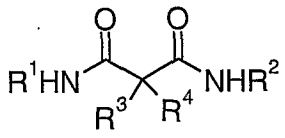
MALONAMIDE DERIVATIVES BLOCKING THE ACTIVITY OF GAMMA-SECRETASE

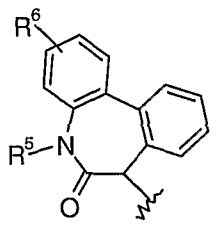
The invention relates to malonamide derivatives of formula



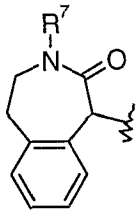
I

wherein

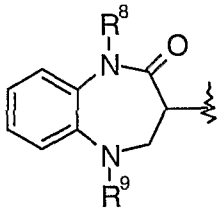
R^1 is one of the following groups



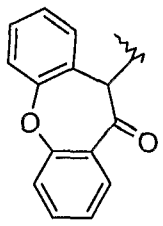
a),



b),



c),



d)

R^2 is lower alkyl, lower alkinyl, -$(CH_2)_n$-O-lower alkyl, -$(CH_2)_n$-S-lower alkyl, -$(CH_2)_n$-CN, -$(CR'R'')_n$-CF_3, -$(CR'R'')_n$-CHF_2, -$(CR'R'')_n$-CH_2F, -$(CH_2)_n$-C(O)O-lower alkyl, -$(CH_2)_n$-halogen, or is -$(CH_2)_n$-cycloalkyl, optionally substituted by one or more substituents, selected from the group consisting of phenyl, halogen or CF_3;

R',R" are independently from n and from each other hydrogen, lower alkyl, lower alkoxy, halogen or hydroxy;

R^3, R^4 are independently from each other hydrogen, lower alkyl, lower alkoxy, phenyl or halogen;

R^5 is hydrogen, lower alkyl, $-(CH_2)_n-CF_3$ or $-(CH_2)_n$-cycloalkyl;

R^6 is hydrogen or halogen;

R^7 is hydrogen or lower alkyl;

R^8 is hydrogen, lower alkyl, lower alkinyl, $-(CH_2)_n-CF_3$, $-(CH_2)_n$-cycloalkyl or $-(CH_2)_n$-phenyl, optionally substituted by halogen;

R^9 is hydrogen, lower alkyl, -C(O)H, -C(O)-lower alkyl, $-C(O)-CF_3$, $-C(O)-CH_2F$, $-C(O)-CHF_2$, -C(O)-cycloalkyl, $-C(O)-(CH_2)_n$-O-lower alkyl, $-C(O)O-(CH_2)_n$-cycloalkyl, -C(O)-phenyl, optionally substituted by one or more substituents selected from the group consisting of halogen or -C(O)O-lower alkyl, or is $-S(O)_2$-lower alkyl, $-S(O)_2-CF_3$, $-(CH_2)_n$-cycloalkyl or is $-(CH_2)_n$- phenyl, optionally substituted by halogen;

n is 0, 1, 2, 3 or 4;

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

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl 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 lower alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "lower alkinyl" denotes a unsaturated straight- or branched-carbon chain containing from 2 to 7 carbon atoms and containing at least one triple bond.

The term “cycloalkyl” denotes a saturated carbocyclic group, containing 3 – 7 carbon atoms.

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

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

The expression "-(CR'R'')$_n$-" may be, for example $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CF_2-$, $-CH_2-CH_2-CF_2-$, $-CH_2-CH_2-CH(OCH_3)-$, $-CH_2CH(OH)-$ or $-C(CH_3)_2-CH(OH)-$.

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.

Alzheimer's disease (AD) is the most common cause of dementia in later life. Pathologically AD is characterized by the deposition in the brain of amyloid in extracellular plaques and intracellular neurofibrillary tangles. The amyloid plaques are mainly composed of amyloid peptides (Abeta peptides) which originate from the β-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 proteolytic enzymes termed β- and γ-secretase. β-Secretase cleaves first in the extracellular domain of APP just outside of the trans-membrane domain (TM) to produce a C-terminal fragment of APP containing the TM- and cytoplasmatic domain (CTFβ). CTFβ is the substrate for γ-secretase which cleaves at several adjacent positions within the TM to produce the Aβ peptides and the cytoplasmic fragment. The majority of Abeta peptides is of 40 amino acids length (Aβ40), a minor species carries 2 additional amino acids at its C-terminus. 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. 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 substates and which are themselves polytopic membrane proteins. Other essential components of γ-secretase may be 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 family, however, γ-secretase has a loose substrate specificity and may cleave further membrane proteins unrelated to APP and Notch.

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 or 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 by blocking the activity of γ-secretase and reducing or preventing the formation of the various amyloidogenic Abeta peptides.

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

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 and
Journ. of Medicinal Chemistry, Vol. 44, No. 13, 2001, 2039-2060.

Objects of the present invention are the compounds of formula I per se, the use of compounds of formula 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.

A further object of the invention are all forms of optically pure enantiomers, recemates or diastereomeric mixtures for compounds of formula I.

Preferred compounds of formula I are those, wherein R^1 is a) and R^2 is $-(CH_2)_n$-cycloalkyl, optionally substituted by CF_3, for example the following compounds:

N-cyclopropylmethyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide or
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(1-trifluoromethyl-cyclopropylmethyl)-malonamide.

Preferred compounds are further those, wherein R^1 is a) and R^2 is lower alkyl, $-(CH_2)_n$-O-lower alkyl or $-(CH_2)_n$-S-lower alkyl, for example the following compounds:

2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-methoxyethyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-methylthioethyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3-methoxy-propyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-propyl-malonamide or
2-fluoro-2-methyl-N-(3-methyl-butyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide.

Preferred compounds are further those, wherein R^1 is a) and R^2 is $-(CR'R'')_n-CF_3$ or $-(CR'R'')_n-CHF_2$, for example

2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,2-trifluoroethyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,3-trifluoro-propyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4-tetrafluoro-butyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4,4,4-trifluoro-butyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4,4,4-trifluoro-3-methoxy-butyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4-tetrafluoro-butyl)-malonamide,
N-(5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,

2-methyl-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2,2-dimethyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(-)-2-methoxy-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2R)-2-fluoro-2-methyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2S)-2-fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methoxy-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
(R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
N-(5-isopropyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-(5-isopropyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-

pentafluoro-propyl)-malonamide,
2,2-dimethyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2R)-2-fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2S)-2-fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2-methoxy-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide or
2,2-dimethyl-N-[(S)-6-oxo-5-(2,2,2-trifluoro-ethyl)-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

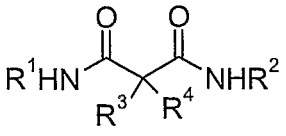
A further preferred group of compounds is those, wherein R^1 is c) and R^2 is $-(CR'R'')_n-CF_3$ for example the following compounds:
2-methyl-N-(1-methyl-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide,
N-((3S)-5-benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(4-fluoro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(4-chloro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(3,5-difluoro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
4-{(3S)-5-methyl-4-oxo-3-[2-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carbonyl}-benzoic acid methyl ester,
N-((3S)-5-acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[5-((3S)-4-fluoro-benzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(4-chloro-benzoyl)-1-cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2RS)-methyl-N-((3S)-1-methyl-2-oxo-5-trifluoromethanesulfonyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,

(2RS)-methyl-N-[(3S)-1-methyl-2-oxo-5-(2,2,2-trifluoro-acetyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(2-methoxy-acetyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(S)-5-methanesulfonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2RS)-methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-5-trifluoromethanesulfonyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
5-methyl-4-oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl estermalonamide,
N-[(S)-5-cyclopropanecarbonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
4-oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester,
N-[(S)-5-acetyl-1-isopropyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide or
N-((S)-5-acetyl-1-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

Preferred compounds are further those, wherein R^1 is b), for example
2-methyl-N-(3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide.

Preferred compounds of formula I are further those, wherein R^1 is d), for example
2-methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide or
2-methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

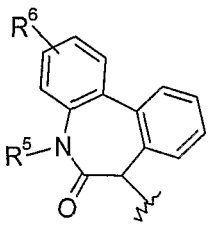
One embodiment of the invention are compounds of the general formula



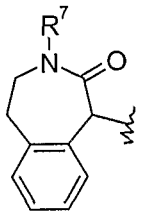
I-1

wherein

R^1 is one of the following groups



a),



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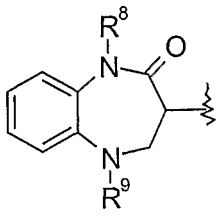

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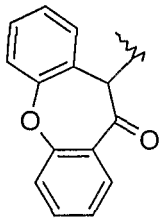


d)

R^2 is lower alkyl, lower alkinyl, -$(CH_2)_n$-O-lower alkyl, -$(CH_2)_n$-S-lower alkyl, -$(CH_2)_n$-CN, -$(CR'R'')_n$-CF_3, -$(CR'R'')_n$-CHF_2, -$(CH_2)_n$-C(O)O-lower alkyl, -$(CH_2)_n$-halogen, or is -$(CH_2)_n$-cycloalkyl, optionally substituted by one or more substituents, selected from the group consisting of phenyl, halogen or CF_3;

R',R'' are independently from n and from each other hydrogen, lower alkyl, lower alkoxy, halogen or hydroxy;

R^3, R^4 are independently from each other hydrogen, lower alkyl, phenyl or halogen;

R^5 is lower alkyl or -$(CH)_2$-cycloalkyl;

R^6 is hydrogen or halogen;

R^7 is hydrogen or lower alkyl;

R^8 is hydrogen, lower alkyl, lower alkinyl or -$(CH)_2$-cycloalkyl;

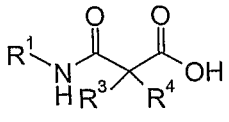
R^9 is hydrogen, lower alkyl, -C(O)-lower alkyl, -C(O)-lower cycloalkyl, -$(CH_2)_n$-cycloalkyl, phenyl, -C(O)-phenyl, optionally substituted by one or more substituents selected from the group consisting of halogen or -C(O)O-lower alkyl, or is $(CH)_2$-phenyl, optionally substituted by halogen;

n is 0, 1, 2, 3 or 4;

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

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

a) reacting a compound of formula

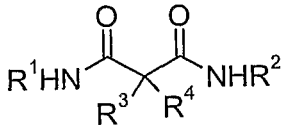


II

with a compound of formula

NH_2R^2 III

to a compound of formula



I

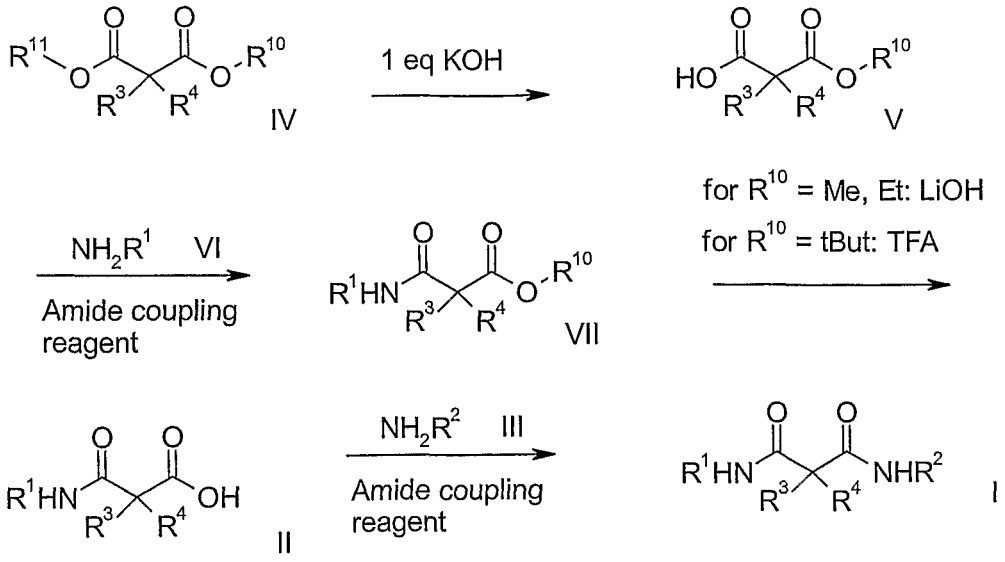
wherein $R^1 - R^4$ have the meaning as described above,

and

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

The detailed description can be found below and in Examples 1 – 121. The starting material of formula IV are known compounds or may be prepared by methods well-known in the art. The amines of formulas VI and III are commercial available products or can be prepared by methods described in the literature.

Scheme 1



In this scheme R^1 and R^2 are as described below and R^{10} and R^{11} are independently lower alkyl.

In accordance with scheme 1 a compound of formula I may be prepared as follows:

To a cooled solution of a compound of formula V, for example 2-methyl-malonic acid mono-*tert*-butyl ester and and an amine of formula VI, for example 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one in THF is added hydroxybenzotriazole, diisopropylethylamine and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, and the mixture is stirred overnight at r.t. The solvent is evaporated, the residue is washed, dried and purified in usual manner.

Then TFA (trifluoroacetic acid) is added to the obtained solution of formula VII, for example 2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid tert-butyl ester in dichloromethane, and the mixture is stirred at r.t. overnight. The mixture is then taken up in more dichloromethane, washed and dried. After evaporation of the solvent, a compound of formula II, for example 2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid is obtained. This obtained compound and a compound of formula III, for example cyclopropylmethylamine are placed in a disposable polypropylene tube and dissolved in DMF. TPTU (2-(2-pyridon-1-yl)-1,1,3,3-tetramethyl uranium tetrafluoroborate) is added, and the mixture is shaken overnight at r.t. The obtained compound of formula I is isolated and purified in conventional manner.

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

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

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

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

Description of γ-secretase assay

The activity of test compounds can be evaluated in assays which measure the proteolytic cleavage of suitable substrates by γ-secretase activity. These can be cellular assays where e.g., a substrate of the γ-secretase is fused in its cytoplasmic domain to a transcription factor. Cells are transfected with this fusion gene and a reporter gene, e.g., firefly luciferase, which expression is enhanced by the transcription factor. Cleavage of the fused substrate by γ-secretase will lead to expression of the reporter gene which can be monitored in appropriate assays. The γ-secretase activity can also be determined in cell-free in vitro asays where e.g., a cell lysate containing the γ-secretase complex is incubated with a suitable APP-derived substrate which is cleaved to the Abeta peptides. The amount of produced peptides can be determined with specific ELISA assays. Cell lines of neuronal origin secrete Abeta peptides which can be measured with the specific

ELISA assay. Treatment with compounds which inhibit γ-secretase leads to a reduction of secreted Abeta thus providing a measure of inhibition.

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

The preferred compounds show a IC_{50}< 0.1 μM. In the list below are described some data to the γ-secretase inhibition:

Table 1

Example No.	IC_{50} in vitro	Example No.	IC_{50} in vitro
1	0.09	70	0.006
4	0.02	71	0.011
5	0.071	72	0.005
6	0.031	73	0.008
8	0.015	74	0.001
13	0.02	75	0.002
14	0.037	76	0.004
21	0.03	77	0.05

23	0.018	78	0.002
24	0.005	79	0.006
26	0.056	80	0.003
28	0.073	81	0.025
29	0.06	82	0.009
30	0.079	83	0.020
35	0.012	84	0.007
36	0.006	85	0.003
37	0.013	86	0.047
38	0.02	87	0.017
39	0.09	88	0.05
40	0.07	89	0.020
43	0.03	95	0.071
44	0.03	98	0.080
49	0.033	99	0.059
50	0.043	101	0.040
51	0.019	106	0.090
65	0.006	108	0.046
66	0.017	109	0.048
67	0.004	113	0.030
68	0.008	115	0.067
69	0.002	121	0.038

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

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

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

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

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

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

of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

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

Manufacturing Procedure

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

Capsule Formulation

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

Manufacturing Procedure

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

Example 1

N-Cyclopropylmethyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid tert-butyl ester

To a cooled solution (0 °C) of 2-methyl-malonic acid mono-*tert*-butyl ester (1.01 g, 5.79 mmol) and 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one (1.15 g, 4.83 mmol) in THF (8 ml) was added hydroxybenzotriazole (652 mg, 4.83 mmol), diisopropylethylamine (624 mg, 4.83 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (925 mg, 4.83 mmol), and the mixture was stirred overnight at r.t. The solvent was evaporated, the residue was taken up in ethyl acetate, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 395.3 ($M+H^+$), (920 mg, 48 %) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

b) 2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid

TFA (3 ml) was added to a solution of 2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid tert-butyl ester (920 mg, 2.33 mmol) in dichloromethane (3 ml) and the mixture was stirred at r.t. overnight. The mixture was then taken up in more dichloromethane, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 339.3 ($M+H^+$), (580 mg, 73 %) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

c) N-Cyclopropylmethyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid (20 mg, 0.059 mmol) and cyclopropylmethylamine (5 mg, 0.059 mmol) were placed in a disposable polypropylene tube and dissolved in DMF (2ml). TPTU (2-(2-pyridon-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, 19mg, 0.065 mmol) was added, and the mixture was shaken overnight at r.t. The title compound, MS: m/e = 392.2 ($M+H^+$), was isolated from the reaction mixture by automated, preparative HPLC (YMC CombiPrep C18 column 50 x 20 mm, solvent gradient 5-95 % CH_3CN in 0.1 % TFA(aq) over 6.0 min, λ = 230 nm, flow rate 40 ml/min).

Example 2

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-ethyl-malonamide

The title compound, MS: m/e = 366.2 ($M+H^+$), was prepared in analogy to example 1 from ethylamine.

Example 3

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-propargyl-malonamide

The title compound, MS: m/e = 376.3 ($M+H^+$), was prepared in analogy to example 1 from propargylamine.

Example 4

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-methoxyethyl)-malonamide

The title compound, MS: m/e = 396.3 ($M+H^+$), was prepared in analogy to example 1 from 2-methoxyethylamine.

Example 5

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-propyl-malonamide

The title compound, MS: m/e = 380.3 ($M+H^+$), was prepared in analogy to example 1 from propylamine.

Example 6

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-methylthioethyl)-malonamide

The title compound, MS: m/e = 412.3 ($M+H^+$), was prepared in analogy to example 1 from 2-Methylthioetylamine.

Example 7

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-cyclobutyl-malonamide

The title compound, MS: m/e = 392.3 ($M+H^+$), was prepared in analogy to example 1 from cyclobutylamine.

Example 8

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3-methoxy-propyl)-malonamide

The title compound, MS: m/e = 410.3 ($M+H^+$), was prepared in analogy to example 1 from 3-methoxypropylamine.

Example 9

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-cyanomethyl-malonamide

The title compound, MS: m/e = 377.3 ($M+H^+$), was prepared in analogy to example 1 from aminoacetonitrile.

Example 10

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-cyclopropyl-malonamide

The title compound, MS: m/e = 378.3 ($M+H^+$), was prepared in analogy to example 1 from cyclopropylamine.

Example 11

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-cyanoethyl)-malonamide

The title compound, MS: m/e = 391.2 ($M+H^+$), was prepared in analogy to example 1 from 3-aminopropionitrile.

Example 12

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-ethoxyethyl)-malonamide

The title compound, MS: m/e = 410.3 ($M+H^+$), was prepared in analogy to example 1 from 2-ethoxyethylamine.

Example 13

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,2-trifluoroethyl)-malonamide

The title compound, MS: m/e = 420.2 ($M+H^+$), was prepared in analogy to example 1 from 2,2,2-trifluoroethylamine.

Example 14

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,3-trifluoro-propyl)-malonamide

The title compound, MS: m/e = 434.3 ($M+H^+$), was prepared in analogy to example 1 from 3,3,3-trifluoropropylamine.

Example 15

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound, MS: m/e = 470.1 ($M+H^+$), was prepared in analogy to example 1 from 2,2,3,3,3-pentafluoropropylamine.

Example 16

[2-(5-Methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-ylcarbamoyl)-propionylamino]-acetic acid tert-butyl ester

The title compound, MS: m/e = 452.3 ($M+H^+$), was prepared in analogy to example 1 from *tert*-butyl glycinate.

Example 17

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,3-trifluoro-2-hydroxy-propyl)-malonamide

The title compound, MS: m/e = 450.2 ($M+H^+$), was prepared in analogy to example 1 from 3-amino-1,1,1-trifluoro-2-propanol.

Example 18

N-(2,2-Difluoro-3-phenyl-cyclopropylmethyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 504.3 ($M+H^+$), was prepared in analogy to example 1 from *C*-(2,2-difluoro-3-phenyl-cyclopropyl)-methylamine.

Example 19

N-(2,2-Difluoro-cyclopropylmethyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 428.2 ($M+H^+$), was prepared in analogy to example 1 from *C*-(2,2-difluoro-cyclopropyl)-methylamine.

Example 20

2-Methyl-N-(3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide

a) 2-Methyl-malonic acid monoethyl ester

To a solution of 6.44 g (115 mmol) potassium hydroxide in 200 ml of ethanol 20.0 g diethyl methyl-malonate (115 mmol) was added and the mixture was refluxed for 4 hours. After cooling the reaction mixture was concentrated on a rotary evaporator, 50 ml of water was added and the mixture was extracted with ether (two times 50 ml). The aqueous solution was acidified with 4M hydrochloric acid and extracted with ethyl acetate (three times 50 ml). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and used without further purification.
MS m/e (%): 101.1 (M-EtO, 100), 147.1 ($M+H^+$, 8).

b) 2-Methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid ethyl ester

To a solution of 1.56 g (10.6 mmol) methyl-malonic acid monoethyl ester in 20 ml of tetrahydrofuran 1.06 g (10.6 mmol) of 2,2,2-trifluoroethylamine, 2.05 g (10.6 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 1.44 g (10.6 mmol) of 1-hydroxybenzotrizole hydrate and 2.75 g (21.2 mmol) of N,N-diisopropyl-ethylamine were added. The mixture was stirred at room temperature for 18 h. The mixture was poured onto 0.5 N HCl (50 ml) and afterwards extracted with dichloromethane (three times 50 ml). The combined organic layers were extracted with 0.5 N aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated on the rotary evaporator. The residue was purified by column filtration (hexane/ethyl acetate = 2:1) to yield 1.48 g (61 %) of the title compound as white crystalline solid.

MS m/e (%): 226,1 ($M-H^+$, 100).

c) 2-Methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid

To a solution of 1.48 g (6.52 mmol) 2-Methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid ethyl ester in 40 ml of tetrahydrofurane, 20 ml of water and 1.09 g (26 mmol) of lithium hydroxide were added and the mixture was stirred overnight at room temperature. After concentration in vacuo water (50 ml) was added and the mixture was extracted with dichloromethane (three times 30 ml). The aqueous phase was acidified with 8 N hydrochloric acid and extracted with dichloromethane (four times 30 ml).

The combined organic layers from the second extraction were dried ($MgSO_4$) and evaporated in vacuo to give 1.09 g (84 %) of the title compound as a white solid.

MS m/e (%): 197,9 ($M-H^+$, 100).

d) 2-Methyl-N-(3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide

To a solution of 0.066 g (0.3 mmol) 2-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid in 2 ml of tetrahydrofuran 0.057 g (0.3 mmol) of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one, 0.058 g (0.3 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 0.040 g (0.3 mmol) of 1-hydroxybenzotrizole hydrate and 0.116 g (0.9 mmol) of N,N-diisopropyl-ethylamine were added. The mixture was stirred at room temperature for 18 h. Then 0.5 N HCl (5 ml) was added and the mixture was extracted with dichloromethane (three times 5 ml). The combined organic layers were extracted with 0.5 N aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate = 3:1) to yield 0.10 g (89 %) of the diastereomeric mixture of title compound as white solid.

MS m/e (%): 372,1 ($M+H^+$, 100).

Example 21

2-Methyl-N-(1-methyl-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-3-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one diethyl methyl-malonate in step d).

MS m/e (%): 449.1 ($M+H^+$, 100).

Example 22

N-(5-Methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-phenyl-N'-(2,2,2-trifluoro-ethyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl phenylmalonate instead of diethyl methyl-malonate in step a) and (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 482.1 ($M+H^+$, 100).

Example 23

2-Fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a) and (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 438.3 ($M+H^+$, 100).

Example 24

2-Fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), pentafluoropropylamine instead of 2,2,2-trifluoroethyl-amine in step b) and (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 488.2 ($M+H^+$, 100).

Example 25

2-Methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-3-Amino-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

To a solution of 5.0 g (18 mmol) (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-3-yl)-carbamic acid tert-butyl ester in 80 ml of tetrahydrofuran at –75 °C 18 ml (18 mmol) of lithium bis(trimethylsilyl)amide solution (1M in tetrahydrofurane) was added. After stirring for 30 min at –75 °C the mixture was allowed to reach room temperature and 3.07 g (21.6 mmol) of methyl iodide was added. The mixture was stirred for 2.5 hours at room temperature and concentrated in vacuo. The residue was distributed between 1M $NaHSO_4$ solution and ethyl acetate. The combined organic layers were reextracted with water and dried ($MgSO_4$). After evaporation of the solvent 20 ml of dichlorometane and 20 ml of trifluoracetic acid was added and the mixture was stirred for 2.5 h at room temperature. For workup the mixture was concentrated in vacuo, then ethylacetate was added and the mixture was extracted two times with water. The aqueouos phase was basified with sodium hydroxide and extracted three times with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (dichloromethane/methanol = 9:1) to yield 2.1 g (65 %) of (S)-3-amino-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4] diazepin-2-one.
MS m/e (%): 192.2 ($M-H^+$, 100).

b) 2-Methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using pentafluoropropylamine instead of 2,2,2-trifluoroethyl-amine in step b) and (S)-3-amino-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 421.2 ($M-H^+$, 100).

Example 26

N-((3S)-5-Benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

To a solution of 0.2 g (0.47 mmol) of 2-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide in 3 ml of dichloromethane 0.096 g (0.95 mmol) of triethylamine and 0.08

mg (0.57 mmol) of benzoylchloride were added. The mixture was stirred for 20 min at room temperature. Hydrochloric acid (10 ml of a 1 N solution) was added and the mixture was extracted two times with dichloromethane. The combined organic layers were extracted with 1N sodiumbicarbonate solution, dried ($MgSO_4$) and concentrated in vacuo. The remaining oil was purified by column chromatography to yield 0.15 g (60 %) of a white foam.

MS m/e (%): 527.3 ($M+H^+$, 100).

Example 27

N-((3S)-5-Benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2,2-dimethyl-N'-(2,2,2-trifluoro-ethyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 25 using diethyl 2,2-dimethylmalonate instead of diethyl methyl-malonate and 2,2,2-trifluoroethylamine instead of pentafluoropropylamine in step b) followed by the reaction with benzoylchloride as described in example 26.

MS m/e (%): 491.3 ($M+H^+$, 100).

Example 28

N-[(3S)-5-(4-Fluoro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using 4-fluorobenzoylchloride instead of benzoylchloride.

MS m/e (%): 545.3 ($M+H^+$, 100).

Example 29

N-[(3S)-5-(4-Chloro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using 4-chlorobenzoylchloride instead of benzoylchloride.

MS m/e (%): 561.4 ($M+H^+$, 100).

Example 30

N-[(3S)-5-(3,5-Difluoro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using 3,5-difluorobenzoylchloride instead of benzoylchloride.

MS m/e (%): 563.4 ($M+H^+$, 100).

Example 31

2-Fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,3-trifluoro-2-hydroxy-1,1-dimethyl-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and rac-3-amino-1,1,1-trifluoro-3-methyl-2-butanol instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 496.2 ($M+H^+$, 100).

Example 32

2-Fluoro-N-(2-fluoro-ethyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2-fluoroethylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 402,2 ($M+H^+$, 100).

Example 33

N-(2,2-Difluoro-ethyl)-2-fluoro-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2,2-difluoroethylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 420.1 ($M+H^+$, 100).

Example 34

2-Fluoro-N-(2-cis-fluoro-cyclopropyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and cis-2-fluorocyclopropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 414.2 ($M+H^+$, 100).

Example 35

2-Fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4-tetrafluoro-butyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 3,3,4,4-tetrafluorobutylamine (available from the corresponding bromide via the Phthalimide method according to Jacobs et al: J.Med.Chem.1994, 37 ,1282) instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 484.2 ($M+H^+$, 100).

Example 36

2-Fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4,4,4-trifluoro-butyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 4,4,4-trifluorobutylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 466.2 ($M+H^+$, 100).

Example 37

2-Fluoro-2-methyl-N-(3-methyl-butyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 3-methyl-butylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 426.2 ($M+H^+$, 100).

Example 38

2-Fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(1-trifluoromethyl-cyclopropylmethyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2-fluoro-2-methylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 1-trifluormethyl-

cyclopropylmethylamine (available from the corresponding alcohol via the Phthalimide method according to Jacobs et al: J.Med.Chem.1994, 37, 1282) instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 478.1 ($M+H^+$, 100).

Example 39

4-{(3S)-5-Methyl-4-oxo-3-[2-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carbonyl}-benzoic acid methyl ester

The title compound was obtained in comparable yields according to the procedures described for example 26 using 4-(methoxycarbonyl)-benzoylchloride instead of benzoylchloride.

MS m/e (%): 583.3 ($M+H^+$, 100).

Example 40

N-((3S)-5-Acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using acetylchloride instead of benzoylchloride.

MS m/e (%): 465.2 ($M+H^+$, 100).

Example 41

2-Methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide

a) (RS)-11-Amino-11H-dibenzo[b,f]oxepin-10-one hydrochloride

To a solution of 1.85 g (8.77 mmol) 11H-dibenzo[b,f]oxepin-10-one in 4 ml of toluene at –20 °C 2.5 g (21.9 mmol) of potassium tert.butoxide was added. The solution was saturated with N2. After stirring for 15 min 1.2g (10.5 mmol) of isoamyl nitrite was added. After stirring overnight at room temperature the solution was cooled at 0 °C for 15 min water (80 ml), acetic acid (4 ml) and ethyl acetate (80 ml) were added. The aqueouos phase was extracted with ethyl acetate. The combined organic layers were reextracted with water and dried ($MgSO_4$). After evaporation of the ethyl acetate the resulting slurry of the oxim in toluene was cooled to 0 °C during an hour and filtered. The solid material was dissolved in tetrahydrofurane (20 ml), 8 ml 1M hydrochloric acid in tetrahydrofurane and 20 mg of platinum oxide were added. The reaction mixture was flushed with N2 and subjected to a hydrogen atmosphere of 50 psi at room temperature. After stirring overnight with hydrogen atmosphere the formed precipitate was collected by filtration, washed with tetrahydrofurane and recrystallised from a methanol tetrahydrofurane mixture to yield 0.9 g of white crystals (Fp.215-217 °C)

b) 2-Methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-11-amino-11H-dibenzo[b,f]oxepin-10-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 407.3 ($M+H^+$, 100).

Example 42

2-Methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using 2,2,3,3,3-pentafluoropropylamine instead of 2,2,2-trifluoroethylamine in step b) and (RS)-11-amino-11H-dibenzo[b,f]oxepin-10-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 457.4 ($M+H^+$, 100).

Example 43

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4,4,4-trifluoro-3-methoxy-butyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 4,4,4-trifluoro-3-methoxy-butylamine (available from 4,4,4-trifluoro-3-methoxybutaneamide via lithium aluminiumhydride reduction according to Jacobs et al: J.Med.Chem.1994, 37, 1282) instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 476.3 ($M-H^+$, 100).

Example 44

2-Fluoro-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4-tetrafluoro-butyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 3,3,4,4-tetrafluorobutylamine (available from the corresponding bromide via the Phthalimide method according to Jacobs et al: J.Med.Chem.1994, 37, 1282) instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 464.2 ($M-H^+$, 100).

Example 45

N-(3-Isopropoxy-propyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 3-Isopropoxy-propylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).
MS m/e (%): 436.3 ($M+H^+$, 100).

Example 46

N-((3S)-1-Cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 25 using cyclopropylmethyl bromide instead of methyl iodide in step a).
MS m/e (%): 463.5 ($M+H^+$, 100).

Example 47

N-((3S)-1,5-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) ((3S)-1-Methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester

To a solution of 5.0 g (18 mmol) (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-3-yl)-carbamic acid tert-butyl ester in 80 ml of tetrahydrofuran at –75 °C 18 ml (18 mmol) of lithium bis(trimethylsilyl)amide solution (1M in tetrahydrofurane) was added. After stirring for 30 min at –75 °C the mixture was allowed to reach room temperature and 3.07 g (21.6 mmol) of methyl iodide was added. The mixture was stirred for 2.5 hours at room temperature and concentrated in vacuo. The residue was distributed between 1M $NaHSO_4$ solution and ethyl acetate. The combined organic layers were reextracted with water and dried ($MgSO_4$) to yield 4.95 g (94 %) of (1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester as a white foam.
MS m/e (%): 292.0 ($M+H^+$, 100).

b) (S)-3-Amino-1,5-dimethyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

To 0.29 g (1 mmol) of (1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in dimethylformamide (3 ml) 0.46 g (3.33 mmol) of

potassium carbonate and 0.17 g (1.2 mmol) of methyl iodide were added and the mixture was stirred at room temperature overnight. Water (10 ml) was added and the mixture was extracted two times with ethyl acetate (10 ml each). The combined organic layers dried ($MgSO_4$) and purified by column chromatography (hexane / ethyl acetate = 1:1) to yield 0.19 g (62 %) of a white solid. This compound was dissolved in a mixture of 2 ml of dichlorometane and 2 ml of trifluoracetic acid and stirred for 2.5 h at room temperature. For workup the mixture was concentrated in vacuo, then dichloromethane was added and the mixture was extracted with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to yield 0.12 g of (S)-3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-benzo[b][1,4] diazepin-2-one as a light yellow solid.
MS m/e (%): 206.4 ($M+H^+$, 100).

c) N-((3S)-1,5-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using pentafluoropropylamine instead of 2,2,2-trifluoroethyl-amine in step b) and (S)-3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).
MS m/e (%): 437.5 ($M+H^+$, 100).

Example 48

N-((3S)-5-Cyclopropylmethyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 47 using cyclopropylmethyl bromide instead of methyl iodide in step b).
MS m/e (%): 477.3 ($M+H^+$, 100).

Example 49

N-[5-((3S)-4-Fluoro-benzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 47 using 4-fluorobenzyl bromide instead of methyl iodide in step b).
MS m/e (%): 531.3 ($M+H^+$, 100).

Example 50

N-[(3S)-5-(4-Chloro-benzoyl)-1-cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using N-((3S)-1-cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide instead of 2-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and using 4-chlorobenzoyl chloride instead of benzoyl chloride.

MS m/e (%): 601.5 ($M+H^+$, 100).

Example 51

N-(5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) 5-Cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one

To a solution of 0.5 g (2.4 mmol) of 5H,7H-dibenzo[b,d]azepin-6-one in 6 ml of dimethylformamide at room temperature 0.143 g (3.58 mmol) of sodium hydride was added. After stirring for 1 hour at 60 °C 0.97 g (7.2 mmol) of cyclopropylmethyl bromide were added and stirring was continued at 60 °C overnight. After cooling to room temperature the mixture was was distributed between water and dichloromethane. The combined organic layers were reextracted with sodium sulphate solution and dried ($MgSO_4$). After concentration in vacuo the residue was purified by column chromatography (hexane / ethyl acetate = 1:1) to yield 0.6 g (95 %) of 5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one as a white crystalline compound.

MS m/e (%): 264.1 ($M+H^+$, 100).

b) (RS)-7-Amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one

To a solution of 0.3 g (1.14 mmol) 5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one in 5 ml of toluene 0.285 g (2.44 mmol) of isoamyl nitrite were added and the mixture was cooled to 0 °C. A solution of 3.6 ml (1.83 mmol) of potassium bis(trimethylsilyl)amide (0.5 M in toluene) was added slowly and stirring was continued for 1 hour at this temperature. Sodium hydrogensulphate solution was added and the mixture was extracted two times with ethylacetate.

The combined organic layers were reextracted with water and dried ($MgSO_4$). After evaporation of the solvent 0.2 g of a white foam was obtained, that was dissolved in ethanol (5 ml). Palladium on carbon (90 mg) was added and the mixture was hydrogenated at 2.5 bar H_2 pressure for 32 hours. The catalyst was filtered off and the

solvent was evaporated. The residue was partitioned between dichloromethane (5 ml) and 4N hydrochloric acid (2 ml). The aqueouos solution was separated, set to basic pH with sodium hydroxide and extracted 2 times with ethyl acetate. After drying ($MgSO_4$) and evaporation of the ethyl acetate 0.1 g (52 %) of an off-white solid material was obtained.

MS m/e (%): 279.3 ($M+H^+$, 100).

c) N-(5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using 2,2,3,3,3-pentafluoropropylamine instead of 2,2,2-trifluoroethylamine in step b) and (RS)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 508.4 ($M-H^+$, 100).

Example 52

N-((3S)-1-Acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) 5-Acetyl-3-amino-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

A solution of 0.5 g (1.8 mmol) (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-3-yl)-carbamic acid tert-butyl ester in 1.7 ml of acetic anhydride is stirred for 3 hours at

65 °C. The mixture was put onto water (5 ml) and extracted two times with dichloromethane (10 ml each). The combined organic layers were dried ($MgSO_4$) and evaporated to yield 0.6 g of a light yellow foam. This compound was dissolved in a mixture of 2 ml of dichlorometane and 2 ml of trifluoracetic acid and stirred for 2.5 h at room temperature. For workup the mixture was concentrated in vacuo, then dichloromethane was added and the mixture was extracted with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to yield 0.31 g of (S)-1-acetyl-3-amino-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one as a light yellow solid.

MS m/e (%): 220.4 ($M+H^+$, 100).

b) N-(1-Acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using pentafluoropropylamine instead of 2,2,2-trifluoroethyl-

amine in step b) and (S)-1-acetyl-3-amino-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 449.2 ($M+H^+$, 100).

Example 53

N-((3S)-5-Acetyl-1-cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using N-((3S)-1-cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide instead of 2-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and using acetyl chloride instead of benzoyl chloride.

MS m/e (%): 503.2 ($M-H^+$, 100).

Example 54

N-(3-tert-Butoxy-propyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 3-tert-butoxy-propylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 396.2 ($M-C_4H_9+H^+$, 100); 452.2 ($M+H^+$, 43).

Example 55

2-Methyl-N-((3S)-2-oxo-1-prop-2-ynyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 25 using prop-2-ynyl bromide instead of methyl iodide in step a).

MS m/e (%): 447.5 ($M+H^+$, 100).

Example 56

N-((3S)-5-Cyclopropanecarbonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using cyclopropanecarbonyl chloride instead of benzoylchloride.

MS m/e (%): 491.5 ($M+H^+$, 100).

Example 57

2-Ethyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl ethyl-malonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2,2,3,3,3-pentafluoropropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 484.5 ($M+H^+$, 100).

Example 58

2-Isopropyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl isopropyl-malonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2,2,3,3,3-pentafluoropropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 498.5 ($M+H^+$, 100).

Example 59

N-((3S)-5-Cyclopropylmethyl-2-oxo-1-prop-2-ynyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 47 using prop-2-ynyl bromide instead of methyl iodide in step a) and cyclopropylmethyl bromide instead of methyl iodide in step b).

MS m/e (%): 501.4 ($M+H^+$, 100).

Example 60

N-((3S)-5-Cyclopropanecarbonyl-2-oxo-1-prop-2-ynyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 26 using 2-methyl-N-((3S)-2-oxo-1-prop-2-ynyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide instead of 2-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and using cyclopropanecarbonyl chloride instead of benzoyl chloride.

MS m/e (%): 515.4 ($M+H^+$, 100).

Example 61

N-(5-Methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl malonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2,2,3,3,3-pentafluoropropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 456.5 ($M+H^+$, 100).

Example 62

2,2-Dimethyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using diethyl 2,2-dimethylmalonate instead of diethyl methyl-malonate in step a), (RS)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2,2,3,3,3-pentafluoropropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 484.5 ($M+H^+$, 100).

Example 63

N-(3-Fluoro-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-7-amino-3-fluoro-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one (prepared in the same manner as the 2-fluoroderivative in WO9932453) instead of 2,2,2-trifluoroethylamine in step b) and 2,2,3,3,3-pentafluoropropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 486.4 ($M-H^+$, 100).

Example 64

N-(2-Fluoro-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using (RS)-7-amino-2-fluoro-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one instead of 2,2,2-trifluoroethylamine in step b) and 2,2,3,3,3-pentafluoropropylamine instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).

MS m/e (%): 486.2 ($M-H^+$, 100).

Example 65

2-Methyl-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) 5-(4-Methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one

To a solution of 0.82 g (4 mmol) of 5H,7H-dibenzo[b,d]azepin-6-one in 15 ml of dimethylformamide at room temperature 0.20 g (5 mmol) of sodium hydride 55% in oil was added. After stirring for 30 min at room temperature 0.75 g (5 mmol) of p-methoxybenzyl chloride were added and stirring was continued at room temperature for 2 hours. For workup the mixture was distributed between water and ethyl acetate. The organic layer was re-extracted with 1 N hydrochloric acid and the aqueous layers were washed with ethyl acetate. The combined organic layers were dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (hexane / ethyl acetate = 1:1) to yield 1.175 g (91%) of 5-(4-methoxybenzyl)-5H,7H-dibenzo[b,d]azepin-6-one as a colourless oil.

MS m/e (%): 330.4 ($M+H^+$, 100).

b) (RS)-7-Amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one

To a solution of 1.15 g (3.5 mmol) 5-(4-methoxybenzyl)-5H,7H-dibenzo[b,d]azepin-6-one in 15 ml of toluene 0.836 g (7 mmol) of isoamyl nitrite were added and the mixture was cooled to 0°C. A solution of 21.4 ml (10.5 mmol) of potassium bis(trimethylsilyl)amide (0.5 M in toluene) was added slowly and stirring was continued for 2 hours at this temperature. Sodium hydrogensulphate solution was added and the mixture was extracted two times with ethylacetate.

The combined organic layers were re-extracted with water and dried (MgSO4). After evaporation of the solvent a solid was obtained, that was purified by column chromatography (dichloromethane / methanol = 95:5) to yield 1.03 g (81%) oxime. This compound was dissolved in ethanol (5 ml) and 1.5 ml of 2N hydrochloric acid were added. Palladium on carbon (10%, Degussa 1835, 100 mg) was added and the mixture was hydrogenated at 5 bar H2 pressure for 24 hours at room temperature. The catalyst was filtered off and the solvent was evaporated. The residue was partitioned between dichloromethane (5 ml) and 4N hydrochloric acid (2 ml). The aqueous solution was separated, set to basic pH with sodium hydroxide and extracted 2 times with ethyl acetate. After drying (MgSO4) and evaporation of the ethyl acetate 0.8 g (63%) of a white solid material was obtained.

MS m/e (%): 345.3 ($M+H^+$, 100).

c) (RS)-7-Amino-5H,7H-dibenzo[b,d]azepin-6-one

To a solution of 0.1 g (0.29 mmol) (RS)-7-amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one in 8 ml of dichloromethane at 0°C temperature 0.67 ml (8.7 mmol) of trifluoroacetic acid and 0.25 ml of trifluoromethansulfonic acid (2.9 mmol) were added and the mixture was stirred for 4 hours at room temperature. After concentration of the mixture at 40°C in vacuo an aqueous $NaHCO_3$ solution was added and the mixture extracted two times with ethyl acetate. The combined organic layers were dried ($MgSO_4$). After evaporation of the solvent a light yellow oil was obtained, that was used directly in the next step.

d) (RS)-2-Methyl-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 20 using and 2,2,3,3,3-pentafluoropropylamine instead of 2,2,2-trifluoroethylamine in step b) and (RS)-7-amino-5H,7H-dibenzo[b,d]azepin-6-one instead of (RS)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[d]azepin-2-one in step d).
MS m/e (%): 456.5 ($M+H^+$, 100).

Example 66

N-((S)-6-Oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-7-amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one

Racemic (RS)-7-amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one was separated by chromatography on Chiralpak AD with isopopanol/heptane 1:3 as solvent to yield
(S)-7-amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one, [α] 589 = -146° (1% in $CHCl_3$) and
(R)-7-amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one,
[α] 589 = +148° (1% in $CHCl_3$).

b) (S)-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The methoxybenzyl group of (S)-7-amino-5-(4-methoxy-benzyl)-5H,7H-dibenzo[b,d]azepin-6-one was removed according to the method described in section c) of example 65 and the resulting (S)-7-amino-5H,7H-dibenzo[b,d]azepin-6-one was

coupled with N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid according to the method described in section d) of example 65 to yield (S)-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
[α] 589 = -79.7° (1% in MeOH), MS m/e (%): 442.4 ($M+H^+$, 100).

Example 67

2,2-Dimethyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)- 7-Amino-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in analogy to the description in examples 65 and 66 to yield 2,2-dimethyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
[α] 589 = -38.8° (1% in $CHCl_3$), MS m/e (%): 470.3 ($M+H^+$, 100).

Example 68

(-)-2-Methoxy-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) 2-Methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid methyl ester

2-Methoxy-malonic acid monomethyl ester was coupled with 2,2,3,3,3-pentafluoro-propylamine in analogy to the description in Example 73 to yield 2-methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid methyl ester as colourless oil,
MS m/e (%): 280.0 ($M+H^+$, 100).

b) 2-Methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid

2-Methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid methyl ester was saponified in analogy to the procedure of example 75b to yield 2-methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid as white solid,
MS m/e (%): 266.0 ($M+H^+$, 100).

c) (-)-2-Methoxy-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-Amino-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2-methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in analogy to the description in examples 65 and 66 to yield (-)-2-methoxy-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid,
[α] 589 = -87.6° (1% in MeOH), MS m/e (%): 472.0 ($M+H^+$, 100).

Example 69

(2R)-2-Fluoro-2-methyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (2S)-2-Fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-malonamic acid ethyl ester

In an analogous manner to that described in Example 1 a), the condensation of (S)-7-amino-5H,7H-dibenzo[b,d]azepin-6-one and (2S)- 2-fluoro-2-methyl-malonic acid mono ethyl ester (96.9% e.e.) yielded the title compound as a white solid; MS: m/e =371 $(M+H)^+$.

The (2S)-2-fluoro-2-methyl-malonic acid mono ethyl ester was obtained by stereoselective hydrolysis of the corresponding diester by *Candida cylindracea* hydrolase following the procedure described in J. Org. Chem. 1986, 51, 1003-6.

b) (2S)-2-Fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-malonamic acid

In an analogous manner to that described in Example WC b), the hydrolysis of the (2S)-2-fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-malonamic acid ethyl ester under basic conditions yielded the title compound as white foam; MS: m/e =341 $(M-H)^-$.

c) (2R)-2-Fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 1 c), the condensation of (2S)-2-fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-malonamic acid and 2,2,3,3,3-pentafluoro-propylamine yielded the title compound as a white solid; MS: m/e =474 $(M+H)^+$; optical integrity 96.4% d.e. .

Example 70

(2S)-2-Fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-7-amino-5H,7H-dibenzo[b,d]azepin-6-one and (2S)-2-fluoro-2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid yielded the title compound as a white solid; MS: m/e =474 $(M+H)^+$.

Example 71

N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one

(RS)-7-Amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was separated by HPLC on Chiralpak AD with isopropanol/heptane 1:4 to give (S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one, [α] 589 = -162° (1% in MeOH), and (R)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one, [α] 589 = +163° (1% in MeOH).

Assignment of the absolute configuration by derivatisation with (-)-(S)-naproxen and x-ray analysis of the derivative (S)-N-((R)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-(6-methoxy-naphthalen-2-yl)-propionamide.

A tetrahydrofurane solution of 0.05 g (0.18 mmol) (+)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was reacted overnight at room temperature with 0.04 g (0.18 mmol) (+)-(S)-naproxen, 0.03 g (0.18 mmol) 1-hydroxybenzotriazole, 0.063 µl (0.36 mmol) diisopropylethylamine and 0.04 g (0.18 mmol) N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimid-hydrochlorid. Extraction with 1 N aqueous hydrochloric acid/ dichloromethane and chromatography on silicagel yielded 0.09 g (97%) (S)-N-((R)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-(6-methoxy-naphthalen-2-yl)-propionamide as white solid which was crystallized from ethanol.

mp.: 151-152 °C, MS m/e (%): 491.4 ($M+H^+$, 100).

b) N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

0.11 g (0.38 mmol) (S)-7-Amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one and 0.09 g (0.38 mmol) 3-oxo-3-(2,2,3,3,3-pentafluoro-propylamino)-propanoic acid in 10 ml tetrahydrofuran were reacted with 0.06 g (0.38 mmol) 1-hydroxybenzotriazole hydrate, 0.13 ul (0.76 mmol) diisopropylethylamine and 0.7 g (0.38 mmol) N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimid-hydrochlorid at 0°C for 4 hours. After stirring at room temperature over night the solvent was removed by distillation and the residue purified by chromatography on silicagel with heptane/ ethylacetate (gradient 100-0/0-100) to yield 0.17 g (89%) N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.

[α] 589 = -63.9° (1% in $CHCl_3$), MS m/e (%): 496.3 ($M+H^+$, 100).

Example 72

(R)-N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

and

Example 73

(S)-N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

0.15 g (0.54 mmol) (S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one and 0.13 g (0.54 mmol) 2-methyl-3-oxo-3-(2,2,3,3,3-pentafluoro-propylamino)-propanoic acid in 13 ml tetrahydrofuran were reacted with 0.07 g (0.54mmol) 1-hydroxybenzotriazole hydrate, 0.19 ul (1.08 mmol) diisopropylethylamine and 0.11 g (0.54 mmol) N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimid-hydrochlorid with stirring at room temperature over night. Extraction with 1N aqueous hydrochloric acid/dichloromethane and chromatography on silicagel with ethylacetate gave 0.22 g solid material which was separated by chromatography on Chiralpak AD with heptane/isopropanol 80/20 to yield 0.10 g (R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide [α] 589 = -74.6° (1% in $CHCl_3$), MS m/e (%): 510.3 ($M+H^+$, 100) as white solid and 0.09 g (S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide [α] 589 = -63.8° (1% in $CHCl_3$), MS m/e (%): 510.3 ($M+H^+$, 100) as white solid.

Example 74

N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in analogy to the description in example 73 to yield N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.

[α] 589 = -60.4° (1% in $CHCl_3$), MS m/e (%): 524.3 ($M+H^+$, 100).

Example 75

(R)-N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid ethyl ester

(S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with (S)-2-fluoro-2-methyl-malonic acid monoethyl ester in analogy to the description in example 73 to yield (S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid ethyl ester as colourless oil.
MS m/e (%): 425.4 ($M+H^+$, 100).

b) (S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid

0.22g (0.52 mmol) (S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid ethyl ester in 3 ml tetrahydrofurane was reacted with a solution of 0.02 g (0.52 mmol) lithium hydroxide monohydrate in 1 ml water at room temperature for 2 hours. Evaporation of the tetrahydrofurane, extraction with diethylether, acidification with 0.5 ml 1 N aqueous hydrochloric acid and extraction with ethylacetate gave 0.18 g (S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid as white solid.
MS m/e (%): 397.4 ($M+H^+$, 100).

c) (R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid was coupled with 2,2,3,3,3-pentafluoropropylamine in analogy to the procedure described for RJR 7 to yield (R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.
$[\alpha]$ 589 = -45.7° (1% in $CHCl_3$), MS m/e (%): 528.2 ($M+H^+$, 100).

Example 76

N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methoxy-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2-methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in analogy to the description in example 73 to yield N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methoxy-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.

$[\alpha]$ 589 = -105.5° (1% in MeOH), MS m/e (%): 526.3 ($M+H^+$, 100).

Example 77

N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

(S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid in analogy to the description in example 73 to yield N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide as white solid.

$[\alpha]$ 589 = -57.5° (1% in $CHCl_3$), MS m/e (%): 510.1 ($M+H^+$, 100).

Example 78

N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

a) 2-Methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid ethyl ester

2-Methyl-malonic acid monoethyl ester was coupled with 3,3,4,4,4-pentafluoro-butylamine in analogy to the description in example 73 to yield 2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid ethyl ester as colourless oil.

MS m/e (%): 292.1 ($M+H^+$, 100).

b) 2-Methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid

2-Methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid ethyl ester was saponified in analogy to the procedure of example 75b to yield 2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid as white solid.

MS m/e (%): 262.1 ($M-H^+$, 100).

c) N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

(S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid in analogy to the description in example 73 to yield N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-

dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide (epimers) as white solid.
MS m/e (%): 524.2 ($M+H^+$, 100).

Example 79

N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

(S)-7-amino-5-cyclopropylmethyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2,2-dimethyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid in analogy to the description in example 73 to yield N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide (epimers) as white solid, [α] 589 = -64.9° (1% in $CHCl_3$), MS m/e (%): 538.3 ($M+H^+$, 100).

Example 80

(R)-N-((S)-5-Cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

(S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-malonamic acid was coupled with 3,3,4,4,4-pentafluoro-butylamine in analogy to the procedure described for example 73 to yield (R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide as white solid.
[α] 589 = -56.7° (1% in $CHCl_3$), MS m/e (%): 542.0 ($M+H^+$, 100).

Example 81

N-(5-Isopropyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 65 using and 2-iodopropane instead of p-methoxybenzyl chloride in step a) while step c) was omitted and directly continued with step d).
MS m/e (%): 496.1 ($M-H^+$, 100).

Example 82

N-(5-Isopropyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 65 using and 2-iodopropane instead of p-methoxybenzyl chloride in step a) while step c) was omitted and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid was used instead of 2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in step d).

MS m/e (%): 510.3 ($M-H^+$, 100).

Example 83

N-((S)-5-Methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-Amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in analogy to the description in example 73 to yield N-((S)-5-Methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.

[α] 589 = -52.7° (1% in $CHCl_3$), MS m/e (%): 456.4 ($M+H^+$, 100).

Example 84

2,2-Dimethyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-Amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2,2-dimethyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid in analogy to the description example 73 to yield 2,2-dimethyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.

[α] 589 = -53.8° (1% in $CHCl_3$), MS m/e (%): 484.0 ($M+H^+$, 100).

Example 85

(2R)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (2S)-2-Fluoro-2-methyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid ethyl ester

In an analogous manner to that described in Example 1 a), the condensation of (S)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and (2S)-2-fluoro-2-methyl-malonic acid mono ethyl ester yielded the title compound as a colourless oil;

MS: m/e =385 $(M+H)^+$.

The (2S)-2-fluoro-2-methyl-malonic acid mono ethyl ester (optical integrity 91% e.e.) was obtained by stereoselective hydrolysis of the corresponding diester by *Candida cylindracea* hydrolase following the procedure described in J.Org.Chem. 1986, 51, 1003-6.

b) (2S)-2-Fluoro-2-methyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid

A solution of 75 mg (0.2 mmol) of (2S)-2-fluoro-2-methyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid ethyl ester in 1 ml of tetrahydrofurane was treated for 2 h at room temperature with a solution of 8 mg (0.2 mmol) of lithium hydroxide monohydrate in 0.5 ml of water. For the working-up, the tetrahydrofurane was evaporated under reduced pressure and the remaining aqueous layer was extracted twice with 10 ml of diethylether. The combined organic layers were washed with 5 ml of water and, thereafter, the combined aqueous layers were acidified with 0.025 ml of hydrochloric acid (25%). Thereupon, the aqueous layer was extracted three times with 15 ml of ethyl acetate. The organic layers were washed with 15 ml of a saturated solution of sodium chloride, then combined, dried over sodium sulphate, and evaporated under reduced pressure. There were obtained 69 mg (99% of theory) of the title compound as a white foam; MS: m/e =355 $(M-H)^-$.

c) (2R)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 1 c), the condensation of (2S)-2-fluoro-2-methyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid and 2,2,3,3,3-pentafluoro-propylamine yielded the title compound as a white foam; MS: m/e =488 $(M+H)^+$; optical integrity 94% d.e.

Example 86

(2S)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and (2S)-2-fluoro-2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid yielded the title compound as a white solid; MS: m/e =488 $(M+H)^+$.

The (2S)-2-fluoro-2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid was obtained in a reaction sequence analogous to that leading to (2RS)-methyl-N-(2,2,2-

trifluoro-ethyl)-malonamic acid [Example 20 c)] by replacing (2RS)-methyl-malonic acid monoester by (2S)-2-fluoro-2-methyl-malonic acid monoester.

Example 87

2-Methoxy-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-Amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2-methoxy-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid in analogy to the description in example 73 to yield 2-methoxy-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid.

$[\alpha]$ 589 = -71.8° (1% in $CHCl_3$), MS m/e (%): 486.4 ($M+H^+$, 100).

Example 88

N-((S)-5-Methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

(S)-7-Amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one was coupled with N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid in analogy to the description example 73 to yield N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide as white solid.

$[\alpha]$ 589 = -51.4° (1% in $CHCl_3$), MS m/e (%): 470.1 ($M+H^+$, 100).

Example 89

2,2-Dimethyl-N-[(S)-6-oxo-5-(2,2,2-trifluoro-ethyl)-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) 7-Amino-5-(2,2,2-trifluoro-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one

Racemic (RS)-7-amino-5-(2,2,2-trifluoro-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one was separated by chromatography on Chiralpak AD with isopopanol/heptane 1:3 as solvent to yield

(S)-7-amino-5-(2,2,2-trifluoro-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one

$[\alpha]$ 589 = -29° (1% in $CHCl_3$) and

(R)-7-amino-5-(2,2,2-trifluoro-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one.

$[\alpha]$ 589 = +26° (1% in $CHCl_3$).

b) (S)-2,2-Dimethyl-N-[(S)-6-oxo-5-(2,2,2-trifluoro-ethyl)-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

(S)-7-amino-5-(2,2,2-trifluoro-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one was coupled with 2,2-dimethyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid in analogy to the description example 73 to yield (S)-2,2-dimethyl-N-[(S)-6-oxo-5-(2,2,2-trifluoro-ethyl)-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide as white solid,

[α] 589 = -13.9° (1.1% in $CHCl_3$), MS m/e (%): 550.5 ($M-H^+$, 100).

Example 90

(2RS)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and (2RS)-2-fluoro-2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid yielded the title compound as a white solid; MS: m/e =502 $(M+H)^+$.

The (2RS)-2-fluoro-2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid was obtained in a reaction sequence analogous to that leading to (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] by replacing (2RS)-methyl-malonic acid monoester by (2RS)-2-fluoro-2-methyl-malonic acid monoester and by replacing 2,2,2-trifluoro-ethylamine by 3,3,4,4,4-pentafluoro-butylamine [J.Fluorine Chemistry 55(1), 85 (1991)].

Examples 91 and 92

(2R)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide and
(2S)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

The separation of 0.2 g of the two isomers of (2RS)-2-fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide (Example WG) was performed on a preparative chiral HPLC column (CHIRALPAK® AD, pressure: flow : 35 ml/min) using a 4:1 mixture of n-heptane and isopropanol as the eluent. There were obtained 23 mg [11% of theory, optical integrity >99.5% d.e., MS: m/e =502 $(M+H)^+$] of the first eluting isomer (2R)-2-Fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide and 22 mg [11% of theory, optical integrity >99.5% d.e., MS: m/e =502 $(M+H)^+$] of the later eluting isomer (2S)-2-fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-

butyl)-malonamide, each as a yellowish foam.

Example 93

(2RS)-2-Methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and (2RS)-2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid yielded the title compound as a white solid;
MS: m/e =484 $(M+H)^+$.

The (2RS)-2-methyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid was obtained in a reaction sequence analogous to that leading to (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] by replacing 2,2,2-trifluoro-ethylamine by 3,3,4,4,4-pentafluoro-butylamine [J.Fluorine Chemistry 55(1), 85 (1991)].

Example 94

2,2-Dimethyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2,2-dimethyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid yielded the title compound as a white solid;
MS: m/e =498 $(M+H)^+$.

The 2,2-dimethyl-N-(3,3,4,4,4-pentafluoro-butyl)-malonamic acid was obtained in a reaction sequence analogous to that leading to (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] by replacing (2RS)-methyl-malonic acid monoester by 2,2-dimethyl-malonic acid monoester and by replacing 2,2,2-trifluoro-ethylamine by 3,3,4,4,4-pentafluoro-butylamine.

Example 95

(2RS)-Methyl-N-((3S)-1-methyl-2-oxo-5-trifluoromethanesulfonyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the reaction of (2RS)-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide [Example 25] with trifluoromethanesulfonic acid anhydride yielded the title compound as a white foam;
MS: m/e =555 $(M+H)^+$.

Example 96

N-((3S)-5-Formyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the acylation of (2RS)-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with acetic acid anhydride and formic acid yielded the title compound as a light yellow foam; MS: m/e =451 $(M+H)^+$.

Example 97

N-[(3S)-5-(2-Fluoro-acetyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the acylation of (2RS)-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with fluoroacetyl chloride yielded the title compound as a light yellow foam;

MS: m/e =483 $(M+H)^+$.

Example 98

(2RS)-Methyl-N-[(3S)-1-methyl-2-oxo-5-(2,2,2-trifluoro-acetyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the acylation of (2RS)-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with trifluoroacetic anhydride yielded the title compound as a white foam; MS: m/e =519 $(M+H)^+$.

Example 99

N-[(3S)-5-(2-Methoxy-acetyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the acylation of (2RS)-methyl-N-((3S)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with methoxyacetyl chloride yielded the title compound as a light yellow foam;

MS: m/e =495 $(M+H)^+$.

Example 100

N-[(S)-5-Methanesulfonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-3-Amino-1-(2,2,2-trifluoro-ethyl)-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride

In an analogous manner to that described in Example 25 a), the alkylation of (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester by 2,2,2-trifluoroethyl triflate followed by the acid catalysed cleavage of the tert-butoxycarbonyl group yielded the title compound as a yellow solid.

b) (2RS)-Methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-3-amino-1-(2,2,2-trifluoro-ethyl)-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white foam;

MS: m/e =491 $(M+H)^+$.

c) N-[(S)-5-Methanesulfonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the reaction of (2RS)-methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with methanesulfonic acid anhydride yielded the title compound as an off-white amorphous material;

MS: m/e =567 $(M-H)^-$.

Example 101

(2RS)-Methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-5-trifluoromethanesulfonyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the reaction of (2RS)-methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with trifluoromethanesulfonic acid

anhydride yielded the title compound as an white amorphous material;
MS: m/e =623 $(M+H)^+$.

Example 102

(2RS)-Methyl-N-[(S)-2-oxo-5-(2,2,2-trifluoro-acetyl)-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 26, the reaction of (2RS)-methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide with trifluoroacetic acid anhydride yielded the title compound as a light yellow solid;
MS: m/e =587 $(M+H)^+$.

Example 103

(S)-N-(5-Methanesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-(1-Methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester

The alkylation of the (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-3-yl)-carbamic acid tert-butyl ester with methyliodide, as described in Example 25 a), yielded, after chromatography on silica gel using a 3:1-mixture of n-heptane and ethyl acetate as the eluent, the (S)-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester as a light yellow foam;
MS: m/e =292 $(M+H)^+$.

b) [(S)-5-Methanesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester

A mixture of 623 mg (3.4 mmol) of methanesulfonic acid anhydride and 0.12 ml (0.7 mmol) of N-ethyl-diisopropylamine was cooled to 0°C and treated with a solution of 200 mg (0.7 mmol) of (S)-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in 2 ml of dichloromethane. The reaction mixture was left to warm to room temperature and stirred during 18h. For the working-up, the reaction mixture was cooled to 0°C and treated with a saturated solution of sodium carbonate. The organic layer was separated, washed with a saturated solution of ammonium hydrochloride and water, finally dried over sodium sulphate and evaporated.

For purification, the crude material was chromatographed on silical gel using a 96:4-mixture of dichloromethane and ethyl acetate as the eluent. There were obtained 100 mg (40% of theory) of the ((S)-5-methanesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester as a white foam;
MS: m/e =370 $(M+H)^+$.

c) (S)-3-Amino-5-methanesulfonyl-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride

A solution of 100 mg (0.27 mmol) of ((S)-5-methanesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in 5 ml of dioxane was treated with 0.22 ml of hydrochloric acid and heated in the sealed flask at 50°C for 1 hour. For the working-up, the solvent was evaporated under reduced pressure and the residue submitted to a azeotropic distillation with toluene. After drying under reduced pressure, the (S)-3-amino-5-methanesulfonyl-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride was obtained in quantitative yield as a light yellow solid; MS: m/e =270 $(M+H)^+$.

d) (S)-N-(5-methanesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-3-amino-5-methanesulfonyl-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white foam;
MS: m/e =501 $(M+H)^+$.

Example 104

N-[(S)-5-(2,2-Dimethyl-propionyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) [(3S)-5-(2,2-Dimethyl-propionyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester

In an analogous manner to that described in Example 103b), the acylation of (S)-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester with pivaloyl chloride yielded the title compound as a white solid; MS: m/e =376 $(M+H)^+$.

b) (S)-3-Amino-5-(2,2-dimethyl-propionyl)-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride

In an analogous manner to that described in Example 103c), the cleavage of the tert-butoxy-carbonyl group of the [(3S)-5-(2,2-dimethyl-propionyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester yielded the title compound as a white solid;

MS: m/e =276 $(M+H)^+$.

c) N-[(S)-5-(2,2-Dimethyl-propionyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-3-amino-5-(2,2-dimethyl-propionyl)-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid yielded the title compound as a white foam;

MS: m/e =493 $(M+H)^+$.

The N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid was obtained in a reaction sequence analogous to that leading to (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] by replacing (2RS)-methyl-malonic acid monoester by malonic acid monoester.

Example 105

N-[(3S)-5-(2,2-Dimethyl-propionyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-3-amino-5-(2,2-dimethyl-propionyl)-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] yielded the title compound as a white foam; MS: m/e =507 $(M+H)^+$.

Example 106

5-Methyl-4-oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl estermalonamide

a) (S)-3-tert-Butoxycarbonylamino-5-methyl-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester

A solution of 350 mg (1.2 mmol) of (S)-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester [Example 103a] in 10 ml of N,N-dimethylformamide was treated successively with about 1 g of solid carbon dioxide, 237 mg (1.7 mmol) of bromomethyl-cyclopropane, and 626 mg (1.9 mmol) of cesium carbonate. The reaction mixture was stirred in a sealed flask at 80°C during the weekend. For the working-up, the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 30 ml of ethyl acetate and 10 ml of water. The organic layer was separated, dried over sodium sulphate and evaporated under reduced pressure. For the purification, the crude compound was chromatographed on silica gel using a 3:1-mixture of heptane and ethyl acetate as the eluent. There were obtained 410 mg (87% of theory) of the (S)-3-tert-butoxycarbonylamino-5-methyl-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester as a white gum; MS: m/e =579 $(M+OAc)^+$.

b) (S)-3-Amino-5-methyl-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester hydrochloride

In an analogous manner to that described in Example 103c), the cleavage of the tert-butoxy-carbonyl group of the (S)-3-tert-butoxycarbonylamino-5-methyl-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester yielded the title compound as a light yellow foam.

c) 5-Methyl-4-oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl estermalonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-3-amino-5-methyl-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester hydrochloride and (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] yielded the title compound as a white solid; MS: m/e =579 $(M+OAc)^+$.

Example 107

N-[(S)-5-Acetyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) [(S)-2-Oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester

In an analogous manner to that described in Example 25 a), the alkylation of the (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-3-yl)-carbamic acid tert-butyl ester with 2,2,2-trifluoroethyl triflate, yielded, after chromatography on silica gel using a 98:2-mixture of dichloromethane and methanol as the eluent, the title compound as a white solid; MS: m/e =360 $(M+H)^+$.

b) [(S)-5-Acetyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester

In an analogous manner to that described in Example 103b, the acylation of the [(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester with acetic acid anhydride yielded the title compound as a white solid;

MS: m/e =419 $(M+NH_4)^+$.

c) (S)-5-Acetyl-3-amino-1-(2,2,2-trifluoro-ethyl)-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride

In an analogous manner to that described in Example 103c, the cleavage of the tert-butoxycarbonyl group of the [(S)-5-acetyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester by hydrochloric acid yielded the title compound as a light yellow solid;

MS: m/e =302 $(M+H)^+$.

d) N-[(S)-5-Acetyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-5-acetyl-3-amino-1-(2,2,2-trifluoro-ethyl)-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid; MS: m/e =533 $(M+H)^+$.

Example 108

N-[(S)-5-Cyclopropanecarbonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) [(S)-5-Cyclopropanecarbonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester

In an analogous manner to that described in Example 103b, the acylation of the [(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester [Example 107b] with cyclopropane-carbonyl chloride yielded the title compound as a yellow solid; MS: m/e =428 $(M+H)^+$.

b) (S)-3-Amino-5-cyclopropanecarbonyl-1-(2,2,2-trifluoro-ethyl)-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride

In an analogous manner to that described in Example 103c, the cleavage of the tert-butoxycarbonyl group of the [(S)-5-cyclopropanecarbonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester by hydrochloric acid yielded the title compound as a yellow solid; MS: m/e =328 $(M+H)^+$.

c) N-[(S)-5-Cyclopropanecarbonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-5-acetyl-3-amino-1-(2,2,2-trifluoro-ethyl)-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid;
MS: m/e =559 $(M+H)^+$.

Example 109

4-Oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester

a) (S)-3-tert-Butoxycarbonylamino-4-oxo-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester

In an analogous manner to that described in Example 106a, the reaction of [(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester [Example 107b] with carbon dioxide and bromomethyl-cyclopropane in presence of cesium carbonate yielded the title compound as a white foam; MS: m/e =475 $(M+NH_4)^+$.

b) (S)-3-Amino-4-oxo-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester hydrochloride

In an analogous manner to that described in Example 103c, the cleavage of the tert-butoxycarbonyl group of the (S)-3-tert-butoxycarbonylamino-4-oxo-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester by hydrochloric acid yielded the title compound as a yellowish foam which was engaged in the next step without further purification and characterisation.

c) 4-Oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester

In an analogous manner to that described in Example 20 d), the condensation of the (S)-3-Amino-4-oxo-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester hydrochloride and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a light yellow solid; MS: m/e =647 $(M+OAc)^+$.

Example 110

(2RS)-N-[(S)-5-Acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) [(S)-5-Acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester

In an analogous manner to that described in Example 103b, the acylation of (S)-(1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester [Example 103a) with acetic acid anhydride yielded the title compound as a white solid;
MS: m/e =334 $(M+H)^+$.

b) (S)-5-Acetyl-3-amino-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride

In an analogous manner to that described in Example 103c, the cleavage of the tert-butoxy-carbonyl group of the [(S)-5-acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester yielded the title compound as a light yellow solid;
MS: m/e =234 $(M+H)^+$.

c) (2RS)-N-[(S)-5-Acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d), the condensation of (S)-5-acetyl-3-amino-1-methyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one hydrochloride and 2-fluoro-2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid yielded the title compound as a white foam;

MS: m/e =483 $(M+H)^+$.

The (2RS)-2-fluoro-2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid was obtained in a reaction sequence analogous to that leading to (2RS)-methyl-N-(2,2,2-trifluoro-ethyl)-malonamic acid [Example 20 c)] by replacing (2RS)-methyl-malonic acid monoester by (2RS)-2-fluoro-2-methyl-malonic acid monoester.

Example 111

N-[(S)-5-Acetyl-1-ethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-1-Acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester

In an analogous manner to that described in Example 52 a), the acetylation of (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4] diazepin-3-yl)-carbamic acid tert-butyl ester with acetic acid anhydride yielded the title compound as a grey solid; MS: m/e =320 $(M+H)^+$.

b) (S)-5-Acetyl-3-amino-1-ethyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

In an analogous manner to that described in Example 25 a), the alkylation of the (S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester with ethyl iodide, followed by the acid catalysed cleavage of the tert-butoxycarbonyl group yielded the title compound as a yellowish waxy solid [MS: m/e =248 $(M+H)^+$] which was engaged in the next step without further purification.

c) N-[(S)-5-Acetyl-1-ethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-ethyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid yielded the title compound as a white solid; MS: m/e =493 $(M+H)^+$.

Example 112

N-((S)-5-Acetyl-1-ethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-ethyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid;
MS: m/e =479 $(M+H)^+$.

Example 113

N-[(S)-5-Acetyl-1-isopropyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-5-Acetyl-3-amino-1-isopropyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

In an analogous manner to that described in Example 25 a), the alkylation of the (S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester with 2-iodo-propane, followed by the acid catalysed cleavage of the tert-butoxycarbonyl group yielded the title compound as a yellowish waxy solid [MS: m/e =262 $(M+H)^+$] which was engaged in the next step without further purification.

b) N-[(S)-5-Acetyl-1-isopropyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-isopropyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid; MS: m/e =493 $(M+H)^+$.

Example 114

N-[(S)-5-Acetyl-1-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-5-Acetyl-3-amino-1-benzyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

In an analogous manner to that described in Example 25 a), the alkylation of the (S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester with benzylbromide, followed by the acid catalysed cleavage of the tert-butoxycarbonyl group yielded the title compound as a light yellow solid [MS: m/e =310 $(M+H)^+$] which was engaged in the next step without further

purification.

b) N-[(S)-5-Acetyl-1-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-benzyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid; MS: m/e =553 $(M-H)^-$.

Example 115

N-((S)-5-Acetyl-1-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-benzyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid; MS: m/e =539 $(M-H)^-$.

Example 116

N-[(S)-5-Acetyl-1-(4-fluoro-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) (S)-5-Acetyl-3-amino-1-(4-fluoro-benzyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one

In an analogous manner to that described in Example 25 a), the alkylation of the (S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester with 4-fluoro-benzylbromide, followed by the acid catalysed cleavage of the tert-butoxycarbonyl group yielded the title compound as a white foam [MS: m/e =328 $(M+H)^+$] which was engaged in the next step without further purification.

b) N-[(S)-5-Acetyl-1-(4-fluoro-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-(4-fluoro-benzyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25

b)] yielded the title compound as a white solid;
MS: m/e =571 $(M-H)^-$.

Example 117

N-((S)-5-Acetyl-1-(4-fluoro-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

In an analogous manner to that described in Example 20 d) and 27, the condensation of (S)-5-acetyl-3-amino-1-(4-fluoro-benzyl-1,3,4,5-tetrahydro-benzo[b][1,4]diazepin-2-one and (2RS)-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid [see Example 25 b)] yielded the title compound as a white solid;
MS: m/e =557 $(M-H)^-$.

Examples 118 and 119

N-[(S)-1-Acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2R or 2S)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and
N-[(S)-1-Acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2S or 2R)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The separation of 0.2 g of the two isomers of N-[(S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide (Example 52) was performed on a preparative chiral HPLC column (CHIRALPAK® AD, pressure: 15 bar, flow : 35 ml/min) using a 4:1 mixture of n-heptane and isopropanol as the eluent. There were obtained 77 mg [35% of theory, optical integrity >99.5% d.e., MS: m/e =449 $(M-H)^-$] of the first eluting isomer (+)-N-[(S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2R or 2S)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and 77 mg [35% of theory, optical integrity 99.4% d.e., MS: m/e =449 $(M-H)^-$] of the later eluting isomer (-)-N-[(S)-1-acetyl-4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2S or 2R)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide, each as a white solid.

Examples 120 and 121

N-[(S)-5-Acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2R or 2S)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and
N-[(S)-5-Acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2S or 2R)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

The separation of 0.6 g of the two isomers of N-[(S)-5-acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide (Example 40) was performed on a preparative chiral HPLC column (CHIRALPAK® AD, pressure: 15 bar, flow : 35 ml/min) using a 4:1 mixture of n-heptane and isopropanol as the eluent. There were obtained 220 mg (36.7% of theory, optical integrity >99.5% d.e.) of the first eluting isomer (+)-N-[(S)-5-acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2R or 2S)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide and 247 mg (41.2% of theory, optical integrity >99.5% d.e.) of the later eluting isomer (-)-N-[(S)-5-acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2S or 2R)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide, each as a white solid.

In analogy to the described examples the following compounds have been prepared:

Example 122

2,2-Dimethyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,

MS: m/e (%) = 484.5 $(M+H)^+$, 100.

Example 123

(R)-2-Fluoro-2-methyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide

Example 124

(3,3,4,4,4-pentafluoro-butyl)-carbamic acid (S)-1-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-ylcarbamoyl)-ethyl ester

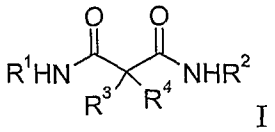
MS: m/e (%) = 488.5 $(M+H)^+$, 100.

Example 125

(R)-2-Fluoro-2-methyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,3-trifluoro-propyl)-malonamide

The title compound [MS m/e (%): 452.3 ($M+H^+$, 100)]was prepared in analogy to example 14 from 3,3,3-trifluoropropylamine and (2S)-2-fluoro-2-methyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid.

Table 2



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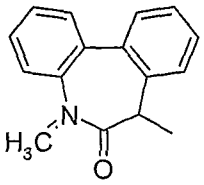
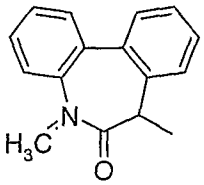
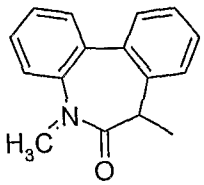
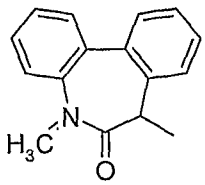
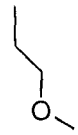
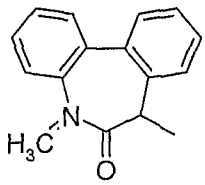
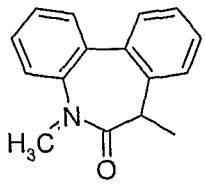
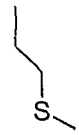
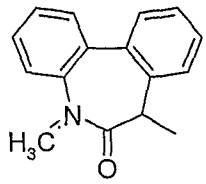
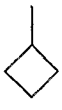
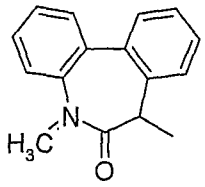
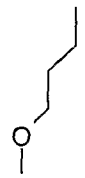
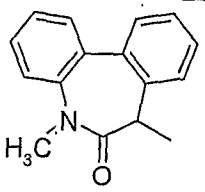
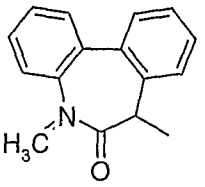
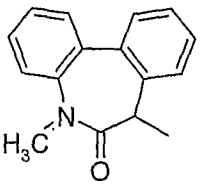
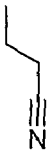
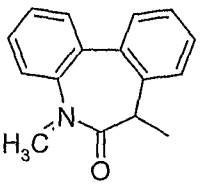
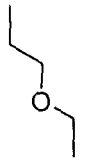
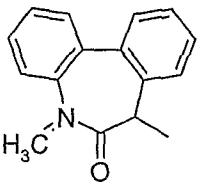
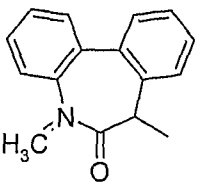
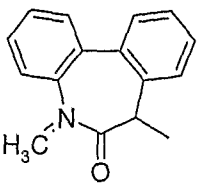
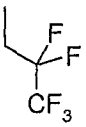
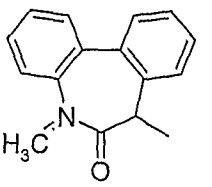
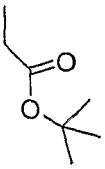
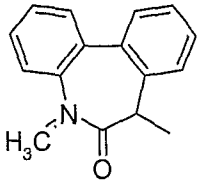
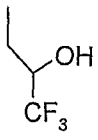
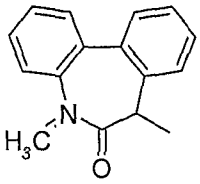
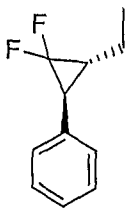
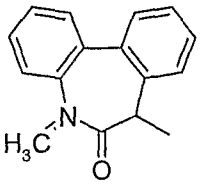
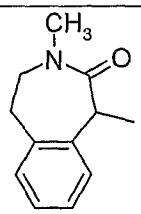
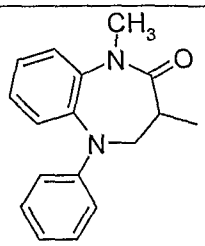
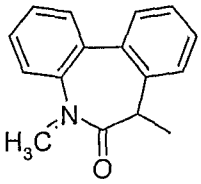
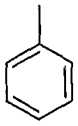
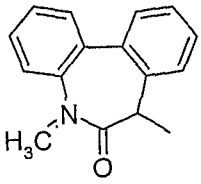
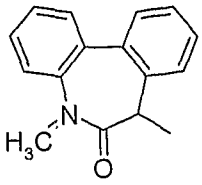
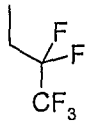
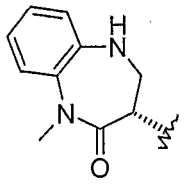
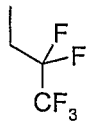
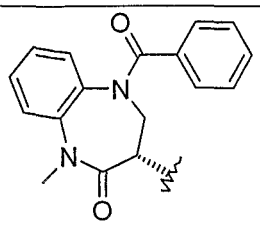
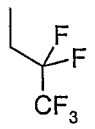
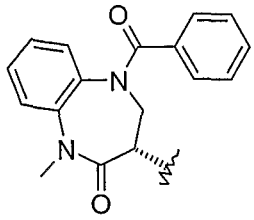
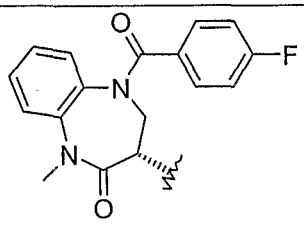
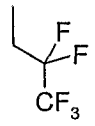
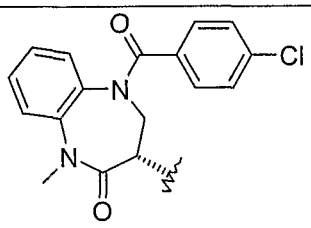
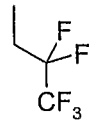
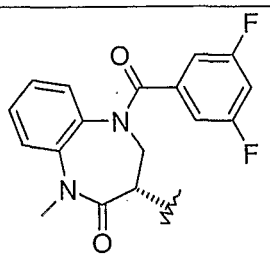
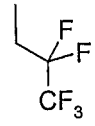
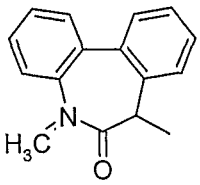
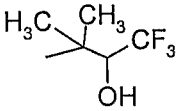
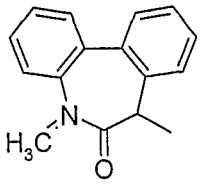
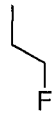
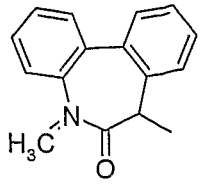
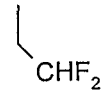
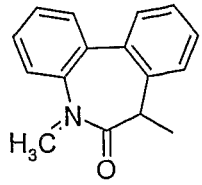
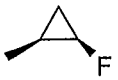
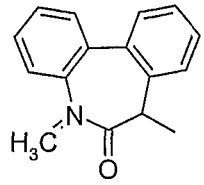
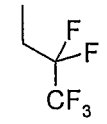
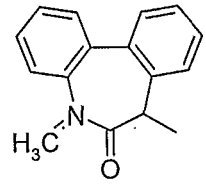
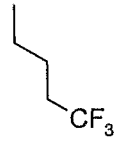
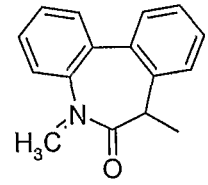
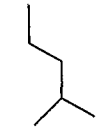
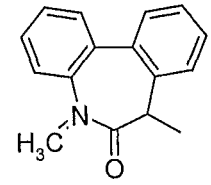
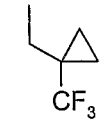
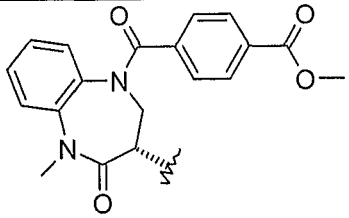
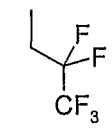
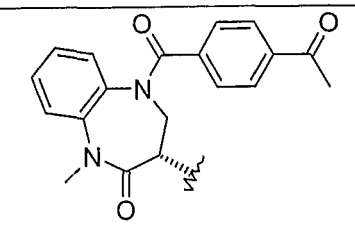
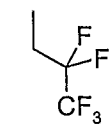
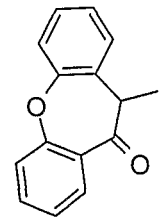
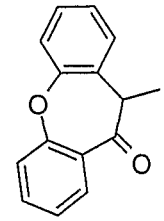
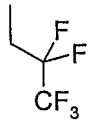
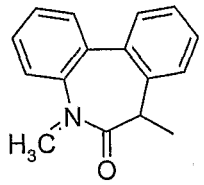
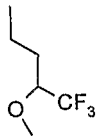
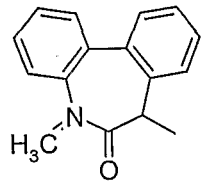
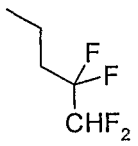
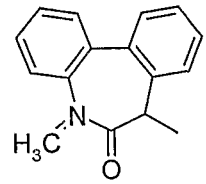
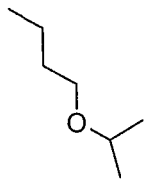
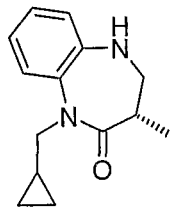
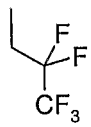
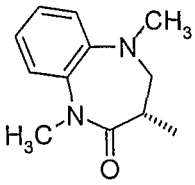
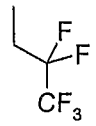
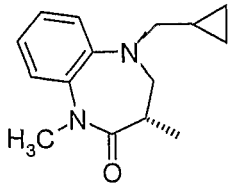
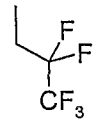
R^1	R^2	R^3	R^4	Example
		CH_3	H	1
	CH_2CH_3	CH_3	H	2
		CH_3	H	3
		CH_3	H	4
		CH_3	H	5
		CH_3	H	6
		CH_3	H	7

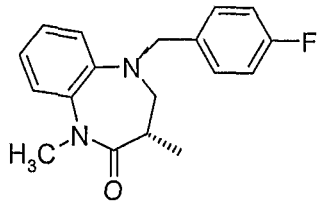
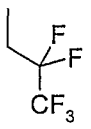
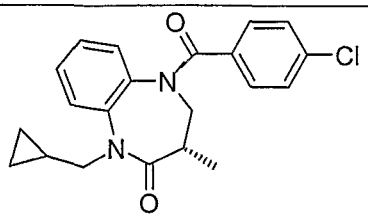
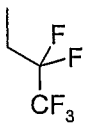
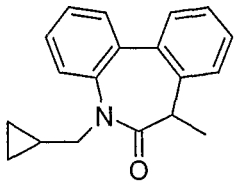
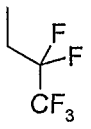
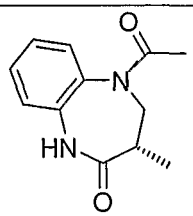
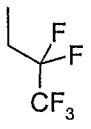
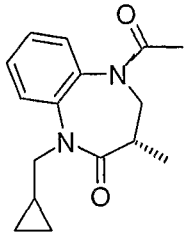
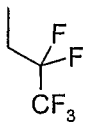
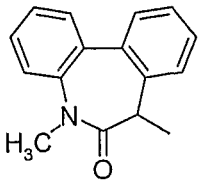
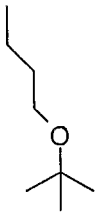
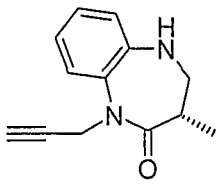
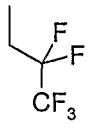
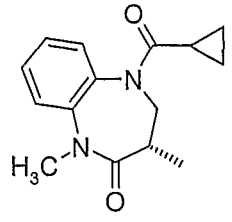
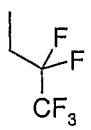
		CH_3	H	8
		CH_3	H	9
		CH_3	H	10
		CH_3	H	11
		CH_3	H	12
		CH_3	H	13
		CH_3	H	14
		CH_3	H	15
		CH_3	H	16

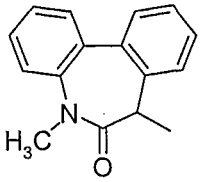
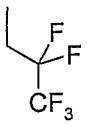
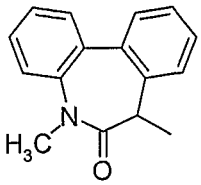
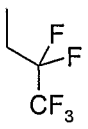
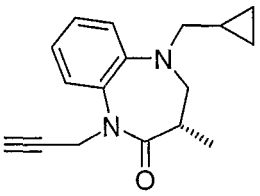
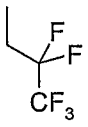
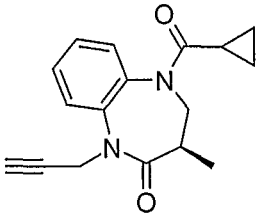
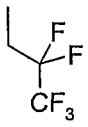
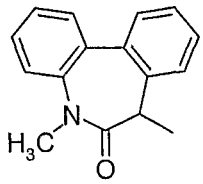
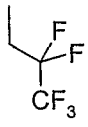
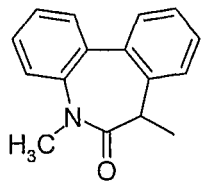
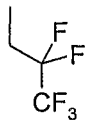
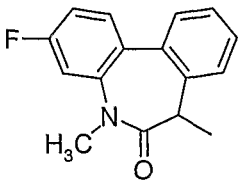
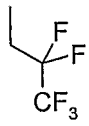
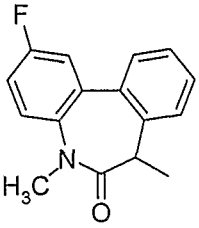
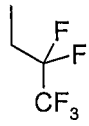
		CH_3	H	17
		CH_3	H	18
		CH_3	H	19
		CH_3	H	20
		CH_3	H	21
			H	22
		CH_3	F	23
		CH_3	F	24

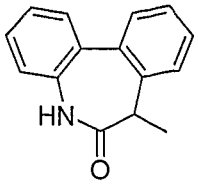
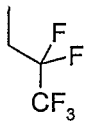
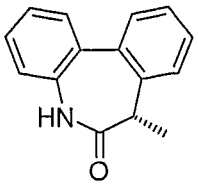
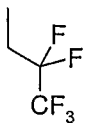
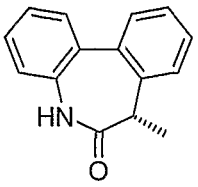
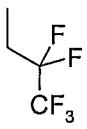
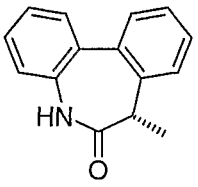
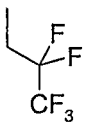
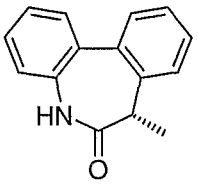
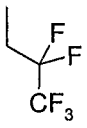
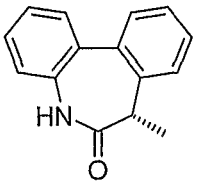
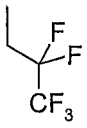
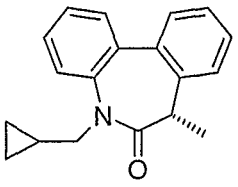
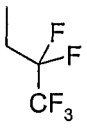
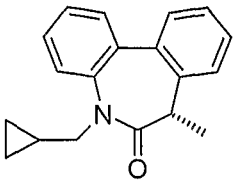
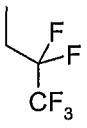
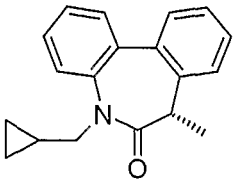
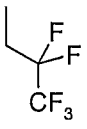
		CH_3	H	25
		CH_3	H	26
		CH_3	CH_3	27
		CH_3	H	28
		CH_3	H	29
		CH_3	H	30
		CH_3	CH_3	31
		CH_3	F	32

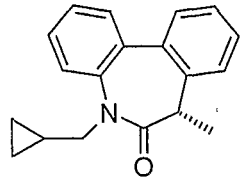
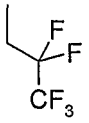
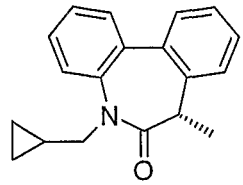
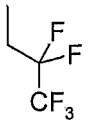
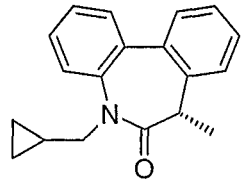
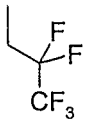
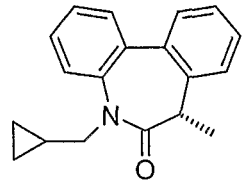
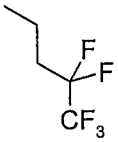
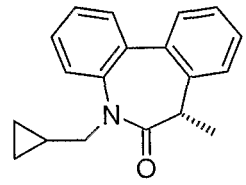
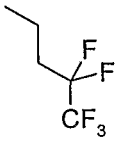
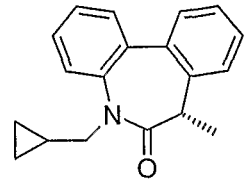
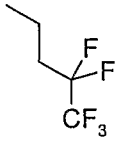
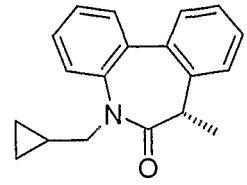
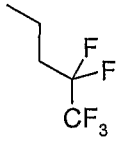
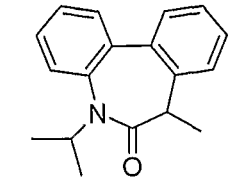
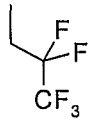
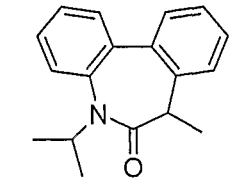
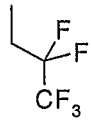
		CH_3	F	33
		CH_3	F	34
		CH_3	F	35
		CH_3	F	36
		CH_3	F	37
		CH_3	F	38
		CH_3	H	39
		CH_3	H	40

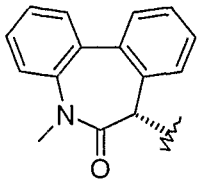
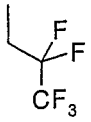
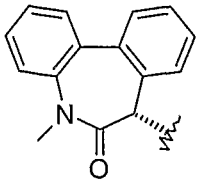
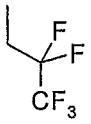
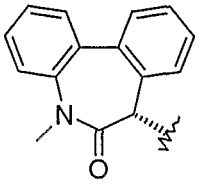
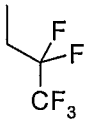
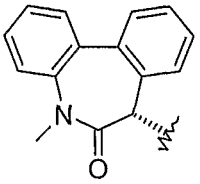
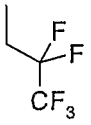
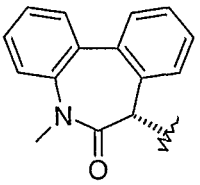
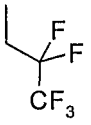
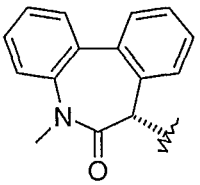
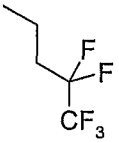
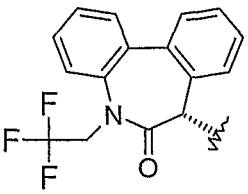
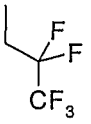
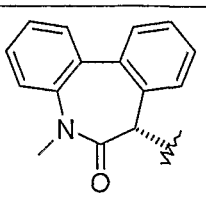
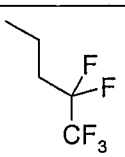
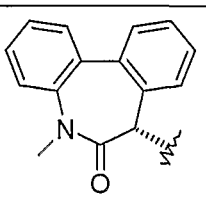
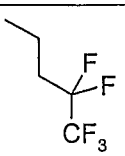
		CH_3	H	41
		CH_3	H	42
		CH_3	H	43
		CH_3	H	44
		CH_3	H	45
		CH_3	H	46
		CH_3	H	47
		CH_3	H	48

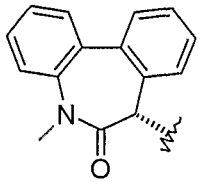
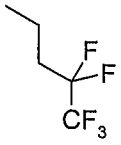
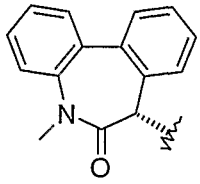
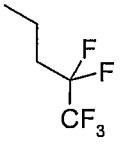
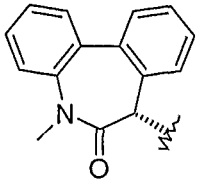
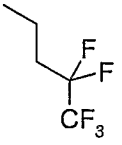
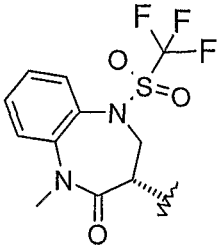
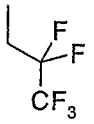
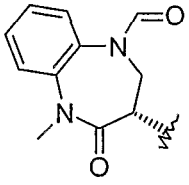
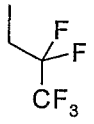
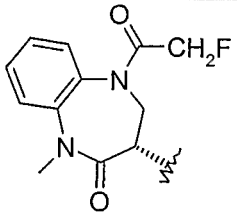
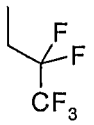
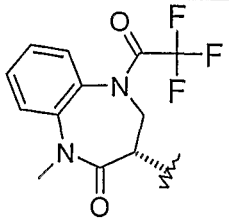
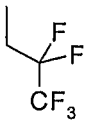
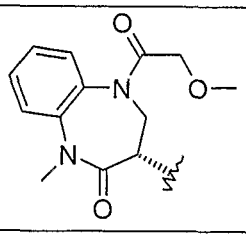
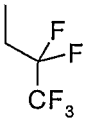
		CH_3	H	49
		CH_3	H	50
		CH_3	H	51
		CH_3	H	52
		CH_3	H	53
		CH_3	H	54
		CH_3	H	55
		CH_3	H	56

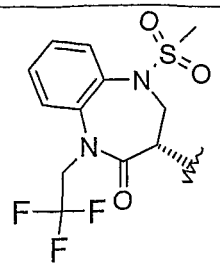
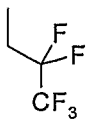
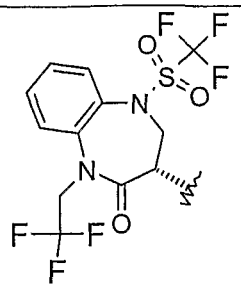
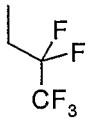
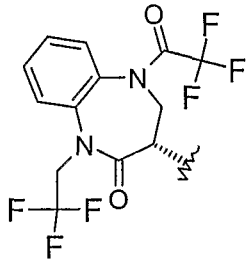
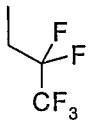
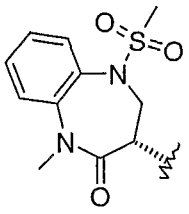
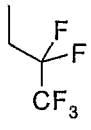
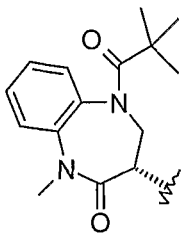
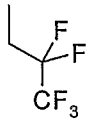
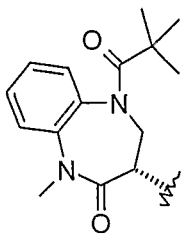
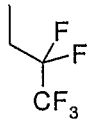
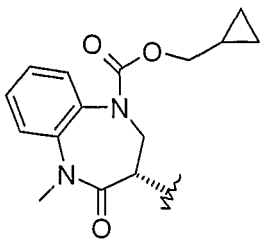
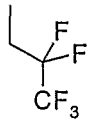
		CH_2CH_3	H	57
		$CH(CH_3)_2$	H	58
		CH_3	H	59
		CH_3	H	60
		H	H	61
		CH_3	CH_3	62
		CH_3	H	63
		CH_3	H	64

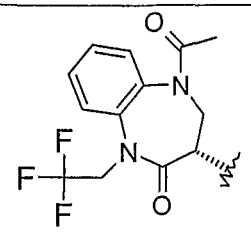
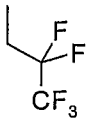
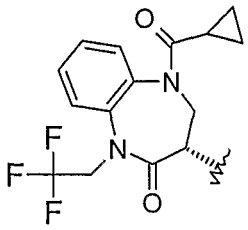
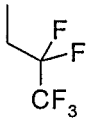
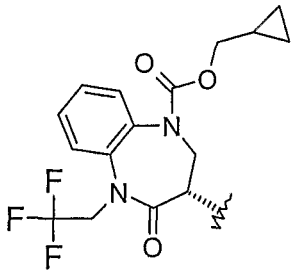
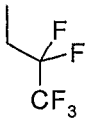
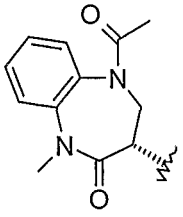
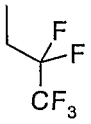
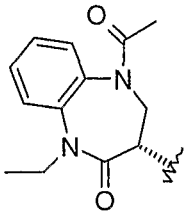
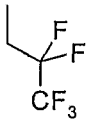
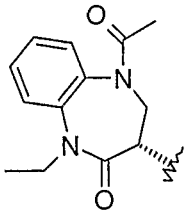
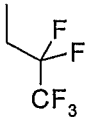
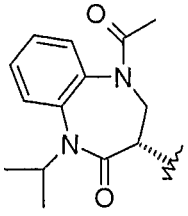
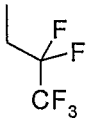
		CH_3	H	65
		H	H	66
		CH_3	CH_3	67
		OCH_3	H	68
				69
				70
		H	H	71
			H	72
			H	73

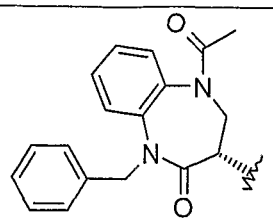
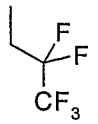
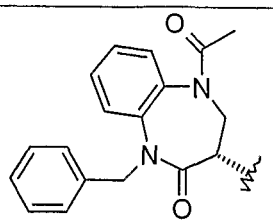
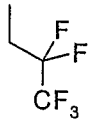
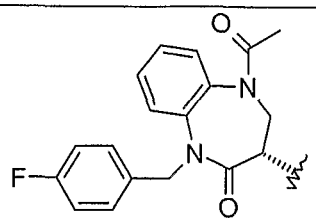
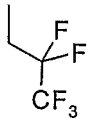
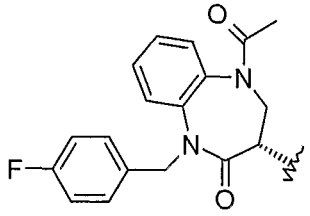
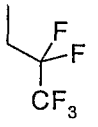
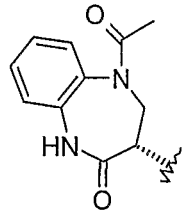
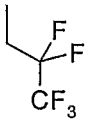
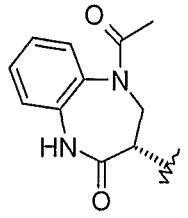
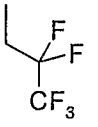
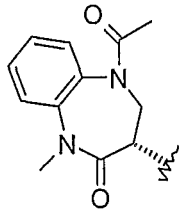
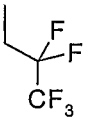
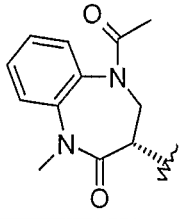
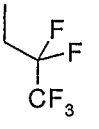
		CH_3	CH_3	74
		—F	···CH_3	75
		OCH_3	H	76
		H	H	77
		CH_3	H	78
		CH_3	CH_3	79
		—F	···CH_3	80
		H	CH_3	81
		CH_3	CH_3	82

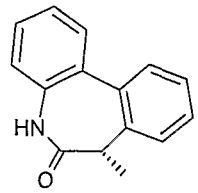
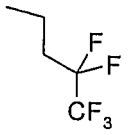
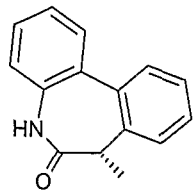
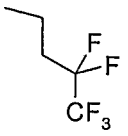
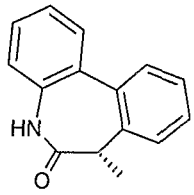
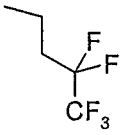
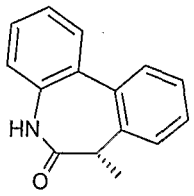
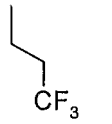
		H	H	83
		CH_3	CH_3	84
		—F	···CH_3	85
		···F	—CH_3	86
		OCH_3	H	87
		H	H	88
		CH_3	CH_3	89
		F	CH_3	90
		—F	···CH_3	91

		···F	—CH_3	92
		CH_3	H	93
		CH_3	CH_3	94
		CH_3	H	95
		CH_3	H	96
		CH_3	H	97
		CH_3	H	98
		CH_3	H	99

		CH_3	H	100
		CH_3	H	101
		CH_3	H	102
		CH_3	H	103
		H	H	104
		CH_3	H	105
		CH_3	H	106

		CH_3	H	107
		CH_3	H	108
		CH_3	H	109
		F	CH_3	110
		CH_3	CH_3	111
		CH_3	H	112
		CH_3	H	113

		CH_3	CH_3	114
		CH_3	H	115
		CH_3	CH_3	116
		CH_3	H	117
		$-CH_3$	H	118
		$\cdots CH_3$	H	119
		$-CH_3$	H	120
		$\cdots CH_3$	H	121

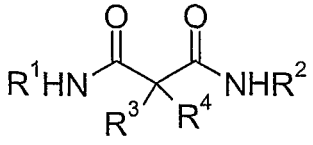
		CH_3	CH_3	122
		''' F	◄ CH_3	123
		''' CH_3	◄ F	124
		◄ F	''' CH_3	125

5

10

Claims

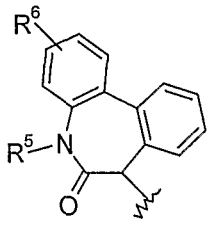
1. Compounds of the general formula



I

wherein

R^1 is one of the following groups



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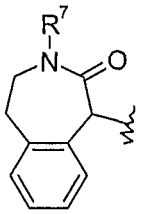

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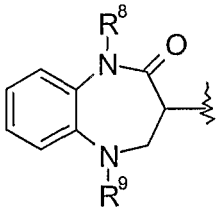
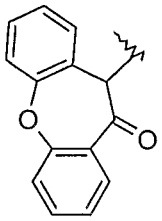


c),



d)

R^2 is lower alkyl, lower alkinyl, $-(CH_2)_n$-O-lower alkyl, $-(CH_2)_n$-S-lower alkyl, $-(CH_2)_n$-CN, $-(CR'R'')_n-CF_3$, $-(CR'R'')_n-CHF_2$, $-(CR'R'')_n-CH_2F$, $-(CH_2)_n$-C(O)O-lower alkyl, $-(CH_2)_n$-halogen, or is $-(CH_2)_n$-cycloalkyl, optionally substituted by one or more substituents, selected from the group consisting of phenyl, halogen or CF_3;

R',R'' are independently from n and from each other hydrogen, lower alkyl, lower alkoxy, halogen or hydroxy;

R^3, R^4 are independently from each other hydrogen, lower alkyl, lower alkoxy, phenyl or halogen;

R^5 is hydrogen, lower alkyl, $-(CH_2)_n-CF_3$ or $-(CH_2)_n$-cycloalkyl;

R^6 is hydrogen or halogen;

R^7 is hydrogen or lower alkyl;

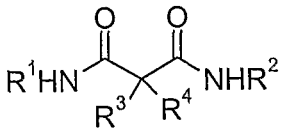
R^8 is hydrogen, lower alkyl, lower alkinyl, $-(CH_2)_n-CF_3$, $-(CH_2)_n$-cycloalkyl or $-(CH_2)_n$-phenyl, optionally substituted by halogen;

R^9 is hydrogen, lower alkyl, -C(O)H, -C(O)-lower alkyl, $-C(O)-CF_3$, $-C(O)-CH_2F$, $-C(O)-CHF_2$, -C(O)-cycloalkyl, $-C(O)-(CH_2)_n$-O-lower alkyl, $-C(O)O-(CH_2)_n$-cycloalkyl, -C(O)-phenyl, optionally substituted by one or more substituents selected from the group consisting of halogen or -C(O)O-lower alkyl, or is $-S(O)_2$-lower alkyl, $-S(O)_2-CF_3$, $-(CH_2)_n$-cycloalkyl or is $-(CH_2)_n$- phenyl, optionally substituted by halogen;

n is 0, 1, 2, 3 or 4;

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

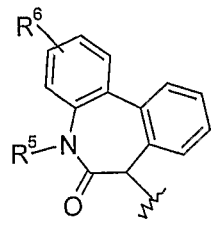
2. Compounds of the general formula



I-1

wherein

R^1 is one of the following groups



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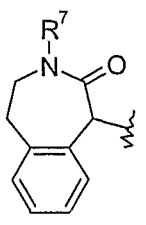

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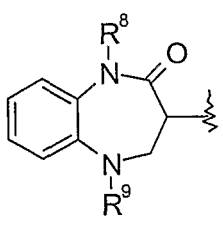

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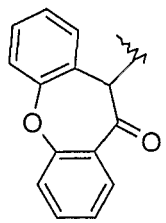


d)

R^2 is lower alkyl, lower alkinyl, $-(CH_2)_n$-O-lower alkyl, $-(CH_2)_n$-S-lower alkyl, $-(CH_2)_n-CN$, $-(CR'R'')_n-CF_3$, $-(CR'R'')_n-CHF_2$, $-(CH_2)_n$-C(O)O-lower alkyl,

$-(CH_2)_n$-halogen, or is $-(CH_2)_n$-cycloalkyl, optionally substituted by one or more substituents, selected from the group consisting of phenyl, halogen or CF_3;

R',R" are independently from n and from each other hydrogen, lower alkyl, lower alkoxy, halogen or hydroxy;

R^3, R^4 are independently from each other hydrogen, lower alkyl, phenyl or halogen;

R^5 is lower alkyl or $-(CH)_2$-cycloalkyl;

R^6 is hydrogen or halogen;

R^7 is hydrogen or lower alkyl;

R^8 is hydrogen, lower alkyl, lower alkinyl or $-(CH)_2$-cycloalkyl;

R^9 is hydrogen, lower alkyl, -C(O)-lower alkyl, -C(O)-lower cycloalkyl, $-(CH_2)_n$-cycloalkyl, phenyl, -C(O)-phenyl, optionally substituted by one or more substituents selected from the group consisting of halogen or -C(O)O-lower alkyl, or is $(CH)_2$-phenyl, optionally substituted by halogen;

n is 0, 1, 2, 3 or 4;

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

3. Compounds of formula I in accordance with claim 1, wherein R^1 is a).

4. Compounds of formula I in accordance with claim 3, wherein R^2 is $-(CH_2)_n$-cycloalkyl, optionally substituted by CF_3.

5. Compounds of formula I in accordance with claim 4, wherein the compounds are

N-cyclopropylmethyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide or
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(1-trifluoromethyl-cyclopropylmethyl)-malonamide.

6. Compounds of formula I in accordance with claim 2, wherein R^2 is lower alkyl, $-(CH_2)_n$-O-lower alkyl or $-(CH_2)_n$-S-lower alkyl.

7. Compounds of formula I in accordance with claim 6, wherein the compounds are
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-methoxyethyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-methylthioethyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3-methoxy-propyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-propyl-malonamide or
2-fluoro-2-methyl-N-(3-methyl-butyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide.

8. Compounds of formula I in accordance with claim 2, wherein R^2 is $-(CR'R'')_n-CF_3$ or $-(CR'R'')_n-CHF_2$.

9. Compounds of formula I in accordance with claim 8, wherein the compounds are
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,2-trifluoroethyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,3-trifluoro-propyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4-tetrafluoro-butyl)-malonamide,

2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4,4,4-trifluoro-butyl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4,4,4-trifluoro-3-methoxy-butyl)-malonamide,
2-fluoro-2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4-tetrafluoro-butyl)-malonamide,
N-(5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2-methyl-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2,2-dimethyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(-)-2-methoxy-N-(6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2R)-2-fluoro-2-methyl-N-((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2S)-2-fluoro-2-methyl-N-[(S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(S)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methoxy-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-

dimethyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
(R)-N-((S)-5-cyclopropylmethyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-fluoro-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
N-(5-isopropyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-(5-isopropyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2,2-dimethyl-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2R)-2-fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2S)-2-fluoro-2-methyl-N-[(S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
2-methoxy-N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-((S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide or
2,2-dimethyl-N-[(S)-6-oxo-5-(2,2,2-trifluoro-ethyl)-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

10. Compounds of formula I in accordance with claim 1, wherein R^1 is b).

11. Compounds of formula I in accordance with claim 10, wherein the compound is
2-methyl-N-(3-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide.

12. Compounds of formula I in accordance with claim 1, wherein R^1 is c).

13. Compounds of formula I in accordance with claim 12, wherein R^2 is $-(CR'R'')_n-CF_3$.

14. Compounds of formula I in accordance with claim 13, wherein the compounds are
2-methyl-N-(1-methyl-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide,

N-((3S)-5-benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(4-fluoro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(4-chloro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(3,5-difluoro-benzoyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
4-{(3S)-5-methyl-4-oxo-3-[2-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carbonyl}-benzoic acid methyl ester,
N-((3S)-5-acetyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[5-((3S)-4-fluoro-benzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(4-chloro-benzoyl)-1-cyclopropylmethyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2RS)-methyl-N-((3S)-1-methyl-2-oxo-5-trifluoromethanesulfonyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2RS)-methyl-N-[(3S)-1-methyl-2-oxo-5-(2,2,2-trifluoro-acetyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(3S)-5-(2-methoxy-acetyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
N-[(S)-5-methanesulfonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
(2RS)-methyl-N-[(S)-2-oxo-1-(2,2,2-trifluoro-ethyl)-5-trifluoromethanesulfonyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
5-methyl-4-oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl estermalonamide,
N-[(S)-5-cyclopropanecarbonyl-2-oxo-1-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,

4-oxo-(3S)-[(2RS)-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-5-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepine-1-carboxylic acid cyclopropylmethyl ester,

N-[(S)-5-acetyl-1-isopropyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide or

N-((S)-5-acetyl-1-benzyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-(2RS)-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

15. Compounds of formula I in accordance with claim 1, wherein R^1 is d).

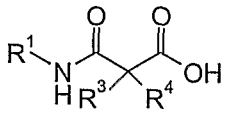
16. Compounds of formula I in accordance with claim 15, wherein the compounds are

2-methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,2-trifluoro-ethyl)-malonamide or

2-methyl-N-(11-oxo-10,11-dihydro-dibenzo[b,f]oxepin-10-yl)-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

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

a) reacting a compound of formula

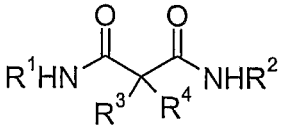


II

with a compound of formula

$$NH_2R^2 \quad III$$

to a compound of formula



I

wherein $R^1 - R^4$ have the meaning as described above,

and

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

18. A compound according to any on of claims 1 – 16, whenever prepared by a process as claimed in claim 14 or by an equivalent method.

19. A medicament containing one or more compounds as claimed in any one of claims 1 – 16 and pharmaceutically acceptable excipients.

20. A medicament according to claim 19 for the treatment of Alzheimer's disease.

21. The use of a compound in any one of claims 1 – 16 for the manufacture of medicaments for the treatment of Alzheimer's disease.

22. The invention as hereinbefore described.

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