂	191 (R)
0.04		H	di- CH ₃	H		CH ₂	192 (R)
0.02		H	di- CH ₃	H		CH ₂	193 (R)
0.13		H	CF ₃	H		CH ₂	194
0.03		H	CF ₃	H		CH ₂	195
0.19		H	CF ₃	H		CH ₂	196
0.02		H	CF ₃	H		CH ₂	197
0.29		H	CF ₃	H		CH ₂	198

0.02		H	CF ₃	H		CH ₂	199
		H	CF ₃	H		CH ₂	200
0.02		H	H	H		CH ₂	201 (R)
		H	H	H		CH ₂	202 (R)
0.19		H	H	H		CH ₂	203
		H	H	H		CH ₂	204 (R)
		H	H	H		CH ₂	205 (R)
		H	H	H		CH ₂	206 (R)
		H	H	H		CH ₂	207 (R)
0.22		H	H	H		CH ₂	208 (R)
		H	H	H		CH ₂	209 (R)
		H	H	H		CH ₂	210 (R)
0.05		H	H	H		CH ₂	211 (R)
		H	H	H		CH ₂	212 (R)

		H	H	H		CH ₂	213 (R)
		H	H	H		CH ₂	214 (R)
		H	H	H		CH ₂	215 (R)
		H	H	H		CH ₂	216
		H	H	H		CH ₂	217 (R)
0.21		H	H	H		CH ₂	218 (R)
0.23		H	H	H		CH ₂	219 (R)
		H	H	H		CH ₂	220 (R)
		di- CH ₃	H	H		CH ₂	221 rac
		H	H	H		CH ₂	222 rac
		H	H	H		CH ₂	223 rac

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
5 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,
10 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
15 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
20 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
25 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
1.	Compound of formula I	5	25	100	500
5 2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

10 Manufacturing Procedure

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

15

Capsule Formulation

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

Manufacturing Procedure

- 25 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.

Numerous intermediates or reagents such as aldehydes, cyclic ketones, aromatic sulfonyl chlorides, alkyl halides, benzyl halides, benzyl alcohols are used to prepare compounds of formula I. These are typically commercially available, or accessible by literature routes. Representative syntheses are described below.

5

Preparation of intermediates

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 CH_2Cl_2 (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% KHSO_4 /10% K_2SO_4 solution, NaCl sat. solution and dried (Na_2SO_4). 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 (CDCl_3) 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^+)

15

Example B

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

20

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 1N 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 (MgSO_4), 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 (CDCl_3) 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^+)

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Example C

(5-Methoxy-pyridin-2-yl)-methanol

1) 5-Methoxy-2-methyl-pyridine

5-Hydroxy-2-methyl pyridine (16.4 g, 150.3 mmol) was added to a suspension of KOH (34.6 g, 616 mmol) in DMSO (250 ml) and stirred for 1 h at r.t. followed by the dropwise addition of methyl iodide (10.3 ml, 165 mmol). The reaction mixture was stirred for a

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further 16 h, poured onto ice-cold water (500 ml) and extracted with diethyl ether (4 x 350 ml). The combined ether extracts were washed with water (50 ml), brine (50 ml) and dried (MgSO₄). Filtration and concentration of the filtrate under reduced pressure gave a crude oil which was purified over silica gel (ethyl acetate/n-heptane 1:2 to 1:1): light brown oil 10.5 g (54%);
¹H NMR (CDCl₃) δ 2.49 (s, 3H), 3.82 (s, 3H), 7.04-7.10 (m, 2H), 8.20 (d, 2H); MS: m/e = 123.0 (M), 108.0 (M-CH₃).

2) 5-Methoxy-2-methyl-pyridine 1-oxide

5-Methoxy-2-methyl-pyridine (10.3 g, 83.6 mmol) was dissolved in CHCl₃ (250 ml) and reacted with methyltrioxorhenium (0.2 g, 0.83 mmol) and hydrogen peroxide (30% in water, 14.6 ml). The resultant mixture was stirred overnight at r.t. and then cooled (ice-water bath). Small portions of MnO₂ were added until no further O₂ gas evolved. The reaction mixture was further stirred at r.t. and then diluted with water (140 ml). The organic layer was collected and the aqueous phase was extracted with CHCl₃ (2x). The combined CHCl₃ fractions were dried (MgSO₄), filtered and evaporated. The resultant white solid was stirred for ca. 1 h in n-pentane, filtered and dried under vacuum: solid 9.31 g (76%);
¹H NMR (CDCl₃) δ 2.45 (s, 3H), 3.81 (s, 3H), 6.83 (dd, 1H), 7.12 (d, 1H), 8.03 (d, 1H); MS: m/e = 139.0 (M), 122.0 (M-OH)

3) Acetic acid 5-methoxy-pyridin-2-ylmethyl ester

5-Methoxy-2-methyl-pyridine 1-oxide (9.25 g, 66.5 mmol) was suspended in acetic anhydride (31 ml) under an argon atmosphere. The mixture was heated to ca. 115°C and this temperature was maintained for a further 5 h and the mixture turned black. Ethanol (2.5 ml) was added and the mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 10% K₂CO₃ and water. The aqueous phases were back extracted with ethyl acetate and the combined organic phases were dried (MgSO₄) filtered and concentrate under reduced pressure. The crude oil was purified using Kugelrohr distillation (90°-100°C/ 0.1 mbar) yielding a colorless oil: 10.7 g (80%); ¹H NMR (CDCl₃) δ 2.13 (s, 3H), 3.86 (s, 3H), 5.16 (s, 2H), 7.18-7.31 (m, 2H), 8.30 (d, 1H) MS: m/e = 181.2 (M), 138.0 (M-COCH₃)

4) (5-Methoxy-pyridin-2-yl)-methanol

Acetic acid 5-methoxy-pyridin-2-ylmethyl ester (10.5 g, 58 mmol) was dissolved in HCl (25%, 30 ml) and the resultant reaction mixture was stirred at ca. 105 °C for 80 min under an argon atmosphere. Solid NaHCO₃ was added in portions followed by aqueous

- K₂CO₃ solution to achieve an alkaline pH 10. This resultant mixture was extracted with ethyl acetate (4x) and the combined organic extracts were washed with water, brine, dried (MgSO₄) filtered and then concentrated under reduced pressure. The crude oil was purified over silica gel (ethyl acetate/n-heptane 1:1 to 2:1): yellow solid 4.8 g (56%);
- 5 ¹H NMR δ (CDCl₃) δ 3.8 (br, 1H), 3.86 (s, 3H), 7.21 (m, 2H), 8.24 (m, 1H); MS: m/e = 138.0 (M), 110.0 (M-CO).

Example D

5-Hydroxymethyl-pyridine-2-carboxylic acid cyclopropylamide

10 1) 5-Hydroxymethyl-pyridine-2-carboxylic acid

- A suspension of LiBH₄ (1.53 g, 70 mmol) in THF (30 ml) was slowly added to a solution of pyridine-2,5-dicarboxylic acid 5-methyl ester (2.5 g, 14 mmol) in dry THF (30 ml) at 0°C and under an argon atmosphere. The reaction mixture was stirred for a further 2 h at r.t., then chilled to 0°C and treated with 2 N HCl (40 ml). The reaction mixture was
- 15 filtered, concentrated under reduced pressure and crystallized from MeOH: 340 mg; ¹H NMR (CDCl₃) δ 4.73 (s, 1H), 4.91 (s, 2H) 8.36 & 8.58 (dd, 2H), 8.72 (s, 1H) MS: m/e = 152.0 (MH⁺)

2) 5-Hydroxymethyl-pyridine-2-carboxylic acid cyclopropylamide

- 20 5-Hydroxymethyl-pyridine-2-carboxylic acid (0.23 g, 1.5 mmol) was dissolved in DMF (3 ml) and activated with TPTU (0.45 g, 1.5 mmol), Hünig's base (0.51 ml, 3.0 mmol) and reacted with cyclopropyl amine (0.12 ml, 1.65 mmol) for 1 h at r.t during which a precipitate was formed. Solvent was removed and the residue dissolved in acetonitrile/water and purified by prep.RP(C₁₈)HPLC: 60 mg;
- 25 ¹H NMR (CDCl₃) δ 0.65-0.69 (m, 2H), 0.85-0.90 (m, 2H), 2.92-2.97 (m, 1H), 4.81 (d, 2H), 7.84-7.86 (m, 1H), 8.05 (br, 1H), 8.19-8.21 (m, 1H), 8.50 (s, 1H) MS: m/e = 193.2 (MH⁺), 215.3 (MNa⁺)

Example E

[3-Fluoro-4-(2-morpholin-4-yl-ethoxy)-phenyl]-methanol

30 1) 3-Fluoro-4-(2-morpholin-4-yl-ethoxy)-benzoic acid ethyl ester

- 3-Fluoro-4-hydroxybenzoic acid ethyl ester (0.20 g, 1.1 mmol) and N-(2-chloroethyl)morpholine (0.22 g, 1.2 mmol) were dissolved in dry DMF (10 ml). Potassium carbonate (1.88 g, 5 mmol) was added and the turbid reaction mixture was stirred overnight at 40°C under an argon atmosphere. The reaction mixture was
- 35 concentrated under reduced pressure and ethyl acetate was added to the residue followed by washing with NaHCO₃ (1/2 sat., 3x), water, brine, dried (MgSO₄), filtered. The crude

oil was purified over silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 39:1): colorless oil 0.16g (49%);

^1H NMR (CDCl_3) δ 1.38 (t, 3H), 2.59-2.61 (m, 4H), 2.85 (t, 2H), 3.71-3.74 (m, 4H), 4.23 (t, 2H), 4.33 (q, 2H), 6.96-7.0 (m, 1H), 7.73-7.81 (m, 2H); MS: $m/e = 298.3$ (MH^+)

5 2) [3-Fluoro-4-(2-morpholin-4-yl-ethoxy)-phenyl]-methanol

To lithium aluminium hydride (0.03 g, 0.90 mmol) suspended in dry THF (1 ml) and cooled to 0°C under an argon atmosphere was added a solution of 3-fluoro-4-(2-morpholin-4-yl-ethoxy)-benzoic acid ethyl ester (0.15 g, 0.5 mmol) in dry THF (1 ml). The cold bath was removed and the reaction mixture further stirred for 2 h at r.t. The
10 reaction mixture was cooled (0°C) and quenched with NaHCO_3 (1/2 sat., 2 ml) and further stirred for 0.5 h at r.t., filtered and concentrated under reduced pressure. The filtrate was dissolved in ethyl acetate and washed with water (2x), brine, dried (MgSO_4) filtered and concentrated under reduced pressure: 0.12 g (86%);

^1H NMR (CDCl_3) δ 1.75 (br, 1H), 2.60 (t, 4H), 2.83 (t, 2H), 3.73 (t, 4H), 4.17 (t, 2H),
15 4.62 (s, 2H), 6.93-7.13 (m, 3H); MS: $m/e = 256.1$ (MH^+)

Example F

4-(2-Hydroxymethyl-phenyl)-butyric acid methyl ester

To an ice cooled solution of methyl 3-butenate (2.0 g, 20 mmol) in THF (20 ml) 9-borabicyclo(3,3,1)nonane (49 ml, 0.5M in tetrahydrofurane) was added within 1 hour.
20 After additional stirring for 4.5 hours potassium carbonate (7.5 g, 54 mmol), 2-bromobenzyl alcohol (3.4 g, 18.2 mmol), dimethylformamide (60 ml) and palladium (dppf)-dichloride (0.665 g, 0.91 mmol) were added and the mixture was stirred at 60°C overnight. After cooling the mixture was filtered over Celite and evaporated. The residue
25 was purified by column chromatography (eluent hexane/ethyl acetate: 4:1 gradually to 1:1) to yield 2.46 g (65%) of product.

^1H NMR (CDCl_3) δ 1.95 (m, 2H), 2.40 (t, 2H), 2.73 (dd, 2H), 3.66 (s, 3H), 4.72 (d, 2H), 7.20-7.25 (m, 3H), 7.35 (dd, 1H).

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Example G

4-(3-Hydroxymethyl-phenyl)-butyric acid methyl ester

The title compound was obtained in comparable yield analogous to the procedure described for Example E, using 3-bromobenzyl alcohol instead of using 2-bromobenzyl alcohol.

^1H NMR (CDCl_3) δ 1.96 (dt, 2H), 2.33 (t, 2H), 2.66 (t, 2H), 3.66 (s, 3H), 4.67 (d, 2H), 7.10-7.30 (m, 4H).

Example 1

5 rac-5-Chloro-thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

a) rac-3-(3-Fluoro-4-methoxy-benzylamino)-azepan-2-one

Rac-amino-azepan-2-one (1.66 g, 128.2 mmol) and 3-fluoro-p-anisaldehyde (2.00 g) were dissolved in dry THF (26 ml). After stirring for 90 min at r.t., acetic acid (1.11 ml, 19.5 mmol) and sodium triacetoxyborohydride (4.58 g, 19.5 mmol) and a further 20 ml dry THF were added and the reaction was stirred overnight at r.t. The reaction mixture was diluted with 2 M K_2CO_3 , and extracted with ethyl acetate (3x). The combined organic extracts were washed with water, brine, dried ($\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$) filtered and concentrated under reduced pressure. The resultant solid was redissolved in ethyl acetate and extracted with 5% KHSO_4 / 10% K_2CO_3 (3x). The pH of the combined aqueous fraction were adjusted to ca. 8.5-9 using solid K_2CO_3 and the aqueous phase was extracted with ethyl acetate (3x). The combined organic fractions were washed as before, dried, filtered and concentrated under reduced pressure: white solid 2.12 g (58%);

^1H NMR (CDCl_3) δ 1.40-1.65 (m, 3H), 1.75-1.83 (m, 1H), 1.90-2.05 (m, 2H), 2.35 (br, 1H), 3.19-3.22 (m, 2H), 3.26-3.29 (m, 1H), 3.61 & 3.80 (dd, 1H), 3.87 (s, 3H), 5.95 (br, 1H), 6.87-6.92 (m, 1H), 7.03-7.05 (m, 1H), 7.10-7.13 (m, 1H) MS: $m/e = 267.5$ (MH^+)

b) rac-5-Chloro-thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

25 rac-3-(3-Fluoro-4-methoxy-benzylamino)-azepan-2-one (213 mg, 0.80 mmol) was dissolved in CH_2Cl_2 (7.7 ml) and treated with DMAP (30 mg, 0.24 mmol), Hünig's base (0.30 ml, 1.76 mmol) and 1/8 of the cooled (0°C) reaction mixture was reacted with 5-chloro-thiophene-2-sulfonyl chloride (48 mg, 0.22 mmol) and shaken overnight in a parallel reaction block. Solvent was removed under reduced pressure and the residue dissolved in aqueous acetonitrile solution and purified using high throughput preparative RP(C_{18}) chromatography: lyophilisate 13 mg; MS: $m/e = 447.2$ (MH^+), 464.2 (MNH_4^+).

Example 2

35 4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide

a) 3R-Amino-azepan-2-one

D-Lysine hydrochloride (48 g, 0.26 mol) and hexamethyldisilazane (424.4 g, 2.6 mol) were suspended in toluene (1.1 litre) and refluxed for 1 week under an argon atmosphere, using a water-trap condenser. The reaction mixture was cooled to r.t. and slowly added to ice-cold MeOH (2.24 litre). The resultant clear solution was stirred for 30 min and concentrated under reduced pressure. The white, waxy solid was stirred in ethyl acetate, filtered and the filtrate concentrated under reduced pressure: white solid 5.4 g, (15%);

^1H NMR (CDCl_3) δ 1.35-2.05 (m, 8H), 3.2-3.26 (m, 2H), 3.53 (dd, 1H), 6.10 (br, 1H)
MS: $m/e = 129.2$ (MH^+)

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b) 4-Chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

3R-Amino-azepan-2-one (3.02 g, 23.6 mmol) was dissolved in CH_2Cl_2 (50 ml), treated with Hünig's base (6.16 ml, 35.4 mmol) and cooled (0°C) under an argon atmosphere. A solution of 4-chlorobenzenesulfonyl chloride (5.5 g, 26 mmol) in CH_2Cl_2 (15 ml) was added dropwise. The cold-bath was removed and the reaction mixture further stirred at r.t. for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with NaHCO_3 (1/2 sat., 3x), 5% KHSO_4 / 10% K_2CO_3 (3x), brine, dried (MgSO_4) filtered and concentrated under reduced pressure. The solid was recrystallized from ethyl acetate/n-heptane: 6.1 g (84%); ^1H NMR (CDCl_3) δ 1.33-1.40 (m, 1H), 1.57-1.69 (m, 2H), 1.78-1.83 (m, 1H), 1.84-2.15 (m, 2H), 3.04-3.21 (m, 2H), 3.81-3.85 (m, 1H), 6.02 (br, 1H) 6.21 (d, 1H), 7.45-7.48 (m, 2H), 7.78-7.80 (m, 2H) MS: $m/e = 301.3$ (MH^+)

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c) 4-[[4-Chloro-benzenesulfonyl]-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide

4-Chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide (0.18 g, 0.60 mmol), 4-bromo-methyl-benzamide (0.19 g, 0.90 mmol), K_2CO_3 (0.83 g, 6 mmol), KI (0.02 g, 0.12 mmol) were added to dry DMF (15 ml) and the resultant reaction mixture was shaken overnight at 60°C under an argon atmosphere. The solvent was removed under reduced pressure and the residue dissolved in acetonitrile and purified using preparative RP(C_{18}) chromatography: lyophilisate 52 mg; MS: $m/e = 436.4$ (MH^+)

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Example 3

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

4-Chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide (0.04 g, 0.12 mmol), (5-Methoxy-pyridin-2-yl)-methanol (0.04 g, 0.30 mmol), triphenyl phosphine (0.08 g, 0.30

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mmol) were dissolved in dry CH_2Cl_2 (6 ml) under an argon atmosphere followed by the dropwise addition of diisopropyl azodicarboxylate (60 mg, 0.30 ml) in dry CH_2Cl_2 (2 ml). The reaction mixture was further stirred overnight at r.t. and then concentrated under reduced pressure. The crude yellow oil was purified over silica gel (ethyl acetate/n-heptane 3:2): colorless gum 0.23 g (43%);
MS: $m/e = 424.0$ (MH^+), 446.0 (MNa^+).

Example 4

4-[[(4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide

a) 5-Isopropyl-azepan-2-one

To a solution of hydroxylamine-O-sulfonic acid (60.5 g, 535 mmol) in formic acid (320 ml) was added dropwise a solution of 4-isopropyl cyclohexanone (50.0 g, 357 mmol) in formic acid (110 ml) at r.t. under an argon atmosphere. The reaction mixture was refluxed for 3 h, cooled to r.t. and slowly treated with ice-water (550 ml). 10 N NaOH (1.1 litre) was added to adjust the pH to 8 and the resultant mixture was extracted with CHCl_3 (4x). The combined organic extracts were washed with water, brine, dried (MgSO_4), filtered and concentrated under reduced pressure. The light-brown solid was crystallized from n-heptane: 42.4 g (75%);
 ^1H NMR (CDCl_3) δ 0.87 (d, 6H), 1.35-1.39 (m, 3H), 1.60 1.68 (m, 1H), 1.76-1.80 (m, 2H), 2.43-2.49 (m, 2H), 3.20-3.24 (m, 2H), 6.25 (br, 1H)
MS: $m/e = 155.1$ (M)

b) 3,3-Dichloro-5-isopropyl-azepan-2-one

5-Isopropyl-azepan-2-one (39.5 g, 254.4 mmol) was dissolved in xylenes (1.1 litre) and phosphorus pentachloride (159.0 g, 763.3 mmol) was added and the reaction mixture slowly warmed to 90°C . $\text{HCl}_{(g)}$ accompanied the slow dissolution of phosphorus pentachloride and after 30 min a clear yellow solution resulted. After a further 90 min at 90°C the reaction mixture was allowed to cool (ice-water bath) and water (500 ml) was added dropwise. The emulsion was stirred for a further 90 min at r.t. and the aqueous layer was washed with CHCl_3 (3x). The xylene fraction was concentrated under reduced pressure and the residue was dissolved in CHCl_3 . The combined organic fractions were washed with water (3x), brine and dried (MgSO_4) filtered and evaporated under reduced pressure. The crude brown oil was purified over silica gel (ethyl acetate/n-heptane 1:2): white solid 39.8 g (58%);
 ^1H NMR (CDCl_3) δ 0.93 (d, 6H), 1.32-1.36 (m, 1H), 1.68-1.72 (m, 1H), 2.00-2.01 (m,

1H), 2.27-2.34 (m, 1H), 2.66-2.70 (m, 1H), 3.23-3.27 (m, 1H), 3.51-3.55 (m, 1H), 6.30 (br, 1H) MS: m/e = 224.1 (MH⁺)

c) 3-Chloro-5-isopropyl-azepan-2-one

- 5 3,3-Dichloro-5-isopropyl-azepan-2-one (5.00 g, 22.3 mmol) was dissolved in acetic acid (125 ml) and sodium acetate (anhydrous, 2.38 g, 29.0 mmol), 10% Pd-c catalyst (0.22 g) were added. The degassed mixture was hydrogenated at r.t. and atmospheric pressure for 90 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified over silica gel (ethyl acetate/n-heptane 1:1): 3.49 g (74%) ¹H NMR
- 10 (CDCl₃) δ 0.88-0.90 (m, 6H), 1.26-1.29 (m, 1H), 1.63-1.67 (m, 2H), 1.76-1.94 (m, 2H), 2.16-2.21 (m, 1H), 3.19-3.23 (m, 1H), 3.30-3.36 (m, 1H), 4.64 & 4.67 (dd, 1H), 6.45 (br, 1H) MS: m/e = 190.3 (MH⁺), 207.2 (MNH₄⁺)

d) 3-Azido-5-isopropyl-azepan-2-one

- 15 3-Chloro-5-isopropyl-azepan-2-one (3.4 g, 18 mmol) and sodium azide (3.51 g, 53.9 mmol) were reacted in dry dimethyl sulfoxide (50 ml) overnight at 80°C under an argon atmosphere. The reaction mixture was allowed to cool to r.t. diluted with water (200 ml) and extracted with CH₂Cl₂ (4x). The combined organic fractions were washed with water (3x), brine and dried (MgSO₄) filtered and evaporated under reduced pressure. The crude
- 20 yellow oil was purified over silica gel (ethyl acetate/n-heptane 1:2): yellow oil 2.6 g (70%); MS: m/e = 197.4 (MH⁺)

e) 4-Chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide

- 3-Azido-5-isopropyl-azepan-2-one (70 mg, 0.36 mmol) was dissolved in ethanol/water
- 25 (2:1 v/v) and hydrogenated over 10% Pd-c (5 mg) for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was taken up in dry CH₂Cl₂ (5 ml) and Hünig's base (0.09 ml, 0.54 mmol) was added and this mixture was cooled (ice-bath) followed by the dropwise addition of 4-chlorobenzylsulfonyl chloride (90.3 mg, 0.43 mmol) in CH₂Cl₂ (0.5 ml). The reaction mixture was stirred at r.t. for 1 h
- 30 and then diluted with CH₂Cl₂ and washed with NaHCO₃ (1/2 sat., 3x), 5% KHSO₄/ 10% K₂SO₄ (3x), water, brine, dried (MgSO₄) and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified over silica gel (ethyl acetate/n-heptane 1:2 to 1:1): white solid 0.08 g (75%); MS: m/e = 343.0 (MH⁺)

- 35 f) 4-[[[4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide

4-Chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide (0.06 g, 0.17 mmol), 4-bromo-methyl-benzamide (0.06 g, 0.25 mmol), K_2CO_3 (0.24 g, 1.7 mmol), KI (0.01 g, 0.06 mmol) were added to dry DMF (5 ml) and the resultant reaction mixture was shaken overnight 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, concentrated under reduced pressure and purified using preparative RP(C_{18}) chromatography: lyophilisate 23 mg; MS: m/e = 478.3 (MH^+), 495.4 (MNH_4^+)

Example 5

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-pyridin-3-ylmethyl-benzenesulfonamide
The title compound, MS: m/e = 393.9 (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3 using 3-(hydroxymethyl)pyridine as the alcohol.

Example 6

rac-4-Chloro-N-(4-fluoro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
The title compound, MS: m/e = 411.0 (MH^+), 433.1 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-fluorobenzylalcohol as the alcohol.

Example 7

rac-4-Chloro-N-(4-chloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
The title compound, MS: m/e = 427.0 (MH^+), 448.8 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-chlorobenzylalcohol as the alcohol.

Example 8

rac-4-Chloro-N-(3-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 441.0 (MH^+), 463.0 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (3-Fluoro-4-methoxy-phenyl)-methanol as the alcohol.

Example 9

rac-4-Chloro-N-(3,4-difluoro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 429.0 (MH^+), 450.9 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 3,4-difluorobenzyl alcohol as the alcohol.

Example 10

rac-4-Chloro-N-(4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 422.9$ (MH^+), 445.0 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-methoxybenzyl alcohol as the alcohol.

Example 11

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

The title compound, MS: $m/e = 459.3$ (MH^+), 476.3 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (2,6-difluoro-4-methoxy-phenyl)-methanol as the alcohol.

Example 12

rac-4-Chloro-N-(3,4-dichloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 460.8$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 3,4-dichlorobenzyl alcohol as the alcohol.

Example 13

rac-Dimethyl-carbamic acid 6-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-pyridin-3-yl ester

The title compound, MS: $m/e = 480.9$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using dimethyl-carbamic acid 6-hydroxymethyl-pyridin-3-yl ester as the alcohol.

Example 14

rac-4-Chloro-N-(6-chloro-pyridin-3-ylmethyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 428.0$ (MH^+), 449.8 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (6-chloro-pyridin-3-yl)-methanol as the alcohol.

Example 15

rac-4-Chloro-N-(6-fluoro-pyridin-3-ylmethyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 412.0$ (MH^+), 434 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (6-fluoro-pyridin-3-yl)-methanol as the alcohol.

Example 16

- 5 **rac-4-Chloro-N-(5-chloro-pyridin-2-ylmethyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide**

The title compound, MS: $m/e = 428.0$ (MH^+), 449.9 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (5-chloro-pyridin-2-yl)-methanol as the alcohol.

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Example 17

- rac-Acetic acid 4-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-phenyl ester**

The title compound, MS: $m/e = 450.8$ (MH^+), 473.0 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using acetic acid
15 4-hydroxymethyl-phenyl ester as the alcohol.

Example 18

- rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-(4-prop-2-ynyloxy-benzyl)-benzenesulfonamide**

The title compound, MS: $m/e = 447.0$ (MH^+), 469.0 (MNa^+), was obtained in
20 comparable yield analogous to the procedure described for Example 3, using (4-prop-2-ynyloxy-phenyl)-methanol as the alcohol.

Example 19

- rac-4-Chloro-N-(3-fluoro-4-methyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide**

25 The title compound, MS: $m/e = 424.9$ (MH^+), 447.0 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (3-fluoro-4-methyl-phenyl)-methanol as the alcohol.

Example 20

- 30 **rac-4-Chloro-N-(4-chloro-3-fluoro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide**

The title compound, MS: $m/e = 445.0$ (MH^+), 466.9 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-chloro-3-fluorobenzylalcohol as the alcohol.

Example 21

rac-4-Chloro-N-(4-difluoromethoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 459.0 (MH⁺), 481.1 (MNa⁺), was obtained in comparable
5 yield analogous to the procedure described for Example 2c, using 4-(difluoromethoxy)benzyl bromide as the benzylating reagent.

Example 22

rac-4-Chloro-N-[3-fluoro-4-(2-morpholin-4-yl-ethoxy)-benzyl]-N-(2-oxo-azepan-3-yl)-
10 benzenesulfonamide

The title compound, MS: m/e = 540.3 (MH⁺), was obtained in comparable yield analogous to the procedure described for Example 3, using [3-fluoro-4-(2-morpholin-4-yl-ethoxy)-phenyl]-methanol as the alcohol.

Example 23

rac-4-[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl-benzamide

The title compound, MS: m/e = 436.3 (MH⁺), 458.0 (MNa⁺), was obtained analogous to the procedure described for Example 2c, using 4-bromomethyl-benzamide as the
15 benzylating reagent.

Example 24

rac-4-Chloro-N-(4-chloro-3-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 457.1 (MH⁺), 478.9 (MNa⁺), was obtained analogous to the procedure described for Example 2c, using 4-bromomethyl-1-chloro-2-methoxy-
20 benzene as the benzylating reagent.

Example 25

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

The title compound, MS: m/e = 441.3 (MH⁺), 463.0 (MNa⁺), was obtained in
30 comparable yield analogous to the procedure described for Example 2c, using 3-fluoro-4-methoxybenzyl bromide as the benzylating reagent.

Example 26

4-Chloro-N-(3,4-dichloro-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 461.0$ (MH^+), 484.9 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (3,4-dichloro-phenyl)-methanol as the alcohol.

Example 27

- 5 Acetic acid 4-[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl ester

The title compound, MS: $m/e = 451.0$ (MH^+), 473.1 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using acetic acid 4-hydroxymethyl-phenyl ester as the alcohol.

10

Example 28

rac-4-Bromo-N-(3-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

- 15 The title compound, MS: $m/e = 486.8$ (MH^+), 503.7 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using 3-fluoro-4-methoxybenzyl bromide as the benzylating reagent and the analogous 4-bromophenyl sulfonamide.

Example 29

rac-4-Chloro-N-(3-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

- 20 The title compound, MS: $m/e = 423.2$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 3-methoxybenzyl alcohol as the alcohol.

Example 30

- 25 rac-4-Chloro-N-(5,6-dichloro-pyridin-3-ylmethyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 462.2$ (MH^+), 479.2 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 5,6-dichloro-pyridin-3-ylmethanol as the alcohol.

30

Example 31

rac-4-Chloro-N-(4-ethoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 437.3$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-ethoxybenzyl alcohol as the alcohol.

35

Example 32

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

The title compound, MS: m/e = 429.4 (MH⁺), 446.2 (MNH₄⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 2,5-difluorobenzyl bromide as the benzylating reagent.

Example 33

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-(2,4,5-trifluoro-benzyl)-benzenesulfonamide

The title compound, MS: m/e = 447.3 (MH⁺), 464.2 (MNH₄⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 2,4,5-trifluorobenzyl bromide as the benzylating reagent.

Example 34

4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluorobenzoic acid methyl ester

The title compound, MS: m/e = 469.2 (MH⁺), 486.4 (MNH₄⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 4-bromomethyl-3-fluorobenzoic acid methyl ester as the benzylating reagent.

20

Example 35

4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid ethyl ester

The title compound, MS: m/e = 465.3 (MH⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 4-bromomethyl-benzoic acid ethyl ester as the benzylating reagent.

Example 36

(3-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-acetic acid methyl ester

The title compound, MS: m/e = 465.0 (MH⁺), was obtained in comparable yield according to the procedure described for Example 2c, using (3-chloromethyl-phenyl)-acetic acid methyl ester as the benzylating reagent.

MS: m/e = 465.0 (MH⁺).

Example 37

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

- 4-[[[4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid ethyl ester (0.08 g, 0.17 mmol) was saponified with 1 N NaOH (0.25 ml) in ethanol (2 ml) for 48 h. The reaction mixture was diluted with acetic acid (0.7 ml) concentrated under reduced pressure and purified directly using preparative RP(C₁₈) chromatography: 5 lyophilisate 27 mg; MS: m/e = 435.0 (MH⁺).

Example 38

3-[[[4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid prop-2-ynyl ester

- 10 The title compound, MS: m/e = 474.9 (MH⁺), 492.0 (MNH₄⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 3-chloromethyl-benzoic acid prop-2-ynyl ester as the benzylating reagent.

Example 39

- 15 3-(4-[[[4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid methyl ester

The title compound, MS: m/e = 478.9 (MH⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 3-(4-chloromethyl-phenyl)-propionic acid methyl ester as the benzylating reagent.

20

Example 40

4-Chloro-N-(6-chloro-pyridin-3-ylmethyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

- The title compound, MS: m/e = 427.9 (MH⁺), was obtained in comparable yield 25 analogous to the procedure described for Example 3, using (6-chloro-pyridin-3-yl)-methanol as the alcohol.

Example 41

4-{1-[[[4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-ethyl]-benzoic acid methyl ester

- 30 The title compound, MS: m/e = 465.0 (MH⁺), was obtained in comparable yield analogous to the procedure described for Example 3, using methyl 4-(1-hydroxyethyl)benzoate as the alcohol.

Example 42

rac-4-Chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-(6-methoxy-pyridin-3-ylmethyl)- 35 benzenesulfonamide

The title compound, MS: $m/e = 466.3$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 6-methoxy-pyridin-3-yl-methanol and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

5

Example 43

rac-4-[[(4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide

The title compound, MS: $m/e = 518.3$ (MH^+), 535.4 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

10

Example 44

rac-4-Chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-(6-methyl-pyridin-3-ylmethyl)-benzenesulfonamide

15

The title compound, MS: $m/e = 450.1$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 5-chloromethyl-2-methyl-pyridine and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

20

Example 45

rac-4-Chloro-N-(4-difluoromethoxy-benzyl)-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 501.3$ (MH^+), 518.3 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-(difluoromethoxy)benzyl bromide and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

25

Example 46

rac-4-Chloro-N-(2-methyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

30

The title compound, MS: $m/e = 407.3$ (MH^+), 429.4 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-2-methyl-benzene as the benzylating reagent.

35

Example 47

rac-4-Chloro-N-(3-methyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 407.3$ (MH^+), 429.4 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-3-methyl-benzene as the benzylating reagent.

5

Example 48

rac-4-Chloro-N-(4-methyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 407.4$ (MH^+), 429.4 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-4-methyl-benzene as the benzylating reagent.

10

Example 49

rac-4-Chloro-N-(2-chloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 427.3$ (MH^+), 449.2 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-

15 bromomethyl-2-chloro-benzene as the benzylating reagent.

Example 50

rac-4-Chloro-N-(3-chloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

20

The title compound, MS: $m/e = 427.3$ (MH^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-3-chloro-benzene as the benzylating reagent.

Example 51

rac-4-Chloro-N-(2-fluoro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

25

The title compound, MS: $m/e = 411.3$ (MH^+), 433.3 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-2-fluoro-benzene as the benzylating reagent.

Example 52

rac-4-Chloro-N-(3-fluoro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

30

The title compound, MS: $m/e = 411.3$ (MH^+), 433.3 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-3-fluoro-benzene as the benzylating reagent.

Example 53

35

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-(3-trifluoromethoxy-benzyl)-benzenesulfonamide

The title compound, MS: $m/e = 477.2$ (MH^+), 499.2 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-3-trifluoromethoxy-benzene as the benzylating reagent.

5

Example 54

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-(4-trifluoromethoxy-benzyl)-benzenesulfonamide

The title compound, MS: $m/e = 477.2$ (MH^+), 499.2 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-4-trifluoromethoxy-benzene as the benzylating reagent.

10

Example 55

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

The title compound, MS: $m/e = 436.1$ (MH^+), 453.0 (MNH_4^+) was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-bromomethyl-3-fluoro-benzonitrile as the benzylating reagent.

15

Example 56

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

20

4-[[[4-Chloro-benzenesulfonyl]-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzimidic acid ethyl ester hydrochloride salt

Dry HCl gas was slowly bubbled through a solution of 4-chloro-N-(4-cyano-2-fluoro-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide (0.09 g, 0.20 mmol) in dry ethanol (3 ml) for 30 min at 0°C . The reaction mixture was allowed to stir for a further 20 h at r.t. and then concentrated under reduced pressure. Trituration of the residue in diethyl ether yielded the HCl salt: 0.09 g; MS: $m/e = 482.2$ (MH^+).

25

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

30

The HCl salt (0.08 g, 0.15 mmol) and formyl hydrazine (0.01 g, 0.17 mmol) were dissolved in pyridine (1.5 ml) and further stirred for 4 h to give the N-formyl amidrazone intermediate. Solvent was removed under reduced pressure and the residue was refluxed in xylenes (5 ml) for 30 min. Solvent was removed under reduced pressure and the residue was purified using preparative RP(C_{18}) chromatography: lyophilisate 0.016 mg; MS: $m/e = 477.9$ (MH^+), 495.1 (MNH_4^+).

35

Example 57

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester

- 5 The title compound, MS: $m/e = 451.3$ (MH^+), was obtained in comparable yield according to the procedure described for Example 2c, using 4-bromomethyl-benzoic acid methyl ester.

Example 58

10 rac-N-(4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-acetamide

The title compound, MS: $m/e = 450.4$ (MH^+), 472.2 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using N-(4-chloromethyl-phenyl)-acetamide.

Example 59

15 rac-4-Chloro-N-(4-methanesulfonyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 471.3$ (MH^+), 493.3 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-4-methanesulfonyl-benzene as the benzylating reagent.

20

Example 60

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N,N-diethylbenzamide

- 25 The title compound, MS: $m/e = 492.3$ (MH^+), 509.3 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using 4-bromomethyl-N,N-diethyl-benzamide as the benzylating reagent.

Example 61

rac-4-Chloro-N-(4-hydroxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

- 30 The title compound, MS: $m/e = 409.2$ (MH^+), 426.2 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using butyl-carbamic acid 4-chloromethyl-phenyl ester as the benzylating reagent.

Example 62

- 35 rac-(4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-carbamic acid ethyl ester

The title compound, MS: $m/e = 497.3$ (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using (4-chloromethyl-phenyl)-carbamic acid ethyl ester as the benzylating reagent.

5

Example 63

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[4-(piperidine-1-carbonyl)-benzyl]-benzenesulfonamide

The title compound, MS: $m/e = 504.4$ (MH^+), 526.23 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using (4-chloromethyl-phenyl)-piperidin-1-yl-methanone as the benzylating reagent.

10

Example 64

rac-4-[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid prop-2-ynyl ester

The title compound, MS: $m/e = 475.3$ (MH^+), 497.2 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 4-chloromethyl-benzoic acid prop-2-ynyl ester as the benzylating reagent.

15

Example 65

rac-4-Chloro-N-(4-formyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 421.3$ (MH^+), 443.2 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 4-bromomethyl-benzaldehyde as the benzylating reagent.

20

Example 66

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[4-(pyrrolidine-1-sulfonyl)-benzyl]-benzenesulfonamide

The title compound, MS: $m/e = 526.2$ (MH^+), 548.3 (MNa^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-(4-bromomethyl-benzenesulfonyl)-pyrrolidine as the benzylating reagent.

30

Example 67

rac-4-Chloro-N-(2-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 441.4$ (MH^+) 458.4 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (2-fluoro-4-methoxy-phenyl)-methanol as the alcohol.

5

Example 68

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

The title compound, MS: $m/e = 441.4$ (MH^+) 458.4 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (2-fluoro-4-methoxy-phenyl)-methanol as the alcohol and the corresponding chiral sulfonamide.

10

Example 69

4-Chloro-N-(4-hydroxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 409.2$ (MH^+), 426.3 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using butyl-carbamic acid 4-chloromethyl-phenyl ester. The title compound was unexpectedly, the main product.

15

Example 70

4-Chloro-N-[4-(4-hydroxy-benzyloxy)-benzyl]-N-((R)-2-oxo-azepan-3-yl)-

benzenesulfonamide

The title compound, MS: $m/e = 515.3$ (MH^+), 532.3 (MNH_4^+), was obtained as a side product when following the procedure described for Example 2c, and using butyl-carbamic acid 4-chloromethyl-phenyl ester as the benzylating reagent.

20

25

Example 71

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid
rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid
methyl ester (0.95 g, 2.10 mmol) in a mixture of MeOH/ CH_3CN (50 ml, 1:1 v/v) was
treated with 1 N NaOH (2.5 ml) for 24 h. Solvent was removed under reduced pressure
and the residue dissolved in ethyl acetate and washed with 5% $KHSO_4$ / 10% K_2SO_4 (2x).
The aqueous washes were extracted with ethyl acetate and the combined organic fractions
were washed with brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure
and lyophilized from water/ CH_3CN : lyophilisate, 0.87 g; MS: $m/e = 435.2$ (MH^+)

30

35

Example 72

rac-N-Benzyl-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 393.1$ (MH^+), 410.4 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using bromomethyl-benzene as the benzylating reagent.

5

Example 73

rac-4-Chloro-N-[4-(1-cyano-cyclopropyl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 458.4$ (MH^+), 475.4 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-(4-bromomethyl-phenyl)-cyclopropanecarbonitrile.

10

Example 74

rac-1-(4-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-cyclopropanecarboxylic acid methyl ester

15 The title compound, MS: $m/e = 491.4$ (MH^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-(4-bromomethyl-phenyl)-cyclopropanecarboxylic acid methyl ester.

Example 75

20 **rac-4-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-N-cyclopropyl-benzamide**

rac-4-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-benzoic acid (0.70 g, 1.6 mmol) was dissolved in DMF and activated with the coupling reagent TPTU (0.48 g, 1.6 mmol) and Hünig's base (0.55 ml, 3.2 mmol) for 2 min. 1/8 of this activated mixture was delivered to a reaction tube on a parallel synthesizer containing cyclopropylamine (0.013 g, 0.22 mmol) and a further amount of Hünig's base (0.04 ml, 0.22 mmol) in DMF (3 ml). The reaction mixture was shaken for 2 h, concentrated under reduced pressure and purified directly using preparative RP(C_{18}) chromatography: lyophilisate 40 mg; MS: $m/e = 476.1$ (MH^+), 493.1 (MNH_4^+).

30

Example 76

rac-4-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-N-methyl-benzamide

The title compound, MS: $m/e = 450.3$ (MH^+), 467.1 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 75, using methylamine in the coupling step.

35

Example 77

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-(2,2,2-trifluoro-ethyl)-benzamide

The title compound, MS: $m/e = 518.3$ (MH^+), 535.4 (MNH_4^+), was obtained in
5 comparable yield according to the procedure described for Example 75, using 2,2,2-trifluoro-ethylamine in the coupling step.

Example 78

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-
10 morpholin-4-yl-benzamide

The title compound, MS: $m/e = 521.4$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using morpholin-4-ylamine in the coupling step.

Example 79

15 rac-4-Chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 479.1$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using N,N-dimethyl-hydrazine in the coupling step.

20 Example 80

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-pyrrolidin-1-yl-benzamide

The title compound, MS: $m/e = 505.4$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using pyrrolidin-1-ylamine in the
25 coupling step.

Example 81

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-piperidin-1-yl-benzamide

The title compound, MS: $m/e = 519.5$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using piperidin-1-ylamine in the
30 coupling step.

Example 82

1-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-cyclopropanecarboxylic acid methyl ester

The title compound, MS: $m/e = 491.3$ (MH^+), 508.5 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-(4-bromomethyl-phenyl)-cyclopropanecarboxylic acid methyl ester.

5

Example 83

(4-{[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl}-phenyl)-acetic acid methyl ester

The title compound, MS: $m/e = 465.3$ (MH^+), 482.5 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using (4-bromomethyl-phenyl)-acetic acid methyl ester.

10

Example 84

4-Chloro-N-(4-nitro-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 438.3$ (MH^+), 455.5 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 2c, using 1-bromomethyl-4-nitro-benzene.

15

Example 85

rac-Thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

The title compound, MS: $m/e = 413.3$ (MH^+), 435.3 (MNH_4^+), was obtained in

20

comparable yield according to the procedure described for Example 1b, using thiophene-2-sulfonyl chloride.

Example 86

rac-5-Bromo-thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

25

The title compound, MS: $m/e = 491.2$ (MH^+), 508.4 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 1b, using 5-bromo-thiophene-2-sulfonyl chloride.

Example 87

rac-4,5-Dichloro-thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

30

The title compound, MS: $m/e = 481.2$ (MH^+), 503.2 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 1b, using 4,5-dichloro-thiophene-2-sulfonyl chloride.

Example 88

35

rac-5-Chloro-4-nitro-thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

The title compound, MS: $m/e = 492.2$ (MH^+), 509.4 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 1b, using 5-chloro-4-nitro-thiophene-2-sulfonyl chloride.

Example 89

- 5 **rac-3-Bromo-5-chloro-thiophene-2-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide**

The title compound, MS: $m/e = 525.1$ (MH^+), 542.1 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 1b, using 3-bromo-5-chloro-thiophene-2-sulfonyl chloride.

10

Example 90

rac-5-Methyl-2-trifluoromethyl-furan-3-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

- The title compound, MS: $m/e = 479.4$ (MH^+), 496.3 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 1b, using 5-methyl-2-trifluoromethyl-furan-3-sulfonyl chloride.

15

Example 91

rac-2,5-Dichloro-thiophene-3-sulfonic acid (3-fluoro-4-methoxy-benzyl)-(2-oxo-azepan-3-yl)-amide

20

The title compound, MS: $m/e = 481.3$ (MH^+), 498.1 (MNH_4^+), was obtained in comparable yield according to the procedure described for Example 1b, using 2,5-dichloro-thiophene-3-sulfonyl chloride.

Example 92

- 25 **N-(4-Amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide**
4-Chloro-N-(4-nitro-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide (0.10 g, 0.22 mmol) was dissolved in ethanol (15 ml) and treated with $SnCl_2$ (0.42 g, 2.2. mmol) overnight at $70^\circ C$. The reaction mixture was concentrated under reduced pressure and purified directly using preparative RP(C_{18}) chromatography: lyophilisate 27 mg; MS: $m/e = 408.2$ (MH^+), 425.3 (MNH_4^+).

30

Example 93

1-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-cyclopropanecarboxylic acid

- 1-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-cyclopropanecarboxylic acid methyl ester (0.03 g, 0.06 mmol) was dissolved in MeOH (1 ml) and treated with 1 N NaOH (0.07 ml) for 24 hr at $50^\circ C$. The reaction mixture was

35

concentrated under reduced pressure and purified directly using preparative RP(C₁₈) chromatography: lyophilisate 8 mg; MS: m/e = 475.0 (MH⁺).

Example 94

- 5 Cyclopropanecarboxylic acid (4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-amide
N-(4-Amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide (0.024 g, 0.06 mmol) was dissolved in CH₂Cl₂ (1 ml) and Hünig's base (0.01 ml, 0.07 mmol) and cyclopropanecarbonyl chloride (0.007 ml, 0.07 mmol) were added. After 30 min at r.t.
10 the solvent was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with 5% KHSO₄/ 10% K₂SO₄, brine, dried (Na₂SO₄), filtered and concentrated. The crude was purified using preparative RP(C₁₈) chromatography: lyophilisate 9 mg; MS: m/e = 493.4 (MNH₄⁺).

Example 95

- 15 rac-N-Benzo[1,3]dioxol-5-ylmethyl-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
The title compound, MS: m/e = 436.9(MH⁺), 459.0 (MNa⁺), was obtained in comparable yield analogous to the procedure described for Example 3, using piperonyl alcohol and
20 rac-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide.

Example 96

- rac-4-Chloro-N-(6-methoxy-pyridin-3-ylmethyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
25 The title compound, MS: m/e = 423.9 (MH⁺), 445.9 (MNa⁺), was obtained in comparable yield analogous to the procedure described for Example 3, using (6-methoxy-pyridin-3-yl)-methanol and rac-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide.

Example 97

- 30 rac-4-Chloro-N-{3-methoxy-4-[2-(4-methyl-thiazol-5-yl)-ethoxy]-benzyl}-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
The title compound, MS: m/e = 565.3 (MH⁺), was obtained in comparable yield analogous to the procedure described for Example 3, using [3-methoxy-4-(2-(4-methyl-thiazol-5-yl)-ethoxy)-phenyl]-methanol (synthesized according to the procedure
35 described for intermediate [3-Fluoro-4-(2-morpholin-4-yl-ethoxy)-phenyl]-methanol

using 5-(2-chloroethyl)-4-methylthiazole) and rac-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide.

Example 98

rac-4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-
5 [1,2,4]triazol-4-yl]-benzamide

The title compound, MS: m/e = 503.3 (MH⁺), 525.3 (MNa⁺), was obtained in comparable yield according to the procedure described for Example 75, using [1,2,4]triazol-4-ylamine in the coupling step.

10

Example 99

rac-4-(2-{1-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-ethyl}-phenyl)-butyric acid

a) rac-4-(2-{1-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-ethyl}-phenyl)-butyric acid methyl ester

15 rac-4-(2-{1-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-ethyl}-phenyl)-butyric acid methyl ester, MS: m/e = 524.4 (MNH₄⁺), was obtained in comparable yield analogous to the procedure described for Example 3, using rac-2-(1-hydroxyethyl)-benzenebutanoic acid methyl ester as the alcohol.

20 b) rac-4-(2-{1-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-ethyl}-phenyl)-butyric acid, MS: m/e = 491.1 (M-H⁺), was obtained by the following: Rac-4-(2-{1-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-ethyl}-phenyl)-butyric acid methyl ester (40 mg) was dissolved in methanol (1 ml) and treated with a solution of aqueous lithiumhydroxide (10 mg in 0.5 ml) for 1 hour. After evaporation of the
25 methanol the pH is adjusted to 6 with 1N hydrochloric acid and the mixture was extracted with ethyl acetate to yield 31 mg of a solid. After chromatography (hexane/ethylacetate = 1:1) 25 mg of the title compound were obtained.

Example 100

30 rac-N-(3-Fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-4-trifluoromethoxy-benzenesulfonamide

The title compound, MS: m/e = 491.3 (MH⁺), 508.5 (MNH₄⁺), was obtained in comparable yield analogous to the procedure described for Example 1b, using 4-trifluoromethoxybenzenesulfonyl chlorid instead of 5-chloro-thiophene-2-sulfonyl
35 chloride.

Example 101

rac-N-(3-Fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-4-cyano-benzenesulfonamide

The title compound, MS: $m/e = 432.4$ (MH^+), 449.3 (MNH_4^+), was obtained in
5 comparable yield analogous to the procedure described for Example 1b, using 4-cyanobenzenesulfonyl chlorid instead of 5-chloro-thiophene-2-sulfonyl chloride.

Example 102

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

The title compound, MS: $m/e = 504.4$ (MH^+), 521.0 (MNH_4^+), was obtained in
comparable yield analogous to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e using 3-
15 azidohexahydro-6,6-dimethyl-2H-azepin-2-one.

Example 103

rac-4-Chloro-N-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-allyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

20 The title compound, MS: $m/e = 532.1$ ($M-H^+$), was obtained in comparable yield analogous to the procedure described for Example 99, using 1-(alpha-hydroxy-o-toluoyl)-proline-tert-butyl ester as the alcohol in step a) followed by the ester cleavage.

Example 104

25 4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-5-phenyl-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide

The title compound, MS: $m/e = 552.2$ (MH^+), 569.4 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-chloro-N-(5-phenyl-2-oxo-azepan-3-yl)-
30 benzenesulfonamide which was prepared analogous to Example 4e starting with 4-phenylcyclohexanone in Example 4a.

Example 105

5-[[[(4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-pyridine-2-carboxylic acid cyclopropylamide

35 The title compound, MS: $m/e = 519.0$ (MH^+), 541.1 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 5-

hydroxymethyl-pyridine-2-carboxylic acid cyclopropylamide and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide in the Mitsunobu protocol.

Example 106

5 N-Cyclopropyl-4-[[[(R)-2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-benzamide

The title compound, MS: m/e = 510.1 (MH⁺), 531.9 (MNa⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-trifluoromethyl-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

Example 107

N-Cyclopropyl-4-[[[(R)-2-oxo-azepan-3-yl)-(4-bromo-benzenesulfonyl)-amino]-methyl]-benzamide

The title compound, MS: m/e = 520.0 (MH⁺), 541.9 (MNa⁺), was obtained in comparable yield according to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-bromo-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

Example 108

4-[[[(5-*tert*-Butyl-2-oxo-azepan-3-yl)-(4-chloro-benzenesulfonyl)-amino]-methyl]-N-cyclopropyl-benzamide

The title compound, MS: m/e = 532.0 (MH⁺), 554.0 (MNa⁺), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-chloro-N-(5-*tert*-butyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e starting with 4-*tert*-butyl cyclohexanone in Example 4a.

Example 109

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

The title compound, MS: m/e = 504.0 (MH⁺), 526.0 (MNa⁺), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-chloromethyl-N-cyclopropyl-benzamide and 4-chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e starting with 4,4-dimethyl cyclohexanone in Example 4a.

Example 110

35 4-Chloro-N-((R)-2-oxo-azepan-3-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide

The title compound, MS: $m/e = 394.2(MH^+)$, was obtained in comparable yield analogous to the procedure described for Example 3, using pyridin-4-yl-methanol.

Example 111

5 4-Chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-*N*-(4-methoxy-benzyl)-benzenesulfonamide

The title compound, MS: $m/e = 465(MH^+)$, 488.1 (MNa^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-methoxybenzyl chloride and 4-chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from

10 Example 4e.

Example 112

4-Chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-*N*-(3-methoxy-benzyl)-benzenesulfonamide

15 The title compound, MS: $m/e = 465(MH^+)$, was obtained in comparable yield analogous to the procedure described for Example 2c, using 3-methoxybenzyl chloride and 4-chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

Example 113

20 4-[[[4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester

The title compound, MS: $m/e = 493(MH^+)$, was obtained in comparable yield analogous to the procedure described for Example 2c, using Methyl 4-(bromomethyl)-benzoate and 4-chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

25

Example 114

4-Chloro-*N*-(3-fluoro-4-methoxy-benzyl)-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide

30 The title compound, MS: $m/e = 483.0(MH^+)$, 505.1(MNa^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 3-fluoro-4-methoxybenzyl bromide and 4-chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

Example 115

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

35 The title compound, MS: $m/e = 543.9(MH^+)$, was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-chloromethyl-*N*-

cyclopropyl-benzamide and 4-chloro-N-(5-trifluoromethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e starting with 4-trifluoromethyl cyclohexanone in Example 4a.

5

Example 116

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

The title compound, MS: $m/e = 483.0$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (2-fluoro-4-methoxy-phenyl)-methanol and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

10

Example 117

4-(2-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-butyric acid methyl ester

15

The title compound, MS: $m/e = 493.4$ (MH^+), 510.5 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-(2-hydroxymethyl-phenyl)-butyric acid methyl ester as the alcohol in the Mitsunobu protocol.

20

Example 118

4-(3-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-butyric acid methyl ester

25

The title compound, MS: $m/e = 493.4$ (MH^+), 510.5 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-(3-hydroxymethyl-phenyl)-butyric acid methyl ester as the alcohol in the Mitsunobu protocol.

Example 119

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

30

The title compound, MS: $m/e = 477.1$ ($M-H^+$) was obtained in comparable yield analogous to the procedure described for Example 99b from 4-(2-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-butyric acid methyl ester.

Example 120

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

35

The title compound, MS: $m/e = 477.1$ ($M-H^+$), 537.1 ($M+CH_3COO^-$) was obtained in comparable yield analogous to the procedure described for Example 99b from 4-(3-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-butyric acid methyl ester.

5

Example 121

rac-3-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid methyl ester

The title compound, MS: $m/e = 450.4$ (MH^+), was obtained in comparable yield according to the procedure described for Example 2c, using methyl 3-

10 (bromomethyl)benzoate as the benzylating reagent.

Example 122

rac-1-(3-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-benzoyl)-piperidine-4-carboxylic acid ethyl ester

15 Rac-3-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 576.2$ (MH^+), 593.4 ($M+NH_4^+$), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid as the acid
20 and piperidine-4-carboxylic acid ethyl ester as the amine in the coupling step.

Example 123

rac-[1-(3-[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl)-benzoyl)-piperidin-4-yl]-acetic acid ethyl ester

25 Rac-3-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 590.5$ (MH^+), 607.3 ($M+NH_4^+$), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid as the acid
30 and piperidin-4-yl-acetic acid ethyl ester as the amine in the coupling step.

Example 124

(3S)-2-(3-[(4-Chloro-benzenesulfonyl)-((3RS)-2-oxo-azepan-3-yl)-amino]-methyl)-benzoylamino)-3-methyl-butyrlic acid tert-butyl ester

35 Rac-3-[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then

the title compound, MS: $m/e = 609.4$ ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and L-valin-tert.-butylester hydrochloride as the amine in the coupling step.

5

Example 125

rac-(3-[[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoylamino)-acetic acid tert-butyl ester

Rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 567.4$ ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and glycine tert.-butylester hydrochloride as the amine in the coupling step.

15

Example 126

rac-3-(3-[[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoylamino)-propionic acid tert-butyl ester

Rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 581.3$ ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and beta-alanine tert.-butylester hydrochloride as the amine in the coupling step.

25

Example 127

Rac-(3-[[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-phenoxy)-acetic acid

The title compound, MS: $m/e = 467.4$ (MH^+), 484.5 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 2c, using 3-bromomethyl phenoxyacetic acid ethyl ester as the benzylating reagent followed by saponification of the ester according to the procedure described in example 99b.

35

Example 128

Rac-4-Chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-N-(4-trifluoromethyl-benzyl)-benzenesulfonamide

The title compound, MS: $m/e = 489.1$ (MH^+), 506.1 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 2c, using 4-(trifluoromethyl)benzyl bromide as the benzylating reagent and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to
5 Example 4e using 3-azidohexahydro-6,6-dimethyl-2H-azepin-2-one.

Example 129

Rac-4-Chloro-N-(4-cyano-benzyl)-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide

10 The title compound, MS: $m/e = 446.0$ (MH^+), 463.0 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 2c, using 4-(bromomethyl)benzonitrile as the benzylating reagent and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e using 3-azidohexahydro-6,6-dimethyl-2H-azepin-2-one.

15

Example 130

Rac-4-Chloro-N-(6-chloro-pyridin-3-ylmethyl)-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 456.2$ (MH^+) was obtained in comparable yield
20 according to the procedure described for Example 2c, using 2-chloro-5-chloromethylpyridine as the alkylating reagent and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e using 3-azidohexahydro-6,6-dimethyl-2H-azepin-2-one.

25

Example 131

rac-3-[[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopentyl-benzamide

Rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then
30 the title compound, MS: $m/e = 504.2$ (MH^+), 521.3 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and cyclopentylamine as the amine in the coupling step.

35

Example 132

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[3-(piperidine-1-carbonyl)-benzyl]-benzenesulfonamide

Rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 504.2$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and piperidine as the amine in the coupling step.

10

Example 133

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[3-(4,4-difluoro-piperidine-1-carbonyl)-benzyl]-benzenesulfonamide

Rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 540.3$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 4,4-difluoropiperidine as the amine in the coupling step.

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Example 134

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[3-(2,6-dimethyl-piperidine-1-carbonyl)-benzyl]-benzenesulfonamide

Rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 532.3$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 2,6-dimethylpiperidine as the amine in the coupling step.

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Example 135

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[3-(4-fluoro-piperidine-1-carbonyl)-benzyl]-benzenesulfonamide

Rac-3-[[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then

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the title compound, MS: $m/e = 522.3$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 4-fluoropiperidine as the amine in the coupling step.

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Example 136

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[3-(3,3-difluoro-piperidine-1-carbonyl)-benzyl]-benzenesulfonamide

Rac-3-[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 540.3$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 3,3-difluoropiperidine as the amine in the coupling step.

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Example 137

rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-[3-(3,3-difluoro-pyrrolidine-1-carbonyl)-benzyl]-benzenesulfonamide

Rac-3-[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester was converted into the corresponding acid according to example 99b. Then the title compound, MS: $m/e = 526.1$ (MH^+), was obtained in comparable yield according to the procedure described for Example 75, using rac-3-[[4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 3,3-difluoropyrrolidine as the amine in the coupling step.

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Example 138

Rac-4-[[4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester

The title compound, MS: $m/e = 479.1$ (MH^+), 496.1 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 2c, using methyl 4-(chloromethyl)benzoate as the benzylating reagent and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e using 3-azidohexahydro-6,6-dimethyl-2H-azepin-2-one.

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Example 139

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

- The title compound, MS: $m/e = 463.4$ ($M-H^+$) was obtained in comparable yield analogous to the procedure described for Example 99b from 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester.

Example 140

- rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-fluoro-ethyl)-benzamide

- The title compound, MS: $m/e = 510.4$ (MH^+), 527.2 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 2-fluoroethylamine as the amine in the coupling step.

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Example 141

rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2,2,2-trifluoro-ethyl)-benzamide

- The title compound, MS: $m/e = 546.3$ (MH^+), 563.3 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 2,2,2-trifluoroethylamine as the amine in the coupling step.

Example 142

- rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-((1R,2S)-2-fluoro-cyclopropyl)-benzamide

- The title compound, MS: $m/e = 522.3$ (MH^+), 539.4 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 2-fluorocyclopropylamine as the amine in the coupling step.

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Example 143

rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-hydroxy-ethyl)-benzamide

- The title compound, MS: $m/e = 508.3$ (MH^+) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-

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benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl}-benzoic acid as the acid and 2-aminoethanol as the amine in the coupling step.

Example 144

5 rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopentyl-benzamide

The title compound, MS: $m/e = 532.2$ (MH^+), 549.4 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic
10 acid as the acid and cyclopentylamine as the amine in the coupling step.

Example 145

rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-methyl-benzamide

15 The title compound, MS: $m/e = 478.2$ (MH^+), 495.3 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and methylamine hydrochloride as the amine in the coupling step.

Example 146

20 rac-4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide

The title compound, MS: $m/e = 464.2$ (MH^+), 481.2 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic
25 acid as the acid and ammonia in methanol (7M solution) as the amine in the coupling step.

Example 147

rac-N-Benzyl-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide

30 The title compound, MS: $m/e = 554.3$ (MH^+), 571.3 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and benzylamine as the amine in the coupling step.

Example 148

rac-(4-[[4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoylamino)-acetic acid methyl ester

- The title compound, MS: $m/e = 536.3$ (MH^+), 553.3 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and glycine methylester hydrochloride as the amine in the coupling step.

Example 149

- 10 rac-4-[[4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-morpholin-4-yl-ethyl)-benzamide

- The title compound, MS: $m/e = 577.4$ (MH^+) was obtained in comparable yield according to the procedure described for Example 75, using 4-[[4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid as the acid and 2-(morpholin-4-yl)-ethylamine hydrochloride as the amine in the coupling step.

Example 150

rac-4-Chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-N-[4-(2H-tetrazol-5-yl)-benzyl]-benzenesulfonamide

- 20 Rac-4-Chloro-N-(4-cyano-benzyl)-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide (80 mg, 0.18 mmol) was dissolved in dimethylformamide (1 ml). Then ammonium chloride (11 mg, 0.2 mmol) and sodium azide (13 mg, 0.2 mmol) was added and the mixture was stirred overnight at 120°C. After cooling the mixture was distributed 3 times between ethyl acetate (10 ml) and hydrochloric acid (10 ml 1N). The combined organic layers were dried and evaporated. The residue was purified on silica gel (eluent hexane/ethyl acetate) to yield 79 mg (89%). MS: $m/e = 506.1$ ($M+NH_4^+$).

Example 151

- 30 rac-(4-[[4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-carbamic acid ethyl ester

- The title compound, MS: $m/e = 446.0$ (MH^+), 463.0 ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 2c, using (4-chloromethyl-phenyl)-carbamic acid ethyl ester as the benzylating reagent and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e using 3-azido-hexahydro-6,6-dimethyl-2H-azepin-2-one.

Example 152

rac-N-(4-[[[(4-Chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-acetamide

- The title compound, MS: $m/e = 495.2$ ($M+NH_4^+$) was obtained in comparable yield according to the procedure described for Example 2c, using 4-acetamido benzylchloride as the benzylating reagent and 4-chloro-N-(6,6-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide which was prepared analogous to Example 4e using 3-azido-hexahydro-6,6-dimethyl-2H-azepin-2-one.

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Example 153

rac-Cyclopropanecarboxylic acid (4-[[[(2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-amide

a) rac-4-Trifluoromethyl-benzenesulfonic acid (4-nitro-benzyl)-(2-oxo-azepan-3-yl)-amide

- 15 rac-4-Trifluoromethyl-benzenesulfonic acid (4-nitro-benzyl)-(2-oxo-azepan-3-yl)-amide was obtained in comparable yield according to the procedure described for Example 1, using 4-nitrobenzaldehyde instead of 3-fluoro-p-anisaldehyde in step 1a and trifluoromethyl-benzenesulfonyl chloride instead of 5-chloro-thiophene-2-sulfonyl chloride in step 1b).

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b) rac-4-Trifluoromethyl-benzenesulfonic acid (4-amino-benzyl)-(2-oxo-azepan-3-yl)-amide

- Rac-4-trifluoromethyl-benzenesulfonic acid (4-nitro-benzyl)-(2-oxo-azepan-3-yl)-amide (2.08 g, 4.4 mmol) was dissolved in methanol (50 ml), palladium on charcoal (200 mg, 10%) was added and the mixture was hydrogenated at room temperature for 2 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was recrystallised from heptane/ethyl acetate to yield a yellowish solid (1.2 g, 61%).

c) rac-Cyclopropanecarboxylic acid (4-[[[(2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-amide

- 30 Rac-4-trifluoromethyl-benzenesulfonic acid (4-amino-benzyl)-(2-oxo-azepan-3-yl)-amide (75 mg, 0.17 mmol) is dissolved in dichloromethane (2 ml), then pyridine (80 mg, 1 mmol) and cyclopropanecarbonyl chloride (21 mg, 0.2 mmol) were added. After shaking the mixture at room temperature for 1 hour hydrochloric acid (5 ml, 0.1M) was added. The organic layer was separated evaporated and the residue was redissolved in 1 ml of

dimethylformamide for preparative HPLC separation (RP-C₁₈, eluent acetonitrile/water) to yield 12 mg (14% of the final product). MS: m/e = 510.4 (MH⁺), 527.2 (M+NH₄⁺).

Example 154

5 rac-Cyclohexanecarboxylic acid (4-[[[(2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-amide

The title compound, MS: m/e = 552.3 (MH⁺), 569.5 (M+NH₄⁺), was obtained in comparable yield analogous to the procedure described for Example 153, using cyclohexanecarbonyl chloride instead of cyclopropanecarbonyl chloride in step 153c).

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Example 155

rac-2-Methoxy-N-(4-[[[(2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-acetamide

The title compound, MS: m/e = 514.3 (MH⁺), 531.2 (M+NH₄⁺), was obtained in

15 comparable yield analogous to the procedure described for Example 153, using methoxyacetyl chloride instead of cyclopropanecarbonyl chloride in step 153c).

Example 156

20 rac-N-(4-[[[(2-Oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-malonamic acid ethyl ester

The title compound, MS: m/e = 556.2 (MH⁺), 573.3 (M+NH₄⁺), was obtained in comparable yield analogous to the procedure described for Example 153, using ethyl malonyl chloride instead of cyclopropanecarbonyl chloride in step 153c).

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Example 157

rac-N-(4-[[[(2-Oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-2-phenyl-acetamide

The title compound, MS: m/e = 560.2 (MH⁺), 577.4 (M+NH₄⁺), was obtained in comparable yield analogous to the procedure described for Example 153, using

30 phenylacetyl chloride instead of cyclopropanecarbonyl chloride in step 153c).

Example 158

rac-Isoxazole-5-carboxylic acid (4-[[[(2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl]-amide

The title compound, MS: $m/e = 537.2$ (MH^+), 554.4 ($M+NH_4^+$), was obtained in comparable yield analogous to the procedure described for Example 153, using isoxazole-5-carbonyl chloride instead of cyclopropanecarbonyl chloride in step 153c).

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Example 159

rac-N-(4-[[(2-Oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl)-benzamide

The title compound, MS: $m/e = 546.3$ (MH^+), 563.3 ($M+NH_4^+$), was obtained in comparable yield analogous to the procedure described for Example 153, using benzoyl chloride instead of cyclopropanecarbonyl chloride in step 153c).

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Example 160

Rac-4-[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl)-benzenesulfonamide

The title compound, MS: $m/e = 512.1$ (MH^+), 529.1 ($M+NH_4^+$), was obtained in comparable yield analogous to the procedure described for Example 1, using N-cyclopropyl-4-formyl-benzenesulfonamide instead of 3-fluoro-p-anisaldehyde in step 1a).

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Example 161

rac-N-(3-Amino-benzyl)-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 408.0$ (MH^+), 425.1 ($M+NH_4^+$), was obtained in comparable yield analogous to the procedure described for Example 92, using 4-chloro-N-(3-nitro-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide instead of 4-chloro-N-(4-nitro-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

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Example 162

rac-4-Chloro-N-(4-methanesulfonylamino-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 484.2$ ($M-H^+$), was obtained in comparable yield analogous to the procedure described for Example 94, using methanesulfonyl chloride instead of cyclopropanecarbonyl chloride.

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Example 163

rac-Cyclopropanecarboxylic acid (3-[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-amide

The title compound, MS: $m/e = 476.0$ (MH^+), 493.1 ($M+NH_4^+$), was obtained in comparable yield analogous to the procedure described for Example 94, using N-(3-

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amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide instead of N-(4-amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

Example 164

5 rac-4-Chloro-N-(3-methanesulfonylamino-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 484.10$ ($M-H^+$), was obtained in comparable yield analogous to the procedure described for Example 94, using N-(3-amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide instead of N-(4-amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide and methanesulfonyl chloride
10 instead of cyclopropanecarbonyl chloride.

Example 165

Rac-N-(4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-malonic acid ethyl ester

15 The title compound, MS: $m/e = 522.1$ (MH^+), 539.3 ($M+NH_4^+$), was obtained in comparable yield analogous to the procedure described for Example 94, using ethyl malonyl chloride instead of cyclopropanecarbonyl chloride.

Example 166

20 N-(2,3-Difluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-4-trifluoromethyl-benzenesulfonamide

The title compound, MS: $m/e = 493.1$ (MH^+), 510.3 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 2, using 4-trifluoromethyl-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide instead of 4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide and 1-bromomethyl-2,3-difluoro-4-methoxy-benzene as the benzylbromide in step 2c, which was previously prepared from
25 2, 3-difluoro-4-methylanisole analogous to the bromination protocol described in Example 185.

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Example 167

3-Methyl-3-(4-[[[(R)-2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino]-methyl]-phenyl)-butyric acid methyl ester

The title compound, MS: $m/e = 558.2$ (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 2, using 4-trifluoromethyl-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide instead of 4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide and 3-(4-bromomethyl-phenyl)-3-methyl-butyric acid methyl ester
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as the benzyl bromide in step 2c, which was previously prepared from 3-methyl-3-phenyl-butyric acid analogous to the bromomethylation and esterification sequence described in Example 190 and from the literature (US patent 4,032,533).

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Example 168

N-(2-Fluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-4-trifluoromethyl-benzenesulfonamide

The title compound, MS: m/e = 475.0 (MH^+), 492.0 (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-trifluoromethyl-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide instead of 4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide and (2-fluoro-4-methoxy-phenyl)-methanol in the Mitsunobu protocol.

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Example 169

15 3-Methyl-3-(4-(((R)-2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino)-methyl)-phenyl)-butyric acid

The title compound, MS: m/e = 525.1 ($M-H^+$), 585.1 ($M+CH_3COO^-$) was obtained in comparable yield analogous to the procedure described for Example 99b from 3-methyl-3-(4-(((R)-2-oxo-azepan-3-yl)-(4-trifluoromethyl-benzenesulfonyl)-amino)-methyl)-phenyl)-butyric acid methyl ester.

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Example 170

Rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-(4-pyrazol-1-yl-benzyl)-benzenesulfonamide
4-Chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide (0.16 g, 0.52 mmol), 1-[4-(bromomethyl)phenyl]-1H-pyrazole (0.26 g, 1.03 mmol), potassium carbonate (0.72 g, 5.17 mmol) and potassium iodide (0.02 g, 0.10 mmol) in 5 ml dimethylformamide were stirred at 65°C for 5 hours. Extraction with water/ethylacetate and chromatography on silicagel with ethylacetate/heptane (90/10 to 1/0) yielded 0.20 g (87%) 4-chloro-N-(2-oxo-azepan-3-yl)-N-(4-pyrazol-1-yl-benzyl)-benzenesulfonamide as light yellow solid,
30 MS: m/e (%) = 459.1 (MH^+ , 100).

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Example 171

Rac-4-Chloro-N-(2-oxo-azepan-3-yl)-N-(4-[1,2,4]triazol-1-yl-benzyl)-benzenesulfonamide

35 4-Chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide (0.16 g, 0.52 mmol), 1-[4-(bromomethyl)phenyl]-1H-1,2,4-triazol (0.25 g, 1.03 mmol), potassium carbonate (0.72

g, 5.17 mmol) and potassium iodide (0.02 g, 0.10 mmol) in 5 ml dimethylformamide were stirred at 65°C for 5 hours. Extraction with water/ethylacetate and chromatography on silicagel with ethylacetate yielded 0.15 g (64%) 4-chloro-N-(2-oxo-azepan-3-yl)-N-(4-[1,2,4]triazol-1-yl-benzyl)-benzenesulfonamide as white solid, MS: m/e (%) = 460.1 (MH⁺, 100).

Example 172

Rac-4-Chloro-N-(4-difluoromethyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
a) 1-Bromomethyl-4-difluoromethyl-benzene

alpha-Bromo-p-tolualdehyde (1.00g, 5.02 mmol) was suspended in 60 ml
10 dichloromethane. Bis(2-methoxyethyl)aminosulfur trifluoride (5.9 ml, 30.5 mmol) and 58 µl (1.01 mmol) ethanol were added. The mixture was stirred at 40°C for 8 hours. After evaporation of the solvent the residue was added drop-wise to cold saturated aqueous sodium bicarbonate solution. Extraction with ethylacetate, washing with saturated aqueous sodium bicarbonate and brine, drying with sodium sulfate and removal of the
15 solvent by distillation yielded 0.81 g (73%) 1-bromomethyl-4-difluoromethyl-benzene, MS: m/e (%) = 141.0 (M-Br, 100), 220/222 (M, 6).

b) 4-Chloro-N-(4-difluoromethyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

4-Chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide (0.45 g, 1.50 mmol), 1-
20 bromomethyl-4-difluoromethyl-benzene (0.66 g, 3.00 mmol), potassium carbonate (2.09 g, 15.0 mmol) and potassium iodide (0.05 g, 0.20 mmol) in 15 ml dimethylformamide were stirred at 65°C for 5 hours. Extraction with water/ethylacetate and chromatography on silicagel with ethylacetate/heptane (90/10 to 1/0) yielded 0.63 g (94%) 4-chloro-N-(4-difluoromethyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide as white solid, MS:
25 m/e (%) = 443.0 (MH⁺, 100).

Example 173

Rac-4-Chloro-N-(4-cyano-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

4-Chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide (1.21 g, 4.00 mmol), 4-(bromomethyl)-benzonitrile (0.79 g, 4.00 mmol), potassium carbonate (5.58 g, 40.0
30 mmol) and potassium iodide (0.13 g, 0.80 mmol) in 200 ml dimethylformamide were stirred at 65°C for 16 hours. Extraction with water/ethylacetate and chromatography on silicagel with ethylacetate yielded 1.05 g (63%) 4-chloro-N-(4-cyano-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide as white solid, MS: m/e (%) = 418.1 (MH⁺, 100).

Example 174

Rac-4-Chloro-N-[4-(5-methoxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

a) 4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-hydroxy-benzamidine

- 5 4-Chloro-N-(4-cyano-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide (2.09 g, 5.00 mmol), sodium bicarbonate (0.52 g, 6.15 mmol) and hydroxylamine hydrochloride (0.43 g, 6.15 mmol) in a mixture of 20 ml ethanol and 4 ml water were refluxed for 11 hours. The solvents were removed by distillation and the residue was recrystallized from water.
- 10 The solid was then suspended in dichloromethane, refluxed, cooled to room temperature and filtered to yield 1.74g (77%) 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-hydroxy-benzamidine as white solid, MS: m/e (%) = 451.0 (MH⁺, 100).

b) 4-Chloro-N-[4-(5-methoxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

- 15 To a solution of methoxyacetic acid (86 µl, 1.10 mmol) in 5 ml dimethylformamide were added 1,1'-carbonyl-diimidazole (0.18g, 1.10 mmol). The mixture was stirred at room temperature for 10 minutes, heated to 40°C for a few minutes and cooled to room temperature. 4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-
- 20 hydroxy-benzamidine (0.45 g, 1.00 mmol) was added and the mixture was stirred at 100°C for 5 hours and then poured into water. Filtration and chromatography on silicagel with ethylacetate/heptane (1/1 to 4/1) yielded 0.46 g (90%) 4-chloro-N-[4-(5-methoxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide as white solid, MS: m/e (%) = 505.0 (MH⁺, 100).

25

Example 175

Rac-4-Chloro-N-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

- To a solution of acetic acid (63 µl, 1.10 mmol) in 5 ml dimethylformamide were added
- 30 1,1'-carbonyl-diimidazole (0.18g, 1.10 mmol). The mixture was stirred at room temperature for 10 minutes, heated to 40°C for a few minutes and cooled to room temperature. 4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-hydroxy-benzamidine (0.45 g, 1.00 mmol) was added and the mixture was stirred at 100°C for 5 hours and then poured into water. Filtration and chromatography on silicagel
- 35 with ethylacetate/heptane (1/1 to 4/1) yielded 0.43 g (91%) 4-chloro-N-[4-(5-methyl-

[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide as white solid, MS: m/e (%) = 474.9 (MH⁺, 100).

Example 176

- 5 Rac-N-[4-(5-Benzyloxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

To a solution of benzyloxyacetic acid (162 μ l, 1.10 mmol) in 5 ml dimethylformamide were added 1,1'-carbonyl-diimidazole (0.18g, 1.10 mmol). The mixture was stirred at room temperature for 10 minutes, heated to 40°C for a few minutes and cooled to room
 10 temperature. 4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-hydroxy-benzamidine (0.45 g, 1.00 mmol) was added and the mixture was stirred at 100°C for 5 hours and then poured into water. Filtration and chromatography on silicagel with ethylacetate/heptane (1/1 to 4/1) yielded 0.51 g (87%) N-[4-(5-benzyloxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-4-chloro-N-(2-oxo-azepan-3-yl)-benzenesulfonamide as
 15 white solid, MS: m/e (%) = 581.1 (MH⁺, 100).

Example 177

- 4-Chloro-N-[4-(5-hydroxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

a) Acetic acid 3-(4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-[1,2,4]oxadiazol-5-ylmethyl ester

To a solution of acetoxyacetic acid (0.13 g, 1.10 mmol) in 5 ml dimethylformamide were added 1,1'-carbonyl-diimidazole (0.18g, 1.10 mmol). The mixture was stirred at room
 25 temperature for 10 minutes, heated to 40°C for a few minutes and cooled to room temperature. 4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-N-hydroxy-benzamidine (0.45 g, 1.00 mmol) was added and the mixture was stirred at 100°C for 5 hours and then poured into water. Filtration and chromatography on silicagel with ethylacetate/heptane (3/1) yielded 0.15 g (29%) acetic acid 3-(4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-[1,2,4]oxadiazol-5-ylmethyl ester as white solid, MS: m/e (%) = 533.0 (MH⁺, 100).
 30

b) 4-Chloro-N-[4-(5-hydroxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

- 35 A solution of 0.03 g (0.05 mmol) acetic acid 3-(4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-[1,2,4]oxadiazol-5-ylmethyl ester in 1 ml

tetrahydrofuran was stirred with 0.2 ml (0.2 mmol) 1 molar aqueous sodium hydroxide for 3 hours at room temperature. Water and aqueous hydrochloric acid was added to reach pH 1. Extraction with ethylacetate, drying with sodium sulfate, filtration and removal of the solvent by distillation yielded 0.02 g (98%) 4-chloro-N-[4-(5-hydroxymethyl-[1,2,4]oxadiazol-3-yl)-benzyl]-N-(2-oxo-azepan-3-yl)-benzenesulfonamide as white solid, MS: m/e (%) = 491.0 (MH^+ , 100).

Example 178

4-Chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-pyridin-4-ylmethyl-benzenesulfonamide

The title compound, MS: m/e = 436.0 (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using 4-(hydroxymethyl)pyridine and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

Example 179

4-Chloro-N-[4-(3-fluoro-propoxy)-benzyl]-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 511.0 (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using [4-(3-fluoropropoxy) phenyl] methanol and 4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

Example 180

4-Chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzyl]-benzenesulfonamide

4-[[[4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester (0.30 g, 0.60 mmol) was treated with hydrazine monohydrate (1.1 g, 22.4 mmol) in methanol (20 ml) for 48 h at r.t. The reaction mixture was concentrated under reduced pressure, diluted with water and extracted with CH_2Cl_2 (3x), The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude foam (0.29 g). 0.10 g of this crude hydrazide was dissolved in pyridine (1.4 ml) treated with ethylacetimidate hydrochloride (0.08 g, 0.66 mmol) under reflux for 1 h. The cooled reaction mixture was concentrated and extracted with ethyl acetate and washed with 1 N HCl (1x), $NaHCO_3$ sat.d(1x), brine, dried ($MgSO_4$) and filtered. The concentrated, crude product was purified using preparative RP(C_{18}) chromatography: lyophilisate 25 mg; MS: m/e = 517.4 (MH^+).

Example 181

4-Chloro-*N*-(5-isopropyl-2-oxo-azepan-3-yl)-*N*-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl]-benzenesulfonamide

- 5 4-[[[(4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester (0.30 g, 0.60 mmol) was saponified to the acid using LiOH.H₂O (0.04 g, 0.90 mmol). The acid (0.10 g, 0.21 mmol) was dissolved in THF (3 ml) and added dropwise to a solution of 1,1-carbonyl diimidazole (CDI, 0.04 g, 0.23 mmol) in THF (0.5 ml). After 30 min, *N*-hydroxy-acetamidine (0.04 g, 0.23 mmol) was added. A further two
10 equivalents each of CDI and *N*-hydroxy-acetamidine were added during a further 48 h stirring at r.t. The reaction mixture was concentrated and crude, coupled amidine was purified over silica gel (gradient ethyl acetate to ethyl acetate/methanol 15%): white solid 0.09 g (73%); MS: *m/e* = 535.5 (MH⁺). Purified amidine (0.08 g, 0.15 mmol) cyclised in the presence of tetrabutylammonium fluoride (1 M, THF 5 ml) over 36 h at r.t. The
15 reaction mixture 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. The concentrated, crude product was purified using preparative RP(C₁₈) chromatography: lyophilisate 15 mg; MS: *m/e* = 517.4 (MH⁺).

20 **Example 182**

3-(4-[[[(4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid

- 3-(4-[[[(4-Chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid methyl ester was prepared according to alkylation protocol
25 Example 2c using 3-(4-bromomethyl-phenyl)-propionic acid methyl ester (prepared analogous to lit. route: US patent 4,032,533). The methyl ester (0.21 g, 0.40 mmol) was saponified using NaOH (0.2 g) in THF (4 ml) for 4 h. The reaction mixture was diluted with water and acidified (KHSO₄/K₂SO₄) to pH 2-3, extracted with ethyl acetate (2x). The combined organic extracts were washed with water, brine, dried (MgSO₄), filtered
30 and concentrated under reduced pressure. The crude was crystallised from ethyl acetate to yield 3-(4-[[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid: 0.04 g; MS: *m/e* = 505.1 (MH⁺).

Example 183

- 35 4-[[[(4-Chloro-benzenesulfonyl)-((*R*)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-*N*-cyclopropyl-benzamide

4-Chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide was obtained following chiral preparative chromatography [Chiralpak AD; isocratic 20%isopropanol/heptane] of racemic 4-chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide intermediate prepared according to Example 4e starting with 4,4-dimethyl cyclohexanone and then alkylated as previously described for Example 2c to give 4-[[4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide MS: m/e = 504.3 (MH⁺).

Example 184

4-[[4-Chloro-benzenesulfonyl)-((S)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide
 4-Chloro-N-((S)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide was obtained following chiral preparative chromatography [Chiralpak AD; isocratic 20%isopropanol/heptane] of racemic 4-chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide intermediate prepared according to Example 4e starting with 4,4-dimethyl cyclohexanone and then alkylated as previously described for Example 2c to give 4-[[4-chloro-benzenesulfonyl)-((S)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide MS: m/e = 504.3 (MH⁺).

Example 185

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

3-Fluoromethyl benzoic acid methyl ester (4.2 g, 25 mmol) , N-bromosuccinimide (4.90 g, 27.50 mmol) and dibenzoyl peroxide (0.18 g, 0.75 mmol) were dissolved in CCl₄ (100 ml) and the mixture was irradiated with a 150 W lamp and refluxed under an argon atmosphere for 5 h. The reaction mixture was allowed to cool to r.t. and then filtered. The concentrated filtrate was purified over silica gel (isopropyl ether/ n-heptane 1:10 v/v): colourless oil 4.6 g (75%); MS: m/e = 248.0 (M), 167.1 (M-Br, 100%) .

4-[[4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester
 4-Chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 4-bromomethyl-3-fluoro-benzoic acid methyl ester analogous to Example 2c to yield 4-[[4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester: MS: m/e = 497.4 (MH⁺).

Example 186

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

4-Chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated
5 using 3-(4-bromomethyl-phenyl)-propionic acid methyl ester analogous to Example 2c to yield 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid methyl ester: MS: m/e = 507.6 (MH⁺).

Example 187

10 3-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid

3-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid methyl ester (0.06 g, 0.11 mmol) was dissolved in methanol (4 ml) and treated with 1 N NaOH (0.2 ml) overnight. The mixture was diluted
15 with water and the methanol removed under reduced pressure. The residue was acidified (KHSO₄/K₂SO₄) and extracted with ethyl acetate (3x). The combined extracts were concentrated and the crude residue was purified using preparative RP(C₁₈) chromatography: lyophilisate 15 mg; MS: m/e = 491.1 (MH⁺).

Example 188

20 4-[[[(4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid

4-[[[(4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester (0.52 g, 1.1 mmol) was dissolved in THF (20
25 ml) and treated with 1 N NaOH (2.1 ml) for 2 h. Work-up as for Example 187 yielded crude which was crystallised from acetonitrile to give 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid: 0.38 g; MS: m/e = 481.1 (MH⁺).

Example 189

30 4-Chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-2-fluoro-benzyl]-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide

4-[[[(4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid (0.15 g, 0.30 mmol) was dissolved in DMF (20 ml) and treated with
35 2-(2-pyridon-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) (0.1 g, 0.33 mmol), Hünig's base (0.15 ml, 0.90 mmol) and N,N-dimethyl hydrazine (0.07 ml, 0.90 mmol). After 1 h the reaction mixture was concentrated under reduced pressure and the

residue was dissolved in ethyl acetate and washed with NaHCO_3 , $\text{KHSO}_4/\text{K}_2\text{SO}_4$, brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure. Crystallisation from isopropyl acetate yielded 4-chloro-N-[4-(*N,N'*-dimethyl-hydrazinocarbonyl)-2-fluorobenzyl]-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide as a crystalline solid: 0.12 g; MS: $m/e = 525.4$ (MH^+).

Example 190

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

HBr gas was passed through a suspension of 3-(3-fluorophenyl)propionic acid (5.1 g, 30 mmol), paraformaldehyde (1.2 g) in aqueous HBr (48%, 20 ml). After 3.5 h at 55°C the suspension was extracted with ethyl acetate (3x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) filtered and evaporated. The crude was recrystallized from CCl_4 -n-hexane to yield crystalline 3-(2-bromomethyl-5-fluoro-phenyl)-propionic acid: 2.7 g; MS: $m/e = 260$ (M), 181 (M-Br).

The acid (2.6 g, 10 mmol) was added to a mixture of sulfuric acid (0.60 ml, 11 mmol) in methanol (30 ml). After 1 h at r.t. the reaction mixture was diluted with water and solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with NaHCO_3 , brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure to yield 3-(2-bromomethyl-5-fluoro-phenyl)-propionic acid methyl ester as a colourless oil: 2.6 g; MS: $m/e = 276$ (M), 195 (M-Br).

4-Chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 3-(2-bromomethyl-5-fluoro-phenyl)-propionic acid methyl ester analogous to Example 2c and then saponified to give 3-(2-[[4-chloro-benzenesulfonyl]-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl)-5-fluoro-phenyl)-propionic acid. MS: $m/e = 509.3$ (MH^+).

Example 191

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

4-Chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide was alkylated using 5-(4-bromomethyl-phenyl)-isoxazole analogous to Example 2c to afford 4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(4-isoxazol-5-yl-benzyl)-benzenesulfonamide MS: $m/e = 488.1$ (MH^+).

Example 192

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

The title compound, MS: $m/e = 469.4$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3, using (2-fluoro-4-methoxy-phenyl)-methanol and 4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide from Example 4e.

Example 193

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

4-[[[(4-Chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid (0.05 g, 0.10 mmol) was dissolved in THF (2 ml) and added dropwise to a suspension of $LiAlH_4$ (0.04 g, 1 mmol) in THF (2 ml). After 6 h to the reaction mixture was added water (0.5 ml), 1 N NaOH (0.2 ml) and after 15 min of vigorous stirring it was filtered. The filtrate was concentrated under reduced pressure and purified using preparative RP(C_{18}) chromatography: lyophilisate 5 mg; MS: $m/e = 469.1$ (MH^+).

Example 194

3-(4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid

The title compound, MS: $m/e = 531.1$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 182 using 4-chloro-N-(5-trifluoromethyl-2-oxo-azepan-3-yl)-benzenesulfonamide and 3-(4-bromomethyl-phenyl)-propionic acid methyl ester in the alkylation step.

Example 195

4-[[[(4-Chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-benzoic acid

The title compound, MS: $m/e = 505.1$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 182 using 4-chloro-N-(5-trifluoromethyl-2-oxo-azepan-3-yl)-benzenesulfonamide and 4-bromomethyl-benzoic acid methyl ester in the alkylation step.

Example 196

4-Chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-benzyl]-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 547.2$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 189 using 4-[[4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-benzoic acid as the precursor to hydrazide formation.

5

Example 197

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

The title compound, MS: $m/e = 537.5$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 185 using 4-chloro-N-(5-trifluoromethyl-2-oxo-azepan-3-yl)-benzenesulfonamide and 4-bromomethyl-3-fluoro-benzoic acid methyl ester in the alkylation step.

Example 198

15 4-Chloro-N-(2-fluoro-4-methoxy-benzyl)-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide

The title compound, MS: $m/e = 509.2$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 3 using 4-chloro-N-(5-trifluoromethyl-2-oxo-azepan-3-yl)-benzenesulfonamide and (2-fluoro-4-methoxy-phenyl)-methanol in the Mitsunobu reaction.

20

Example 199

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

25 4-[[4-Chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester (0.03 g, 0.06 mmol) was dissolved in THF (2 ml) and 1 N NaOH (4 ml) was added. The reaction mixture was stirred for 6 h at pH 10. A $KHSO_4/K_2SO_4$ aqueous buffer was added to adjust the pH to 3. The mixture was extracted with ethyl acetate and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure and lyophilised yielding a solid: 11 mg; MS: $m/e = 521.2$ (MH^+).

30

Example 200

4-Chloro-N-(2-fluoro-4-hydroxymethyl-benzyl)-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide

35 4-[[4-Chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester (0.05 g, 0.09 mmol) in THF (1 ml) was added

dropwise to a cooled (ice-bath) suspension of LiAlH_4 (0.02 g, 0.44 mmol) in THF (1 ml) under an argon atmosphere. The cold bath was removed and the reaction mixture was further stirred for 3.5 h. Ethyl acetate and a $\text{KHSO}_4/\text{K}_2\text{SO}_4$ buffer was added to the reaction mixture. The organic fraction was further washed with a $\text{KHSO}_4/\text{K}_2\text{SO}_4$ (2x),
5 water, brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified using preparative RP(C_{18}) chromatography to give 4-chloro-*N*-(2-fluoro-4-hydroxymethyl-benzyl)-*N*-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide as a lyophilisate: 13 mg; MS: $m/e = 509.4$ (MH^+).

10 Example 201

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

The title compound, MS: $m/e = 465.3$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 187 from its corresponding methyl
15 ester.

Example 202

4-(4-[[4-Chloro-benzenesulfonyl]-((*R*)-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-butyric acid methyl ester

The title compound, MS: $m/e = 510.6$ (MNH_4^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-(4-bromomethyl-phenyl)-
20 butyric acid methyl ester as the benzylating reagent.

Example 203

rac-4-[[4-Chloro-benzenesulfonyl]-(2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-
25 benzoic acid methyl ester

The title compound, MS: $m/e = 469.4$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 4-bromomethyl-3-fluoro-benzoic acid methyl ester as the benzylating reagent and the achiral sulfonamide.

30

Example 204

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

The title compound, MS: $m/e = 496.4$ (MNH_4^+), was obtained in comparable yield from
35 4-(4-[[4-chloro-benzenesulfonyl]-((*R*)-2-oxo-azepan-3-yl)-amino]-methyl)-phenyl)-butyric acid methyl ester analogous to the procedure described for Example 182.

Example 205

(4-[[[4-Chloro-benzenesulfonyl]-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-acetic acid

- The title compound, MS: $m/e = 449.1$ (MH^+), was obtained in comparable yield from (4-
5 [[[4-chloro-benzenesulfonyl]-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-acetic acid methyl ester analogous to the procedure described for Example 182.

Example 206

4-Chloro-N-(4-oxazol-5-yl-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

- 10 The title compound, MS: $m/e = 460.1$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 5-(4-bromomethyl-phenyl)-oxazole as the benzylating reagent.

Example 207

- 15 N-[2-(4-[[[4-Chloro-benzenesulfonyl]-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-ethyl]-acetamide

The title compound, MS: $m/e = 478.0$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using N-[2-(4-chloromethyl-phenyl)-ethyl]-acetamide as the benzylating reagent.

20

Example 208

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

- The title compound, MS: $m/e = 460.1$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 5-(4-bromomethyl-
25 phenyl)-isoxazole as the benzylating reagent.

Example 209

4-Chloro-N-(4-hydroxymethyl-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide

- The title compound, MS: $m/e = 423.0$ (MH^+), 440.3 (MNH_4^+), was obtained in
30 comparable yield analogous to the procedure described for Example 193.

Example 210

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

The title compound, MS: $m/e = 459.1$ (MH^+), was obtained in comparable yield analogous to the procedure described for Example 2c, using 1-bromomethyl-2,5-difluoro-4-methoxy-benzene as the benzylating reagent.

5

Example 211

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

The title compound, MS: $m/e = 459.0$ (MH^+), 479.0 (MNH_4^+) was obtained in comparable yield analogous to the procedure described for Example 2c, using 1-bromomethyl-2,3-difluoro-4-methoxy-benzene which was previously prepared from 2,3-difluoro-4-methylanisole analogous to the bromination protocol described in Example 185.

Example 212

3-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-3-methyl-butyl)-butyric acid methyl ester

The title compound, MS: $m/e = 507.3$ (MH^+), 524.2 (MNH_4^+) was obtained in comparable yield analogous to the procedure described for Example 2c, using 3-(4-bromomethyl-phenyl)-3-methyl-butyl butyric acid methyl ester which was previously prepared from 3-methyl-3-phenyl-butyl butyric acid analogous to the bromomethylation and esterification sequence described in Example 190 and from the literature (US patent 4,032,533).

Example 213

3-(4-[[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-2,2-dimethyl-propionyl)-propionic acid methyl ester

The title compound, MS: $m/e = 507.2$ (MH^+), 524.1 (MNH_4^+) was obtained in comparable yield analogous to the procedure described for Example 2c, using 3-(4-bromomethyl-phenyl)-2,2-dimethyl-propionyl propionic acid methyl ester which was previously prepared from 2,2-dimethyl-3-phenyl-propionyl propionic acid analogous to the bromomethylation and esterification sequence described in Example 190 and from the literature (US patent 4,032,533).

Example 214

3-(3-Chloro-4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionyl)-propionic acid methyl ester

The title compound, MS: $m/e = 513.1$ (MH^+), 530.1 (MNH_4^+) was obtained in comparable yield analogous to the procedure described for Example 2c, using 3-(4-bromomethyl-3-chloro-phenyl)-propionyl propionic acid methyl ester which was previously

prepared from 3-(3-chloro-phenyl)-propionic acid analogous to the bromomethylation and esterification sequence described in Example 190 and from the literature (US patent 4,032,533).

Example 215

- 5 5-[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzofuran-2-carboxylic acid ethyl ester

The title compound, MS: m/e = 505.2 (MH⁺), 522.2 (MNH₄⁺) was obtained in comparable yield analogous to the procedure described for Example 2c, using 5-chloromethyl-benzofuran-2-carboxylic acid ethyl ester.

10

Example 216

rac-4-[[(4-Chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-3-fluorobenzoic acid

- The title compound, MS: m/e = 453.2 (MH⁺), 522.2 (MOAc⁻) was obtained in comparable yield by saponification of rac-4-[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-3-fluorobenzoic acid methyl ester analogous to the procedure described for Example 199.

15

Example 217

- 20 4-[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluorobenzoic acid

The title compound, MS: m/e = 453.1 (MH⁺), 513.1 (MOAc⁻) was obtained in comparable yield by saponification of 4-[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluorobenzoic acid methyl ester analogous to the procedure described for Example 199.

25

Example 218

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

- The title compound, MS: m/e = 491.1 (MH⁺), 551.1 (MOAc⁻) was obtained in comparable yield by saponification 3-(4-[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-3-methyl-butyric acid methyl ester analogous to the procedure described for Example 199.

30

Example 219

- 35 3-(4-[[(4-Chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-2,2-dimethyl-propionic acid

The title compound, MS: $m/e = 491.0(MH^+)$, $551.0(MOAc^-)$ was obtained in comparable yield by saponification 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-2,2-dimethyl-propionic acid methyl ester analogous to the procedure described for Example 199.

5

Example 220

3-(3-Chloro-4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid

The title compound, MS: $m/e = 497.0(MH^+)$, $557.0(MOAc^-)$ was obtained in comparable
 10 yield by saponification 3-(3-chloro-4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl]-propionic acid methyl ester analogous to the procedure described for Example 199.

Example 221

rac-4-[[[(4-Chloro-benzenesulfonyl)-(4,4-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-
 15 N-cyclopropyl-benzamide

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

2-[[[(1,1-Dimethylethoxy)carbonyl]amino]-3,3-dimethyl-4-pentenoic acid (322 mg, 1.32 mmol; Synthesis see Bartlett, Paul A.; Barstow, James F. Journal of Organic Chemistry
 20 (1982), 47(20), 3933-41) was dissolved in dimethylformamide (6 ml) and activated with the coupling reagent TATU (469 mg, 1.46 mmol) and Hünig's base (376 mg, 2.91 mmol) for 2 min. Allyl-(2,4-dimethoxy-benzyl)-amine (274 mg, 1.32 mmol) dissolved in dimethylformamide (2ml) was added and the mixture was stirred overnight. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with saturated
 25 $NaHCO_3$ solution, 1 M $KHSO_4$ solution and brine. After drying with magnesiumsulfate the organic layer was concentrated and purified by flash chromatography (heptane/ethyl acetate = 2:1) to yield 510 mg (89%) of {1-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-2,2-dimethyl-but-3-enyl}-carbamic acid tert-butyl ester; MS: $m/e = 433.6(MH^+)$, $450.6(M+NH_4^+)$.

30 b) {1-(2,4-Dimethoxy-benzyl)-4,4-dimethyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl}-carbamic acid tert-butyl ester

{1-[Allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-2,2-dimethyl-but-3-enyl}-carbamic acid tert-butyl ester (0.5 g, 1.16 mmol) was dissolved in dichloromethane (400 ml), bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (145 mg, 0.17 mmol) was

added and the purple solution was refluxed for 48 hours. The solvent was evaporated, the residue was dissolved in ethyl acetate and washed with NaHCO_3 solution, 1M KHSO_4 solution and brine. After drying with magnesium sulfate the organic layer was concentrated and purified by flash chromatography (heptane/ethyl acetate = 4:1) to yield
5 295 mg (63%) of [1-(2,4-dimethoxy-benzyl)-4,4-dimethyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl]-carbamic acid tert-butyl ester; MS: $m/e = 405.5$ (MH^+).

c) [1-(2,4-Dimethoxy-benzyl)-4,4-dimethyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester

[1-(2,4-Dimethoxy-benzyl)-4,4-dimethyl-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-yl]-carbamic acid tert-butyl ester (260 mg, 0.64 mmol) was dissolved in methanol (10 ml). Palladium on charcoal (30 mg, 10%) was added and the mixture was hydrogenated at room temperature for 90 minutes. The catalyst was filtered off and the filtrate was evaporated. The residue was purified by flash chromatography (heptane/ethyl acetate = 1:1) to yield 220 mg (84%) of [1-(2,4-dimethoxy-benzyl)-4,4-dimethyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester as a colourless oil; MS: $m/e = 407.4$ (MH^+).
15

d) 4-((4-Chloro-benzenesulfonyl)-[1-(2,4-dimethoxy-benzyl)-4,4-dimethyl-2-oxo-azepan-3-yl]-amino)-methyl-N-cyclopropyl-benzamide

For Boc-deprotection [1-(2,4-dimethoxy-benzyl)-4,4-dimethyl-2-oxo-azepan-3-yl]-carbamic acid tert-butyl ester (210 mg, 0.52 mmol) was dissolved in dichloromethane (2 ml) and trifluoroacetic acid (0.5 ml) was added dropwise. After stirring for 90 minutes the solvent and excess trifluoroacetic acid was evaporated and the residue was dried under high vacuum. Then it was dissolved in tetrahydrofuran (3 ml), 4-chlorobenzenesulfonyl chloride (121 mg, 0.57 mmol) and Hünig's base (202 mg, 1.56 mmol) was added and the mixture was stirred overnight. The mixture was diluted with
25 dichloromethane and washed with 0.1N hydrochloric acid and water. The organic layer was dried over magnesium sulfate and evaporated. Flash chromatography (heptane/ethyl acetate = 2:1) yielded 150 mg (60%) sulfonamide that was then dissolved in dimethylformamide (5 ml) for the alkylation step. To this solution 4-chloromethyl-N-cyclopropyl-benzamide (157 mg, 0.75 mmol), potassium carbonate (862 mg, 6.24 mmol) and potassium iodide (10 mg) were added and the mixture was stirred for 48 hours at
30 80°C . The solvent was evaporated and the residue was distributed between ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated. Flash chromatography (heptane/ethyl acetate gradient) yielded 99 mg (48%) of the title compound as a foam; MS: $m/e = 654.4$ (MH^+), 671.3 ($\text{M} + \text{NH}_4^+$).

e) 4-[[[(4-Chloro-benzenesulfonyl)-(4,4-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide

4-(((4-Chloro-benzenesulfonyl)-[1-(2,4-dimethoxy-benzyl)-4,4-dimethyl-2-oxo-azepan-3-yl]-amino)-methyl)-N-cyclopropyl-benzamide (95 mg) was dissolved in a mixture of
5 trifluoroacetic acid/trifluoromethanesulfonic acid/dichloromethane= 40:1:59 (2 ml) and stirred at room temperature for 15 minutes. After evaporation flash chromatography (heptane/ethyl acetate gradient) yielded 65 mg (90%) of 4-[[[(4-chloro-benzenesulfonyl)-(4,4-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide as a foam; MS: m/e = 504.2 (MH⁺), 521.3 (M+NH₄⁺).

10

Example 222

rac-4-Chloro-N-cyclopropylmethyl-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 357.2 (MH⁺), 379.3 (MNa⁺), was obtained in comparable yield according to the procedure described for Example 2c, using bromomethyl-cyclopropane as the alkylating reagent.

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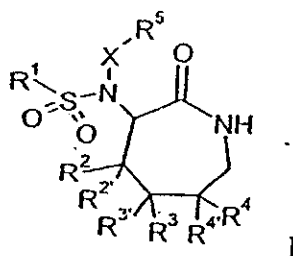
Example 223

rac-4-Chloro-N-cyclobutylmethyl-N-(2-oxo-azepan-3-yl)-benzenesulfonamide

The title compound, MS: m/e = 371.2 (MH⁺), was obtained in comparable yield according to the procedure described for Example 2c, using bromomethyl-cyclobutane
20 as the alkylating reagent.

Claims

1. Compounds of the general formula



wherein

- R^1 is phenyl, thiophenyl or furanyl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, lower alkyl substituted by halogen, -O-lower alkyl substituted by halogen, NO_2 or CN;
- R^2 , R^4 and $R^{2'}$, $R^{4'}$ are hydrogen, lower alkyl, phenyl or lower alkyl substituted by halogen;
- R^5 is phenyl, pyridinyl, benzo[1,3]dioxolyl or benzofuranyl, unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl, lower alkyloxy, CN, nitro, amino, hydroxy, lower alkyl substituted by hydroxy, lower alkyl substituted by halogen, or are substituted by
- C(O)-NR''₂,
 - (CR₂)_m-C(O)-R',
 - (CH₂)_m-heterocycloalkyl,
 - (CH₂)_m-heteroaryl, unsubstituted or substituted by -(CH₂)_m-lower alkoxy, lower alkyl, -(CH₂)_m-O-benzyl or CH₂OH,
 - O-C(O)-lower alkyl,
 - O-C(O)-NR₂,
 - O-(CH₂)_m-C(O)OH,
 - O-lower alkynyl,
 - O-lower alkyl substituted by halogen,
 - O-(CH₂)_m-heterocyclyl,
 - O-(CH₂)_m-phenyl, unsubstituted or substituted by hydroxy,
 - O-(CH₂)_m-heteroaryl, unsubstituted or substituted by lower alkyl,
 - (CH₂)_m-NH-C(O)R',

$-(CH_2)_m-NH-S(O)_2-R'$,
 $-S(O)_2$ -lower alkyl,
 $-S(O)_2$ -heterocyclyl,
 $-S(O)_2NH$ -cycloalkyl,
or is cycloalkyl;

R' is hydrogen, lower alkyl, lower alkynyloxy, hydroxy, cycloalkyl, heterocycloalkyl, which is unsubstituted or substituted by one or more substituents, selected from $COOH$, $-C(O)O$ -lower alkyl $-CH_2C(O)O$ -lower alkyl, halogen or lower alkyl, or is phenyl, benzyl, heteroaryl, $-(CH_2)_m$ -lower alkoxy or $-(CHR)_m-C(O)O$ -lower alkyl;

R'' is hydrogen, cycloalkyl, which is unsubstituted or substituted by one or more substituents, selected from halogen, or is lower alkyl, lower alkyl substituted by halogen, lower alkyl substituted by hydroxy, $-(CH_2)_m$ -heterocycloalkyl, $-NR_2$, heteroaryl, benzyl or $-(CHR)_m-C(O)O$ -lower alkyl;

R is hydrogen or lower alkyl;

R^6 is hydrogen or lower alkyl;

X is $-CHR-$;

m is 0, 1, 2 or 3;

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

2. Compounds of formula I in accordance with claim 1, wherein R^1 is phenyl, substituted by halogen and R^5 is phenyl, substituted by $-C(O)-NR''_2$.

3. Compounds of formula I in accordance with claim 2, which compounds are
4-[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
4-[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
rac-4-[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,

- 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-phenyl-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
- 5-[[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-pyridine-2-carboxylic acid cyclopropylamide,
- 5 N-cyclopropyl-4-[[[(R)-2-oxo-azepan-3-yl)-(4-bromo-benzenesulfonyl)-amino]-methyl]-benzamide,
- 4-[[[(5-*tert*-butyl-2-oxo-azepan-3-yl)-(4-chloro-benzenesulfonyl)-amino]-methyl]-N-cyclopropyl-benzamide,
- 4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
- 10 cyclopropyl-benzamide,
- 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-fluoro-ethyl)-benzamide,
- 15 rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2,2,2-trifluoro-ethyl)-benzamide,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-((1R,2S)-2-fluoro-cyclopropyl)-benzamide,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-hydroxy-ethyl)-benzamide,
- 20 rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopentyl-benzamide,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-methyl-benzamide,
- 25 rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
- rac-N-benzyl-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzamide,
- rac-(4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoylamino)-acetic acid methyl ester,
- 30 rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-(2-morpholin-4-yl-ethyl)-benzamide,
- 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
- 35 4-chloro-N-[4-(*N*',*N*'-dimethyl-hydrazinocarbonyl)-2-fluoro-benzyl]-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide or

4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-N-cyclopropyl-benzamide,
4-chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-2-fluoro-benzyl]-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-benzenesulfonamide or
4-chloro-N-[4-(N',N'-dimethyl-hydrazinocarbonyl)-benzyl]-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide.

4. Compounds of formula I in accordance with claim 1, wherein R¹ is phenyl, substituted by halogen or lower alkyl substituted by halogen and R⁵ is phenyl, substituted by halogen or lower alkyl substituted by halogen, or halogen and lower alkoxy or CH₂OH.

5. Compounds of formula I in accordance with claim 4, wherein the compounds are
rac-4-chloro-N-(4-chloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
rac-4-chloro-N-(3-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
rac-4-chloro-N-(4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
rac-4-chloro-N-(3,4-dichloro-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
4-chloro-N-(3-fluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide,
rac-4-bromo-N-(3-fluoro-4-methoxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide,
4-chloro-N-(2-fluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide,
4-chloro-N-(3-fluoro-4-methoxy-benzyl)-N-(5-isopropyl-2-oxo-azepan-3-yl)-benzenesulfonamide,
N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-4-trifluoromethyl-benzenesulfonamide,
Rac-4-chloro-N-(4-difluoromethyl-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide
4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(2-fluoro-4-methoxy-benzyl)-benzenesulfonamide,
4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(2-fluoro-4-hydroxymethyl-benzyl)-benzenesulfonamide,
4-chloro-N-(2-fluoro-4-methoxy-benzyl)-N-(2-oxo-5-trifluoromethyl-azepan-3-yl)-benzenesulfonamide or
4-chloro-N-(2,3-difluoro-4-methoxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

6. Compounds of formula I in accordance with claim 1, wherein R¹ is phenyl, substituted by halogen and R⁵ is phenyl, substituted by -(CR₂)_m-C(O)-R' or -(CR₂)_m-C(O)-R' and halogen.

7. Compounds of formula I in accordance with claim 6, which compounds are

- 4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid ethyl ester,
- 4-{1-[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-ethyl}-benzoic acid methyl ester,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester,
- 4-[[[(4-chloro-benzenesulfonyl)-(5-isopropyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester,
- Rac-4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid methyl ester,
- 4-[[[(4-chloro-benzenesulfonyl)-(5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-benzoic acid,
- 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid methyl ester,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid,
- 4-[[[(4-chloro-benzenesulfonyl)-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid,
- 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-5-trifluoromethyl-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-propionic acid,
- rac-4-[[[(4-chloro-benzenesulfonyl)-(2-oxo-azepan-3-yl)-amino]-methyl]-3-fluoro-benzoic acid methyl ester,
- 3-(4-[[[(4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino]-methyl]-phenyl)-3-methyl-butyric acid or

3-(4-(((4-chloro-benzenesulfonyl)-((R)-2-oxo-azepan-3-yl)-amino)-methyl)-phenyl)-2,2-dimethyl-propionic acid.

8. Compounds of formula I in accordance with claim 1, wherein R¹ is phenyl, substituted by halogen and R⁵ is phenyl, substituted by hydroxy.

9. Compounds of formula I in accordance with claim 8, wherein the compounds are rac-4-chloro-N-(4-hydroxy-benzyl)-N-(2-oxo-azepan-3-yl)-benzenesulfonamide or 4-chloro-N-(4-hydroxy-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

10. Compounds of formula I in accordance with claim 1, wherein R¹ is phenyl, substituted by halogen and R⁵ is phenyl, substituted by NH₂.

11. A compounds of formula I in accordance with claim 10, wherein the compound is N-(4-amino-benzyl)-4-chloro-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

12. Compounds of formula I in accordance with claim 1, wherein R¹ is thiophenyl or furanyl unsubstituted or substituted by one or more substituents as described in formula I in claim 1.

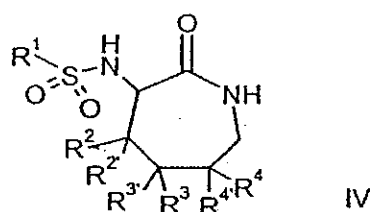
13. Compounds of formula I in accordance with claim 1, wherein the compounds are rac-4-chloro-N-(5,5-dimethyl-2-oxo-azepan-3-yl)-N-[4-(2H-tetrazol-5-yl)-benzyl]-benzenesulfonamide,
4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzyl]-benzenesulfonamide,
4-chloro-N-(5-isopropyl-2-oxo-azepan-3-yl)-N-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl]-benzenesulfonamide,
4-chloro-N-((R)-5,5-dimethyl-2-oxo-azepan-3-yl)-N-(4-isoxazol-5-yl-benzyl)-benzenesulfonamide,
4-chloro-N-(4-isoxazol-5-yl-benzyl)-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide or
4-Chloro-N-[2-fluoro-4-(2H-[1,2,4]triazol-3-yl)-benzyl]-N-((R)-2-oxo-azepan-3-yl)-benzenesulfonamide.

14. Compounds of formula I in accordance with claim 1, wherein X is -CH₂-.

15. Compounds of formula I in accordance with claim 1, wherein R^1 is phenyl and R^5 is phenyl.

16. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



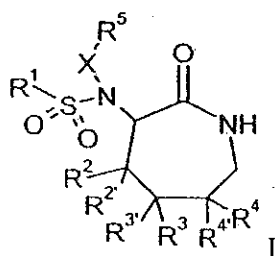
with a compound of formula

R^5Xhal in the presence of a base, or

with a compound of formula

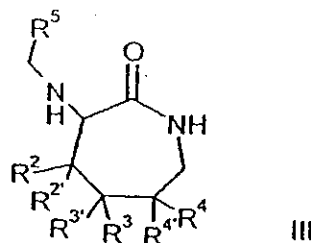
R^5XOH in the presence of diethylazodicarboxylate and triphenylphosphine

to a compound of formula



wherein $R^1 - R^5$ and X have the meaning as described in claim 1,
or

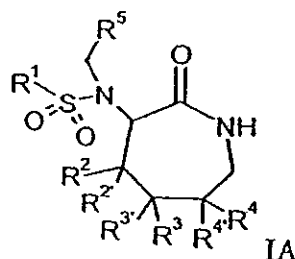
b) reacting a compound of formula



with a compound of formula

$R^1-S(O)_2-Cl$ in the presence of a base

to a compound of formula



wherein $R^1 - R^5$ and X have the meaning as described in claim 1, and

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

17. A compound according to claim 1, whenever prepared by a process as claimed in claim 16, or by an equivalent method.

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

19. A medicament according to claim 18, for the treatment of Alzheimer's disease or common cancers.

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