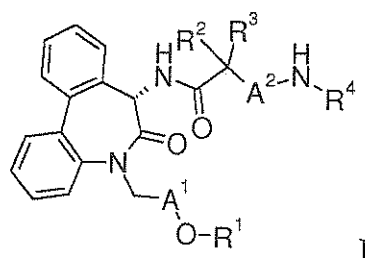


MALONAMIDE DERIVATIVES AS GAMMA SECRETASE INHIBITORS

The invention relates to malonamide derivatives of formula



wherein

A^1 is $-CHR-$ or $-C(O)-$;

5 A^2 is $-C(O)-$ and

R^2/R^3 are independently from each other hydrogen, lower alkyl, halogen, hydroxy or lower alkoxy;

or

A^2 is $-O-C(O)-$ and

10 R^2/R^3 are independently from each other hydrogen or lower alkyl;

R is hydrogen or lower alkyl substituted by halogen;

R^1 is hydrogen, lower alkyl or $-(CH_2)_n$ -aryl, optionally substituted by halogen;

R^4 is lower alkyl substituted by halogen

n is 0, 1 or 2;

15 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.

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

- 5 The term "lower alkyl substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example CF_3 , CHF_2 , CH_2F , CH_2CF_3 , $\text{CH}_2\text{CH}_2\text{F}$, $\text{CH}_2\text{CF}_2\text{CF}_3$, $\text{CH}_2\text{CH}_2\text{CF}_2\text{CF}_3$, $\text{CH}_2\text{CH}_2\text{CF}_3$ and the like.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon radical, for example phenyl, naphthyl, biphenyl or indanyl.

- 10 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
15 inhibitors and the related compounds may be useful in the treatment of Alzheimer's disease. The advantage of compounds of formula I for use in a drug is their good solubility in comparison with compounds, disclosed in WO2004/069826, WO 2005/023772 and WO2005/040126. Furthermore, the present compounds may be used for the treatment of all forms of cancer.

- 20 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
25 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
30 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 ($\text{CTF}\beta$). $\text{CTF}\beta$ is the substrate for

γ -secretase which cleaves at several adjacent positions within the TM to produce the A β peptides and the cytoplasmic fragment. The majority of Abeta peptides is of 40 amino acids length (A β 40), a minor species carries 2 additional amino acids at its C-terminus. Latter is supposed to be the more pathogenic amyloid peptide.

- 5 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 substrates and which are themselves polytopic membrane proteins. Other essential components of
- 10 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.

- 15 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.

- 20 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:

- 25 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,
- 30 Drug Discovery Today, Vol. 6, No. 9, May 2001, 459-462,
FEBS Letters, 483, (2000), 6-10,

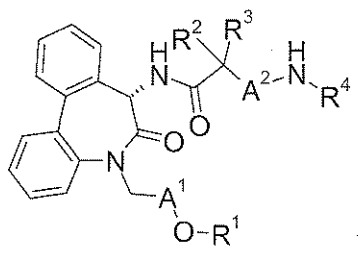
Science, Vol. 297, 353-356, July 2002 and

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

Objects of the embodiments disclosed herein are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the
5 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 disclosure 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 disclosure are all forms of optically pure enantiomers,
10 racemates or diastereomeric mixtures for compounds of formula I.

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



wherein

15 A¹ is -CHR- or -C(O)-;

A² is -C(O)- and

R²/R³ are independently from each other hydrogen, C₁ to C₇ alkyl, halogen, hydroxy or C₁ to C₇ alkoxy;

or

20 A² is -O-C(O)- and

R²/R³ are independently from each other hydrogen or C₁ to C₇ alkyl;

R is hydrogen or C₁ to C₇ alkyl substituted by halogen;

R¹ is hydrogen, C₁ to C₇ alkyl or -(CH₂)ₙ-aryl, optionally substituted by halogen;

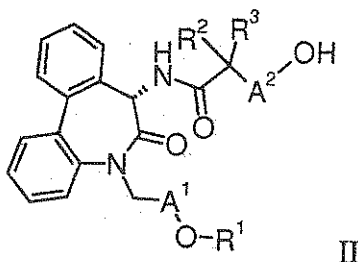
R⁴ is C₁ to C₇ alkyl substituted by halogen

25 n is 0, 1 or 2;

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

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

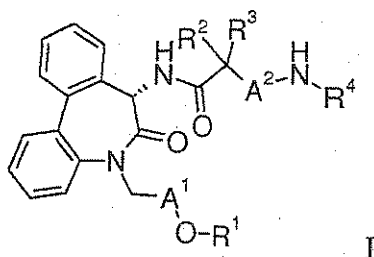
a) reacting a compound of formula



with a compound of formula



to a compound of formula

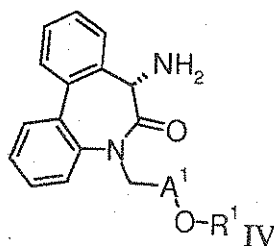


wherein A^1 and $\text{R}^1 - \text{R}^4$ have the meaning as described above and A^2 depicts CO,
and

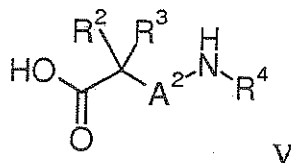
15 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

or

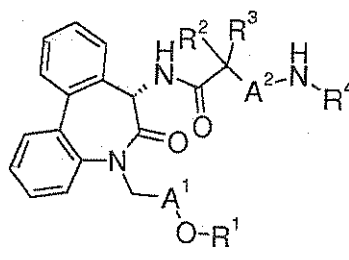
b) reacting a compound of formula



with a compound of formula



to a compound of formula



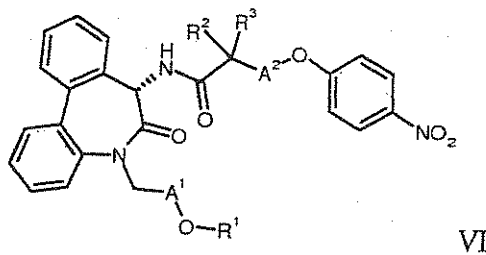
5

wherein A^1 and $R^1 - R^4$ have the meaning as described above and A^2 depicts CO, and

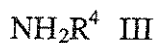
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

10 or

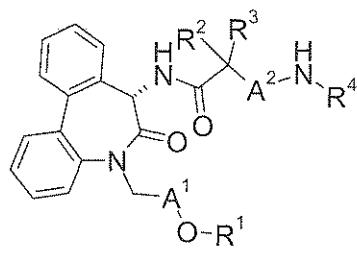
c) reacting a compound of formula



with a compound of formula



to a compound of formula



wherein A¹ and R¹ – R⁴ have the meaning as described above and A² depicts O-CO,
and

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

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

- 10 In a fourth aspect, there is provided the use of a compound as defined above for the manufacture of medicaments for the treatment of Alzheimer's disease.

The most preferred compounds of formula I are those, wherein A¹ is CH₂, A² is CO, R¹ is hydrogen or lower alkyl, for example the following compounds:

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

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

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

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

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

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

- 25 2-ethoxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-

N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide,

(S or R)-2-ethoxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A,

[R or S] 2-ethoxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer B,

- 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A,
- 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide epimer B,
- 5 *N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- (*S*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- 10 *N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(3,3,3-trifluoro-propyl)-malonamide,
- N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
- 15 (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
- (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide,
- (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide,
- 20 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
- (*R*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide,
- 25 (*S*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide,
- (*R* or *S*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide, epimer A,

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

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

- 5 (R or S)-2-hydroxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, epimer A and

(S or R)-2-hydroxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, epimer B.

Preferred compounds are further those, wherein A¹ is CH₂, A² is O-CO and R¹ is

- 10 hydrogen or lower alkyl, for example the following compounds:

(2,2,3,3,3-pentafluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester,

(2,2,3,3,3-pentafluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester,

- 15 (3,3,4,4,4-pentafluoro-butyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester,

(3,3,3-trifluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester,

- 20 (2-fluoro-ethyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester or

(2,2,2-trifluoro-ethyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester.

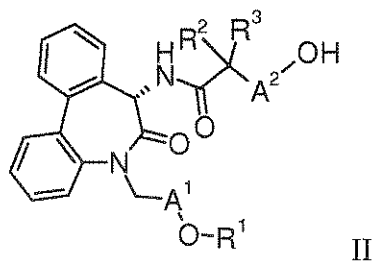
Preferred compounds are further those, wherein A¹ is CHCF₃, A² is CO and R¹ is hydrogen or lower alkyl, for example the following compound:

- 25 2,2-dimethyl-*N*-[(S)-6-oxo-5-(3,3,3-trifluoro-2-hydroxy-propyl)-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

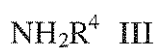
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which processes comprise

- 30 a) reacting a compound of formula

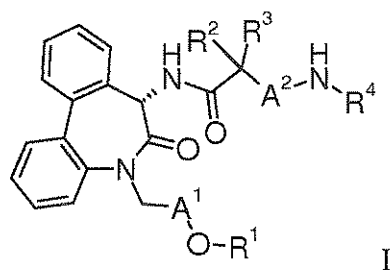
- 7 -



with a compound of formula



to a compound of formula



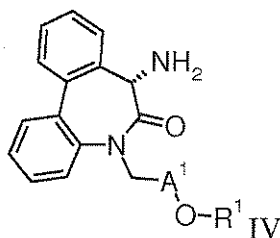
5

wherein A^1 and $\text{R}^1 - \text{R}^4$ have the meaning as described above and A^2 depicts CO,
and

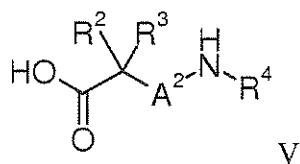
if desired, converting the compounds obtained into pharmaceutically acceptable
acid addition salts.

10 or

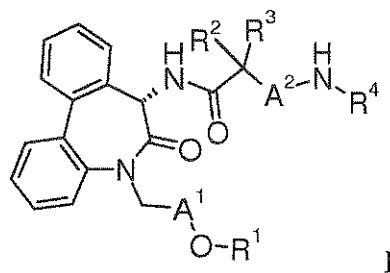
b) reacting a compound of formula



with a compound of formula



to a compound of formula

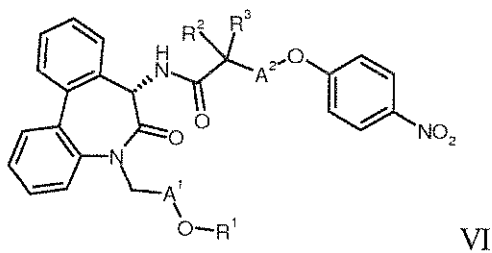


wherein A^1 and $R^1 - R^4$ have the meaning as described above and A^2 depicts CO,
and

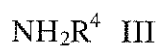
- 5 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

or

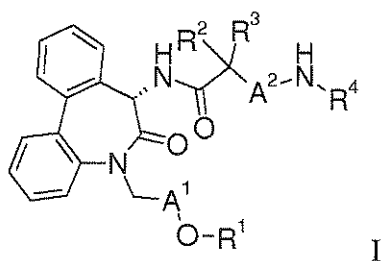
c) reacting a compound of formula



- 10 with a compound of formula



to a compound of formula

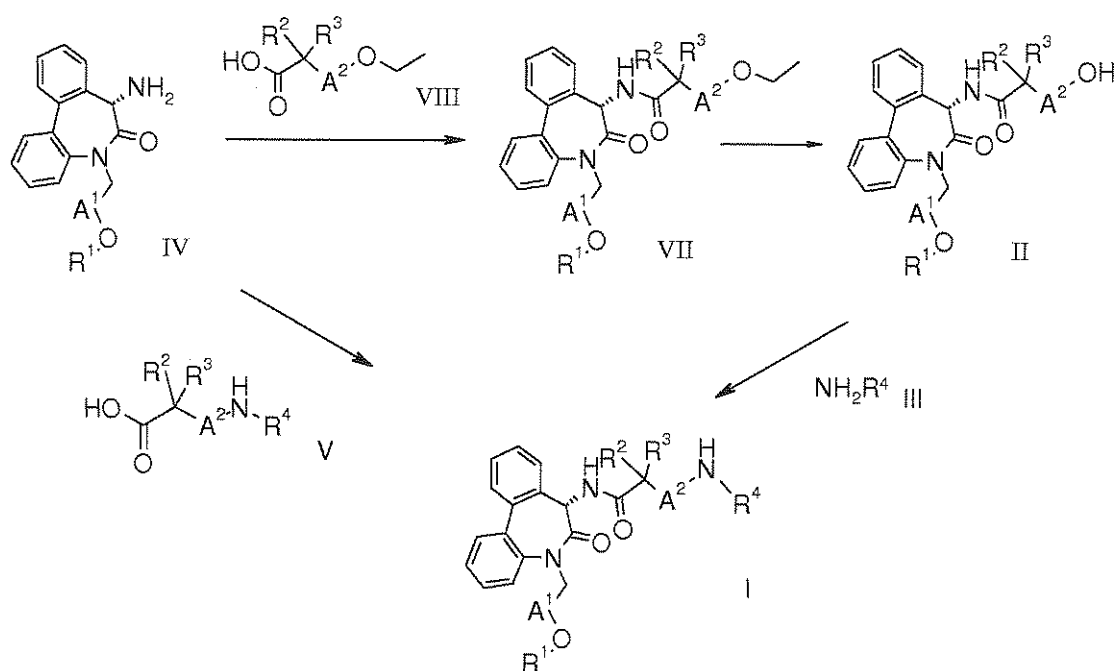


- 15 wherein A^1 and $R^1 - R^4$ have the meaning as described above and A^2 depicts O-CO,
and

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

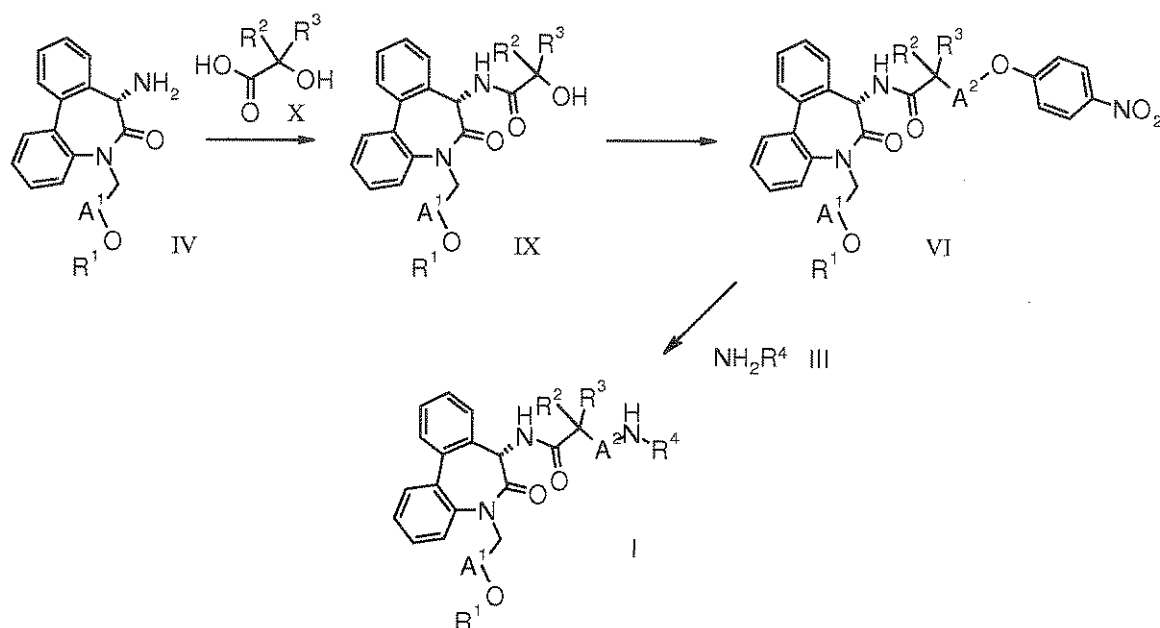
The detailed description can be found below and in Examples 1 – 73. The starting materials of formulas III, V, VIII, X, XI, XIII and XIV are known compounds or may be prepared by methods well-known in the art. The amines of formula III are commercial available products.

Scheme 1



10 In this scheme A^1 and $R^1 - R^3$ are as described above and A^2 depicts CO;

Scheme 2



In this scheme A¹ and R¹ – R³ are as described above and A² depicts O-CO;

- 5 In accordance with scheme 1 a compound of formula II may be prepared as follows:
To a solution of a compound of formula IV, for example (S)-7-amino-5-(2-benzyloxy-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one and an acid of formula VIII, for example (S)-2-fluoro-2-methyl-malonic acid monoethyl ester in THF is added 1-hydroxybenzotriazole, N-ethyldiisopropylamine and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydro-
- 10 chloride (EDC), and the mixture is stirred for 2.5 hours at r.t. The reaction mixture is quenched with water and ethyl acetate, the two phases are separated and the organic layer is washed, dried and purified in the usual manner.
- Then compound of formula VII, for example (S)-7-amino-5-(2-benzyloxy-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one and 2,2-dimethyl-malonic acid monoethyl ester is then
- 15 dissolved in THF and treated with LiOH and water for 18 hours at r.t. Workup and purification in the usual manner afford the compound of formula II. This obtained compound and a compound of formula III, for example 2,2,3,3,3-pentafluoropropylamine are dissolved in THF, treated with 1-hydroxybenzotriazole, N-ethyldiisopropylamine and EDC and the mixture is stirred for 2.5 hours at r.t. The
- 20 obtained compound of formula I is isolated and purified in conventional manner.

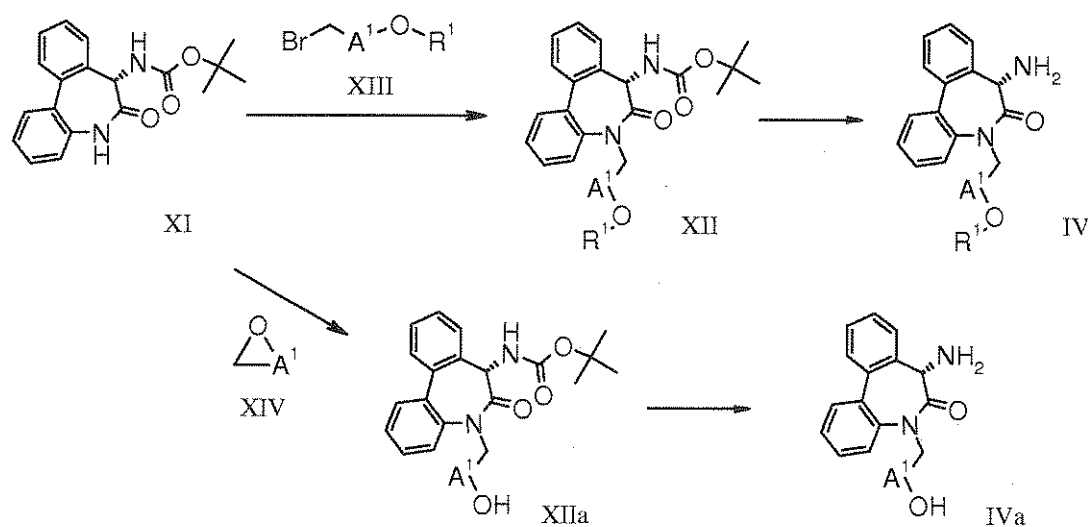
In accordance with scheme 2 a compound of formula I may be prepared as follows:

To a cooled solution of a compound of formula IV, for example (S)-7-amino-5-(2-benzyloxy-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one and an acid, for example L-(+)-lactic

acid, in THF is added 1-hydroxybenzotriazole, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and *N*-ethyldiisopropylamine, and the mixture is stirred for 0.5 hours at 0°C and 3 hours at r.t. The reaction mixture is quenched with water/ethyl acetate. Washing, drying and purification in the usual manner affords a compound of formula IX.

Then compound of formula IX, for example (S)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-propionamide, is dissolved in dichloromethane and reacted with 4-nitrophenyl-chloroformate and pyridine for 7 hours. Workup and purification in the usual manner afford the compound of formula VI. This obtained compound and a compound of formula III, for example 2,2,3,3,3-pentafluoropropylamine are reacted for 24 hours at r.t. After evaporation of all volatile components, purification in the usual manner affords a compound of formula I.

Scheme 3



In this scheme A¹ and R¹ are as described above;

In accordance with scheme 3 a compound of formula IV may be prepared as follows: A compound of formula XI, for example ((S)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl ester is dissolved in DMF and treated with sodium hydride. After stirring for 0.5 hours, a compound of formula XII, for example benzyl 2-bromoethyl ether is added and the reaction mixture stirred for 6 hours. Alternatively, a compound of formula XI, for example ((S)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl ester is dissolved with a compound of formula XIV, for example 1,1,1-trifluoro-2,3-epoxypropane in DMF and stirred for 22 hours at 90°C. Washing, drying and purification in the usual manner afford a compound of formula XII.

Then compound of formula XII and trifluoroacetic acid are dissolved in dichloromethane and stirred for 3 hours at r.t. Workup and purification in the usual manner affords the compound of formula IV.

- 5 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 such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, 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.
- 10
- 15

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.

- 20 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

- 25 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 assays where e.g., a cell lysate containing the γ -secretase complex is incubated
- 30

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
 5 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
 10 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
 15 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:

Example No.	IC_{50} in vitro	Example No.	IC_{50} in vitro
1	0.010	38	0.012
2	0.006	39	0.016
3	0.001	40	0.005
4	0.009	41	0.480
5	0.011	42	0.001
6	0.002	43	0.013
7	0.022	44	0.009
8	0.006	45	0.009

9	0.019	46	0.002
10	0.049	47	0.755
11	0.007	48	0.014
12	0.010	49	0.157
13	0.010	50	0.016
14	0.008	51	0.007
15	0.001	52	0.010
16	0.003	53	0.009
17	0.004	54	0.008
18	0.007	55	0.012
19	0.004	56	0.002
20	0.003	57	0.090
21	0.001	58	0.008
22	0.002	59	0.190
23	0.016	60	0.004
24	0.034	61	
25	0.006	62	0.001
26	0.001	63	0.002
27	0.004	64	0.010
28	0.068	65	0.039
29	0.018	66	0.001
30	0.075	67	0.005

31	0.200	68	0.009
32	0.018	69	0.006
33	0.004	70	0.007
34	0.004	71	0.006
35	0.022	72	0.001
36	0.013		
37	0.018		

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
5 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,
10 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,
15 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
20 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.

- 5 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
 10 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)

15	<u>Item</u> <u>Ingredients</u>	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
	1. Compound of formula I	5	25	100	500
	2. Lactose Anhydrous DTG	125	105	30	150
	3. Sta-Rx 1500	6	6	6	30
20	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.
- 25 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

<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500 mg
5	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
10	Total	200	200	300	600

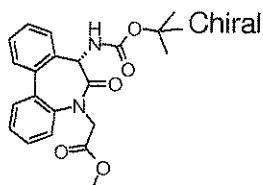
Manufacturing Procedure

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

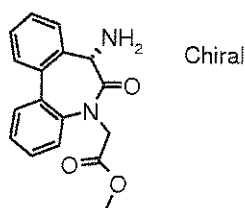
{(S)-6-Oxo-7-[2-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-6,7-dihydro-dibenzo[*b,d*]azepin-5-yl}-acetic acid methyl ester

- 5 a) ((S)-7-*tert*.-Butoxycarbonylamino-6-oxo-6,7-dihydro-dibenzo[*b,d*]azepin-5-yl)-acetic acid methyl ester



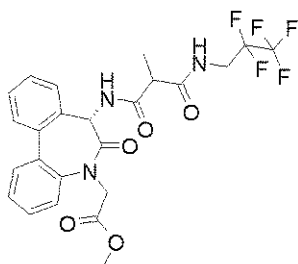
- ((S)-6-Oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl ester (284 mg, 0.88 mmol) were diluted in DMF (5 ml) and treated with sodium hydride (60 mg of 60% suspension in mineral oil, 1.5 mmol). After stirring for 30 minutes, methyl
10 bromoacetate (0.14 ml, 1.5 mmol) were added and the solution stirred for another 6h. The pH is adjusted to 1.5 with 2N hydrogen chloride and extracted with ethyl acetate (10 ml). After back-extraction of the aqueous phases with ethyl acetate, the combined organic phases were washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated to dryness. After chromatography (silica, eluent
15 cyclohexane/ethyl acetate 88/12), the product was obtained as off-white viscous oil (63%); MS: $m/e = 397(M+H^+)$.

- b) ((S)-7-Amino-6-oxo-6,7-dihydro-dibenzo[*b,d*]azepin-5-yl)-acetic acid methyl ester



- ((S)-7-*tert*-Butoxycarbonylamino-6-oxo-6,7-dihydro-dibenzo[*b,d*]azepin-5-yl)-acetic
20 acid methyl ester (60 mg, 0.15 mmol) were dissolved in dichloromethane (3 ml), treated with 0.15 ml (2.3 mmol) orthophosphoric acid and stirred for 18 h. The reaction mixture is adjusted to pH 7.5 with 2N aqueous sodium hydroxide, diluted with dichloromethane (5 ml) and the phases separated. After extraction of the organic phases with water (5 ml) and saturated aqueous sodium chloride (5 ml), the solution is dried with magnesium
25 sulfate and evaporated to dryness. White solid (60%); MS: $m/e = 297(M+H^+)$, which was used without further purification.

c) {(S)-6-Oxo-7-[2-(2,2,3,3,3-pentafluoro-propylcarbamoyl)-propionylamino]-6,7-dihydro-dibenzo[*b,d*]azepin-5-yl}-acetic acid methyl ester



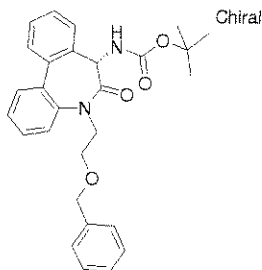
5 ((S)-7-Amino-6-oxo-6,7-dihydro-dibenzo[*b,d*]azepin-5-yl)-acetic acid methyl ester (25 mg, 0.85 mmol) were dissolved in THF and subsequently treated with 2-methyl-*N*-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid (25 mg, 0.1 mmol), 1-hydroxy-benzotriazole (11.6 mg, 0.85 mmol), *N*-ethyldiisopropylamine (0.03 ml, 0.17 mmol) and EDC (16.5 mg, 0.85 mmol). After stirring for 2.5 h at ambient temperature, the reaction mixture is quenched with water and extracted with ethyl acetate. The aqueous phase is
10 extracted twice with ethyl acetate and the combined organic layers are extracted with water (2x 5 ml) and saturated aqueous sodium chloride (5 ml), combined, dried over anhydrous sodium sulfate and evaporated to dryness. Chromatography (silica, eluent cyclohexane/ethyl acetate 65/35) afforded the product as colorless solid (70%). MS: $m/e = 528$ ($M+H^+$).

15

Example 2

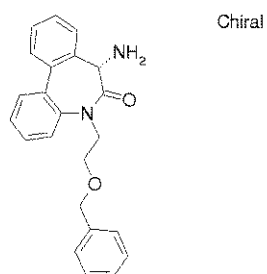
N-[(S)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

a) [(S)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-carbamic acid *tert*-butyl ester

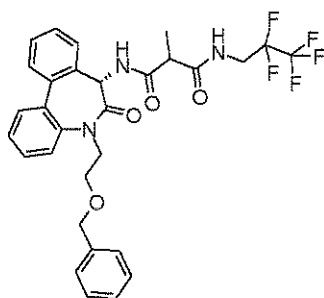


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Using ((S)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl ester and benzyl 2-bromoethyl ether, the title compound was prepared in the same manner as described for example 1a. White crystals, mp. 132-134°C (84%). MS: $m/e = 459$ ($M+H^+$), mp 133°C.

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

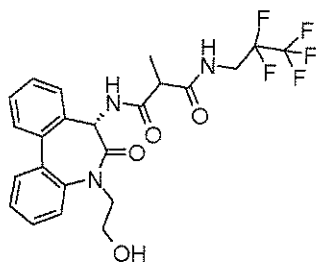
Using [(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-carbamic acid *tert*-butyl ester, the title compound was prepared in the same manner as described for example 1b). Light yellow, viscous oil (>98%). MS: $m/e = 359(M+H^+)$.

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

Using (S)-7-amino-5-(2-benzyloxy-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid, the title compound was prepared in the same manner as described for example 1c). White solid (89% yield). MS: $m/e = 490(M+H^+)$.

Example 3

N-[(S)-5-(2-Hydroxy-ethyl)-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-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide (113 mg, 0.19 mmol) were

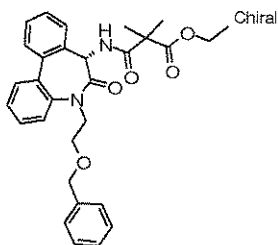
dissolved in methanol (20 ml) and treated with 37% aqueous HCl (0.1 ml) and palladium on carbon (10%, 6 mg) and stirred for 2 days under an atmosphere of hydrogen. After filtration and evaporation of the solvent, the title compound was obtained as white solid (94%). MS: $m/e = 450(M+H^+)$.

5

Example 4

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

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

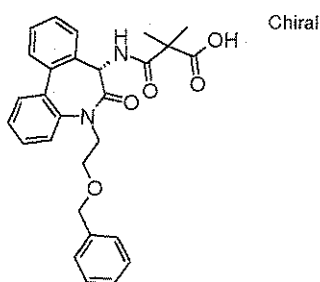


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Using (*S*)-7-amino-5-(2-benzoyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2,2-dimethyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil (>98%). MS: $m/e = 501(M+H^+)$.

b) *N*-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2,2-dimethyl-malonamic acid

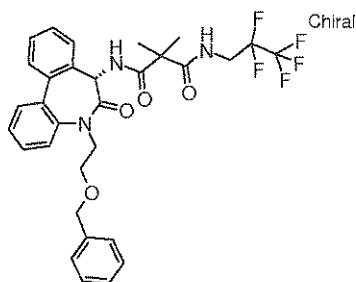
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N-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2,2-dimethyl-malonamic acid ethyl ester (127 mg, 0.25 mmol) were dissolved in THF (4.5 ml) and water (1.1 ml), treated with lithium hydroxide (25 mg, 1 mmol) and stirred for 18 h at ambient temperature. The mixture is diluted with aqueous saturated sodium carbonate and extracted twice with ethyl acetate. The aqueous phase is acidified with concentrated aqueous hydrogen chloride to pH 0 and extracted twice with ethyl acetate. The acidic organic layers were combined, dried over magnesium sulfate and evaporated to afford 112 mg (93%) of white foam. MS: $m/e = 472(M-H^+)$.

20

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

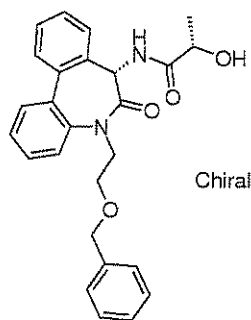


- Using *N*-[(*S*)-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2,2-dimethyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid (76%). MS: $m/e = 604(M+H^+)$.

Example 5

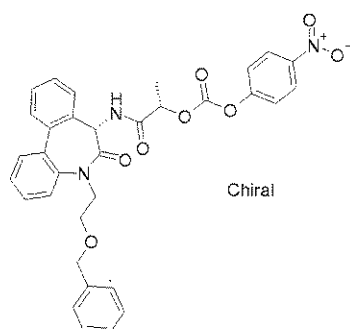
- (2,2,3,3,3-Pentafluoro-propyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester

a) (*S*)-*N*-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-propionamide



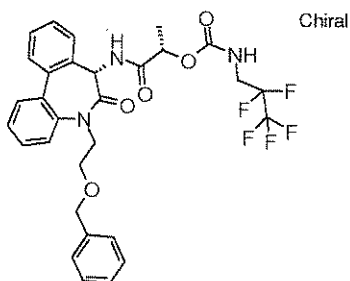
- (*S*)-7-Amino-5-(2-benzoyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one (50 mg, 0.14 mmol) and *L*-(+)-lactic acid (14 mg, 0.15 mmol) were dissolved in THF (2 ml), cooled to 0°C and under exclusion of moisture subsequently treated with 1-hydroxybenzotriazole (21 mg, 0.15 mmol), EDC (33 mg, 0.17 mmol) and *N*-diisopropyl-ethylamine (0.05 ml, 0.28 mmol). After stirring for 30 min. at 0°C and 3 h at ambient temperature, the mixture was diluted with water and ethyl acetate (10 ml each), the phases separated and the organic layer extracted with water, 1*N* aqueous HCl and saturated aqueous NaCl. After drying over magnesium sulphate and evaporation of the solvent, the title compound was afforded as colourless oil (98%). MS: $m/e = 431(M-H^+)$.

b) Carbonic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester



- (S)-N-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-propionamide (113 mg, 0.26 mmol) was dissolved in dichloromethane (2.5 ml) and subsequently treated with 4-nitrophenyl-chloroformate (96 mg, 0.45 mmol) and pyridine (0.038 ml, 0.47 mmol). After stirring for 7 h, the mixture was evaporated to dryness. Chromatography (silica, gradient of heptane/ethyl acetate 0 to 100% afforded the title compound as white, viscous oil (82%). MS: $m/e = 596(M+H^+)$.

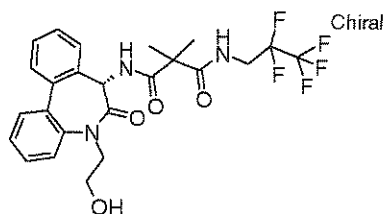
- c) (2,2,3,3,3-Pentafluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester



- Carbonic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester (65 mg, 0.11 mmol) and 2,2,3,3,3-pentafluoropropylamine (663 mg, 4.3 mmol) were stirred for 24 h at ambient temperature. After evaporation of all volatile components and chromatography on silica (gradient of heptane/ethyl acetate 0 to 80%), the title compound was obtained as white solid (>98%). MS: $m/e = 606(M+H^+)$.

Example 6

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



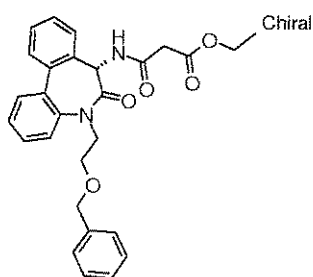
Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2,2-dimethyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). White solid. MS: *m/e*= 514(*M*+*H*⁺).

5

Example 7

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

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

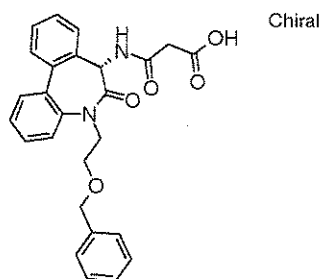


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Using (*S*)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil (>98%). MS: *m/e*=473(*M*+*H*⁺).

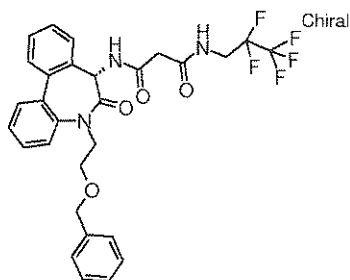
b) *N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-malonamic acid

15



Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-malonamic acid ethyl ester, the title compound was prepared in the same manner as example 4b. White, viscous oil (95%). MS: *m/e*= 443(*M*-*H*⁺).

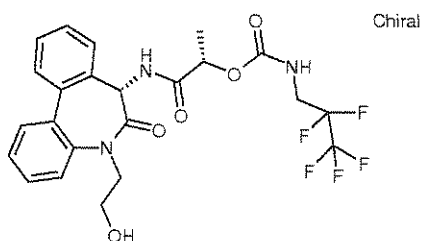
c) *N*-[*(S)*-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



Using *N*-[*(S)*-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-malonic acid and *N*-(2,2,3,3,3-pentafluoro-propyl amine, the title compound was prepared in the same manner as example 1c (73%). White solid. MS: $m/e = 576(M+H^+)$.

Example 8

(2,2,3,3,3-Pentafluoro-propyl)-carbamic acid (*S*)-1-[*(S)*-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester



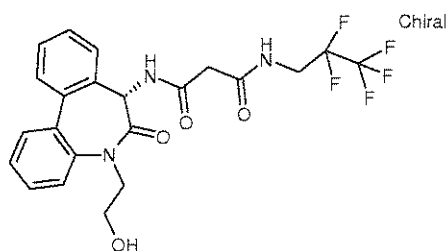
10

Using (2,2,3,3,3-pentafluoro-propyl)-carbamic acid (*S*)-1-[*(S)*-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester, the title compound was prepared in the same manner as example 3 (96%). White solid. MS: $m/e = 516(M+H^+)$.

15

Example 9

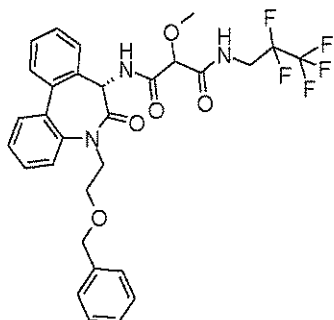
N-[*(S)*-5-(2-Hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). White solid. MS: *m/e*= 486(*M*+*H*⁺).

Example 10

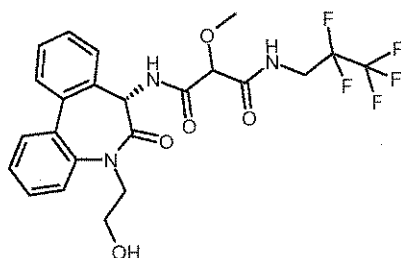
- 5 *N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methoxy-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



- Using (*S*)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-methoxy-*N*-(2,2,3,3,3-pentafluoro-propyl)-malonic acid, the title compound was prepared in the same manner as example 1c (99%). White solid. MS: *m/e*= 606(*M*+*H*⁺).

Example 11

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

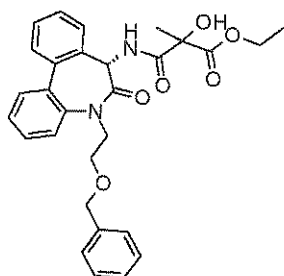


- 15 Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methoxy-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, the title compound was prepared in the same manner as example 3 (97%). White solid. MS: *m/e*= 516(*M*+*H*⁺).

Example 12

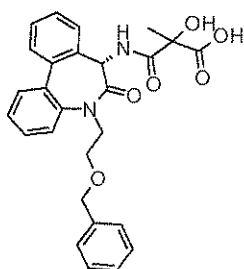
- 20 *N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

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



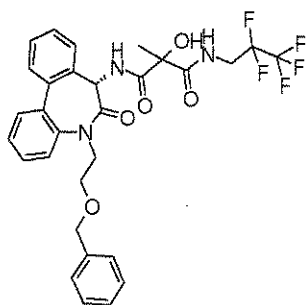
- Using (*S*)-7-amino-5-(2-benzoyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-hydroxy-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. White solid (>98%). MS: $m/e = 503(M+H^+)$.

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



- Using *N*-[(*S*)-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as example 4b. White solid (90%). MS: $m/e = 473(M-H^+)$.

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



15

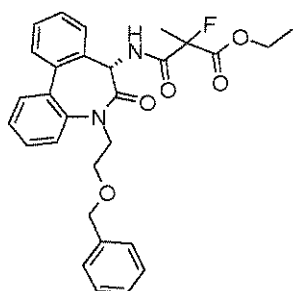
Using *N*-[(*S*)-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoro-propylamine, the title

compound was prepared in the same manner as example 1c (59%). White solid. MS: $m/e = 606(M+H^+)$.

Example 13

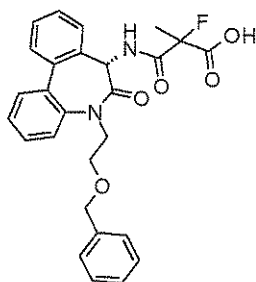
N-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

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



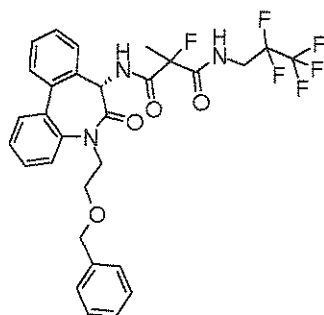
Using (*S*)-7-amino-5-(2-benzoyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-fluoro-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil (>98%). MS: $m/e = 505(M+H^+)$.

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



Using *N*-[(*S*)-5-(2-benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as example 4b. Colorless oil (85%). MS: $m/e = 4757(M-H^+)$.

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

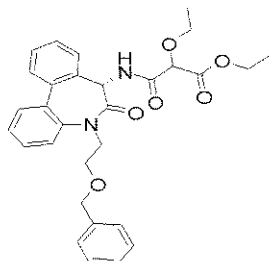


- Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. Whites solid.
- 5 (64%). MS: $m/e = 608(M+H^+)$.

Example 14

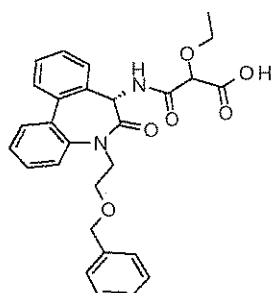
N-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

- a) *N*-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-malonamic acid ethyl ester
- 10



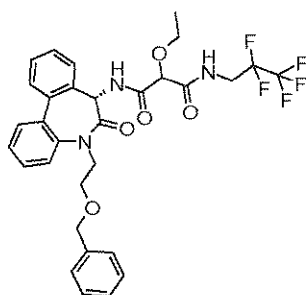
Using (*S*)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-ethoxy-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil (94%). MS: $m/e = 517(M+H^+)$.

- b) *N*-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-malonamic acid
- 15



Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-malonamic acid ethyl ester, the title compound was prepared in the same manner as example 4b. Colorless oil (88%). MS: *m/e*= 487(*M*-H⁺).

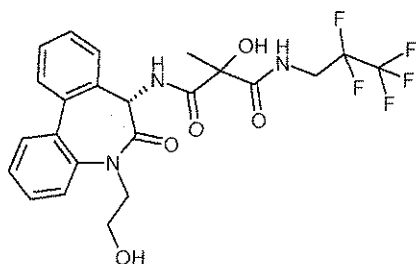
- 5 c) *N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



- Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid. (82%). MS: *m/e*=
10 620(*M*+H⁺).

Example 15

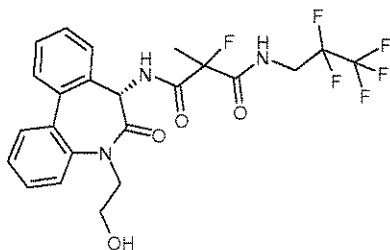
2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



- 15 Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, the title compound was prepared in the same manner as described for example 3. White solid (>98%). MS: *m/e*= 516(*M*+H⁺).

Example 16

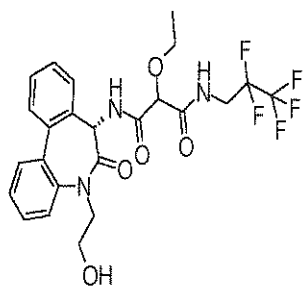
- 20 2-Fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



- Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 3. White solid (94%). MS: $m/e = 518(M+H^+)$.

Example 17

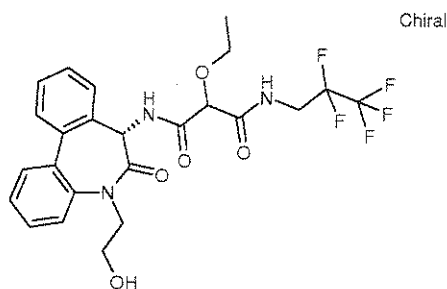
2-Ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



- Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-ethoxy-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 3. White solid (83%). MS: $m/e = 530(M+H^+)$.

Example 18

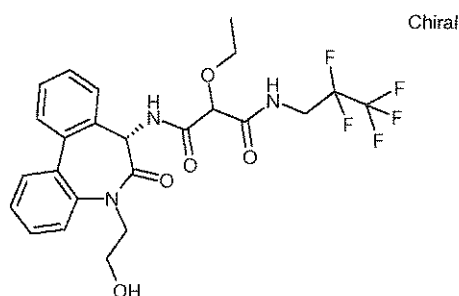
- (*S* or *R*)-2-Ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A



- Separation of 2-ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide (HPLC on Chiralpak AD, eluent heptane/ethyl acetate 3/7) afforded the title compound as first eluting material with negative rotation. Off-white, viscous oil (39%). MS: $m/e=$ 530($M+H^+$).

Example 19

[*R* or *S*] 2-Ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer B

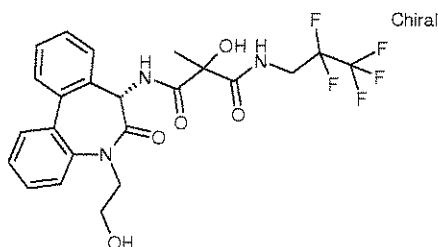


- Separation of 2-ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide (HPLC on Chiralpak AD, eluent heptane/ethyl acetate 3/7) afforded the title compound as second eluting material with negative rotation. Off-white, viscous oil (52%). MS: $m/e=$ 530($M+H^+$).

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Example 20

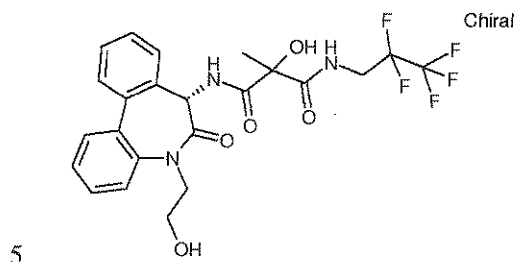
2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A



- Separation of 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide on chiral HPLC (Chiralpak OD) afforded the title compound as first eluting material with negative rotation (36%). White solid. MS: $m/e=$ 516($M+H^+$).

Example 21

2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide epimer B



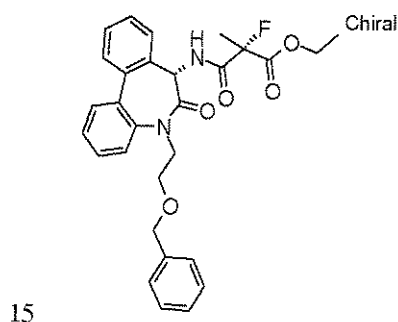
Separation of 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide on chiral HPLC (Chiralpak OD) afforded the title compound as second eluting material with negative rotation (38%). White solid. MS: $m/e = 516(M+H^+)$.

10

Example 22

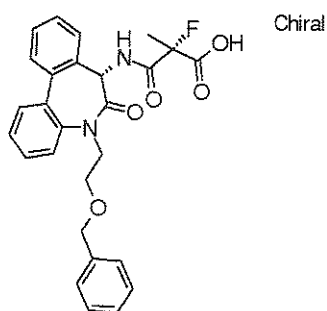
(*R*)-*N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

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



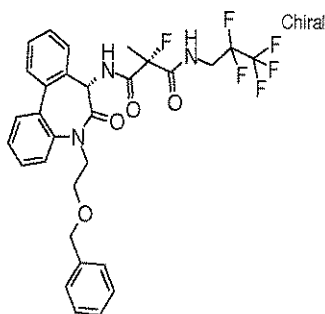
Using (*S*)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and (*S*)-2-fluoro-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Light yellow oil (>98%). MS: $m/e = 505(M+H^+)$.

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



Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as described for example 4b. White solid. (71%). MS: $m/e = 475(M-H^+)$.

c) (R)-N-[(S)-5-(2-Benzyloxy-ethyl)-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

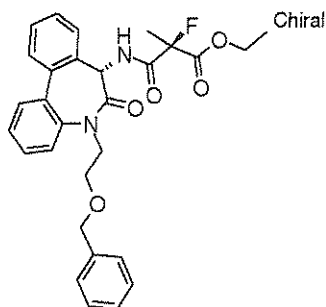


Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid (74%). MS: $m/e = 608(M+H^+)$.

Example 23

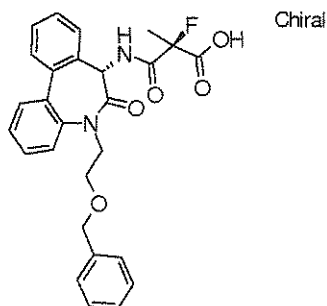
(S)-N-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide

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



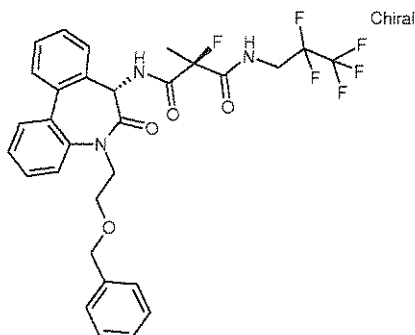
Using (S)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and (R)-2-fluoro-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Light yellow oil (96%). MS: $m/e = 505(M+H^+)$.

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



- Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as described for example 4b. White solid. (83%). MS: $m/e = 475(M-H^+)$.
- 10

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



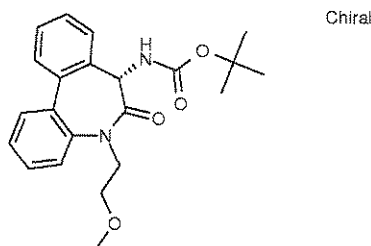
- Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title
- 15

compound was prepared in the same manner as described for example 1c. White solid (63%). MS: $m/e = 608(M+H^+)$.

Example 24

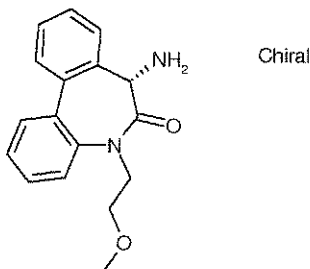
N-[(*S*)-5-(2-Methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-
5 (2,2,3,3,3-pentafluoro-propyl)-malonamide

a) [(*S*)-5-(2-Methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-5-yl]-carbamic acid *tert*-butyl ester



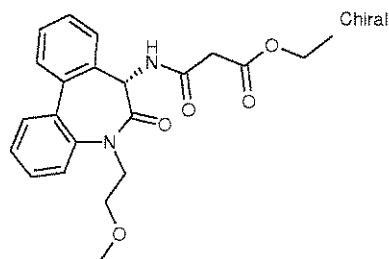
Using ((*S*)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl
10 ester and 1-bromo-2-methoxy-ethane, the title compound was prepared in the same manner as example 1a. Pink solid (90%). MS: $m/e = 383(M+H^+)$.

b) (*S*)-7-Amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one



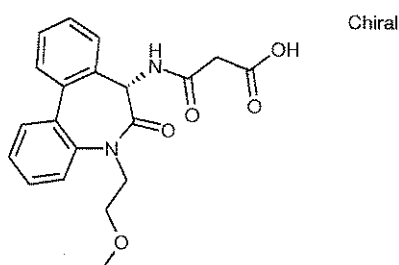
[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-5-yl]-carbamic
15 acid *tert*-butyl ester (637 mg, 1.7 mmol) and trifluoroacetic acid (10 equivalents) were dissolved in dichloromethane (10 ml) and stirred for 3 h at ambient temperature. Work-up and isolation as described in example 1b afforded the title compound as colorless, viscous oil (99%). MS: $m/e = 283(M+H^+)$.

c) *N*-[(*S*)-5-(2-Methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-
20 malonamic acid ethyl ester



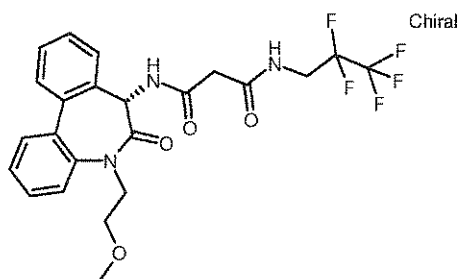
Using (S)-7-Amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless, viscous oil (>98%). MS: $m/e = 397(M+H^+)$.

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



- Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-malonamic acid ethyl ester, the title compound was prepared in the same manner as described for example 4b. White solid. (85%). MS: $m/e = 367(M-H^+)$.
- 10

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

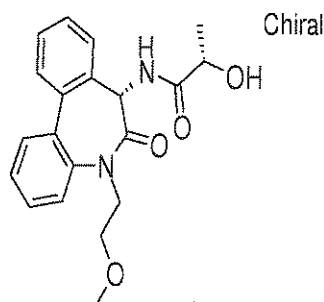


- Using *N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid (80%). MS: $m/e = 500(M+H^+)$.
- 15

Example 25

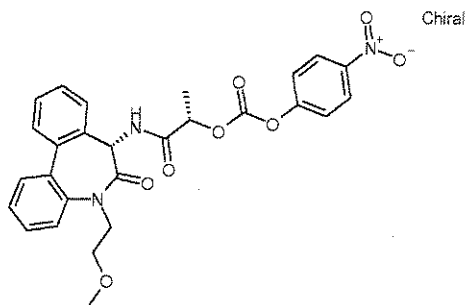
(2,2,3,3,3-Pentafluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester

- 5 a) (S)-2-Hydroxy-N-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-propionamide



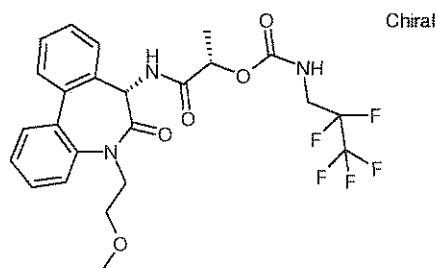
Using (S)-7-amino-5-(2-methoxy-ethyl)-5H,7H-dibenzo[*b,d*]azepin-6-one and *L*-(+)-lactic acid, the title compound was prepared in the same manner as described for example 5a. Colourless, viscous oil (>98%). MS: $m/e = 355(M+H^+)$.

- 10 b) Carbonic acid (S)-1-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester



- 15 Using (S)-2-hydroxy-N-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-propionamide, the title compound was prepared in the same manner as described for example 5b. White solid (89%). MS: $m/e = 520(M+H^+)$.

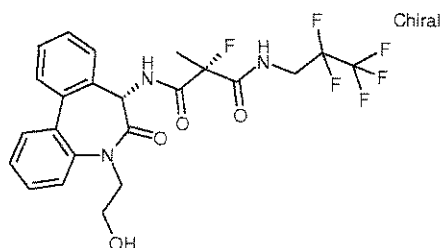
- c) (2,2,3,3,3-Pentafluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester



- Using carbonic acid (S)-1-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 5c. White solid (49%). MS: $m/e = 530(M+H^+)$.

Example 26

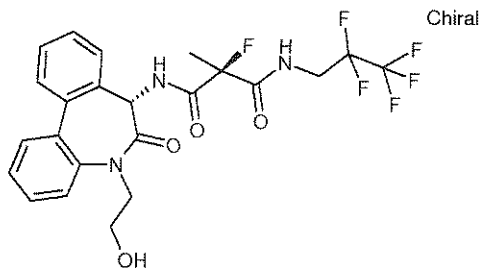
(R)-2-Fluoro-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide



- 10 Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-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, the title compound was prepared in the same manner as example 3 (>98%). White solid. MS: $m/e = 518(M+H^+)$.

Example 27

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

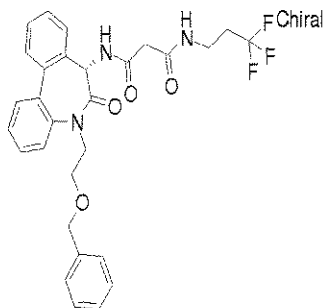


Using (S)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, the title

compound was prepared in the same manner as example 3 (96%). White solid. MS: $m/e=518(M+H^+)$.

Example 28

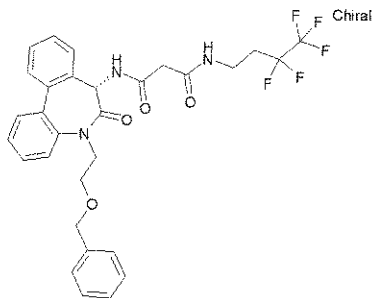
N-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-
5 (3,3,3-trifluoro-propyl)-malonamide



Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-malonamic acid and ,3,3,3-trifluoropropylamine, the title compound was prepared in the same manner as described for example 1c. Colorless, waxy solid (90%). MS: $m/e=$
10 540($M+H^+$).

Example 29

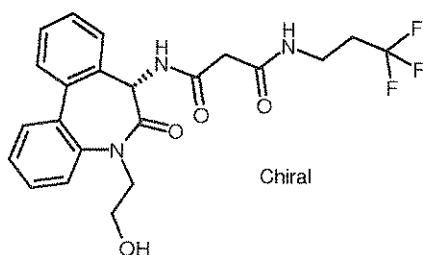
N-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-
(3,3,4,4,4-pentafluoro-butyl)-malonamide



Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-malonamic acid and ,3,3,4,4,4-pentafluorobutylamine, the title compound was prepared in the same manner as described for example 1c. Colorless, waxy solid (98%). MS: $m/e=$
15 590($M+H^+$).

Example 30

N-[(*S*)-5-(2-Hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(3,3,3-trifluoro-propyl)-malonamide
20

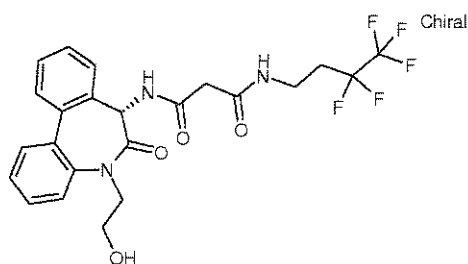


Using *N*-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(3,3,3-trifluoro-propyl)-malonamide, the title compound was prepared in the same manner as example 3 (85%). White solid. MS: $m/e = 450(M+H^+)$.

5

Example 31

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



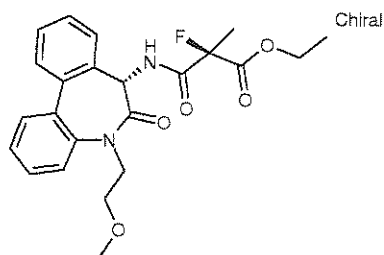
Using *N*-[(*S*)-5-(2-Benzoyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). Light brown solid. MS: $m/e = 500(M+H^+)$.

10

Example 32

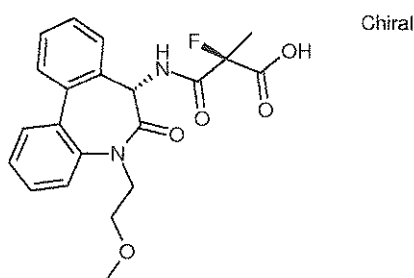
(*S*)-2-Fluoro-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

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



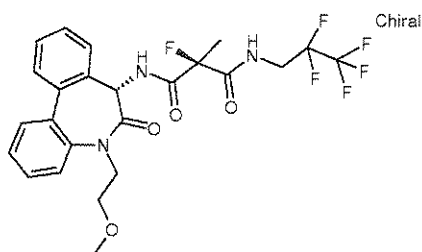
Using (S)-7-amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and (R)-2-fluoro-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil (59%). MS: $m/e = 429(M+H^+)$.

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



- Using (R)-2-fluoro-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as described for example 4b. White semisolid. (>98%). MS: $m/e = 399(M-H^+)$.
- 10

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

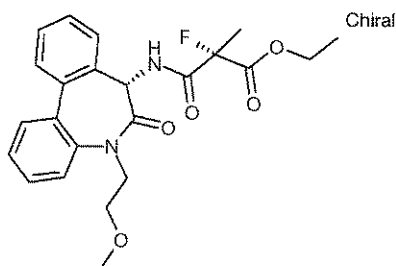


- Using (R)-2-fluoro-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid (69%). MS: $m/e = 532(M+H^+)$.
- 15

Example 33

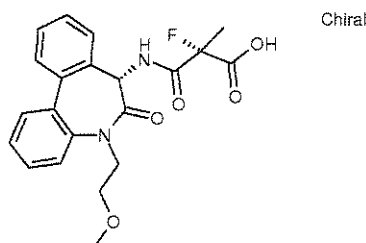
- (R)-2-Fluoro-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide
- 20

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



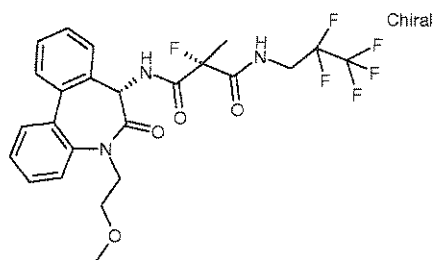
Using (S)-7-amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and (S)-2-fluoro-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil (50%). MS: $m/e = 429(M+H^+)$.

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



- 10 Using (S)-2-fluoro-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as described for example 4b. White solid. (>98%). MS: $m/e = 399(M-H^+)$.

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

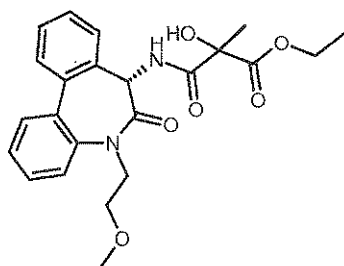


- 15 Using (S)-2-fluoro-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid (71%). MS: $m/e = 532(M+H^+)$.

Example 34

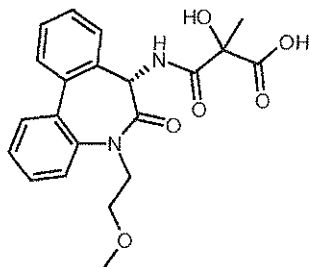
2-Hydroxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

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



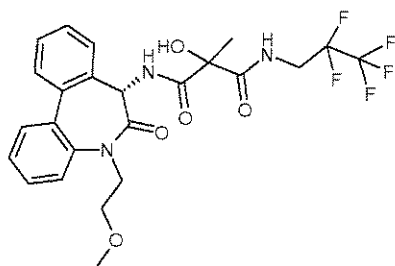
Using (*S*)-7-amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-hydroxy-2-methyl-malonic acid monoethyl ester, the title compound was prepared in the same manner as described for example 1c. Colorless oil. (66%). MS: *m/e*= 426(*M*+*H*⁺).

- 10 b) 2-Hydroxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid



- 15 Using 2-hydroxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid ethyl ester, the title compound was prepared in the same manner as described for example 4b. White solid. (>98%). MS: *m/e*= 397(*M*-*H*⁺).

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

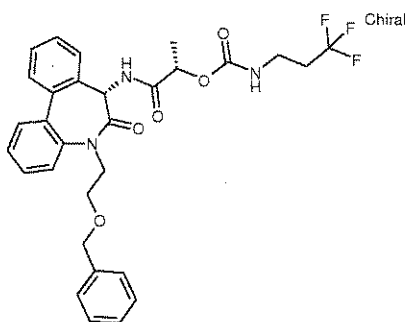


Using 2-hydroxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-malonamic acid and 2,2,3,3,3-pentafluoropropylamine, the title compound was prepared in the same manner as described for example 1c. White solid (78%). MS: $m/e = 530(M+H^+)$.

5

Example 35

(3,3,3-Trifluoro-propyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester



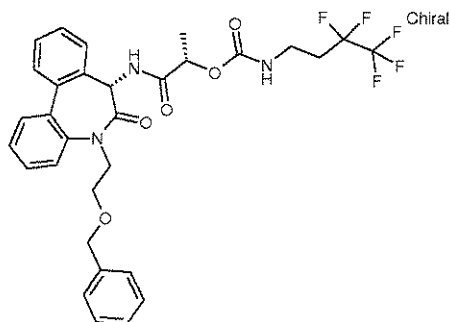
Using carbonic acid (*S*)-1-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester and 3,3,3-trifluoropropylamine, the title compound was prepared in the same manner as described for example 5c. Colorless, waxy solid (94%). MS: $m/e = 570(M+H^+)$.

10

Example 36

(3,3,4,4,4-Pentafluoro-butyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester

15

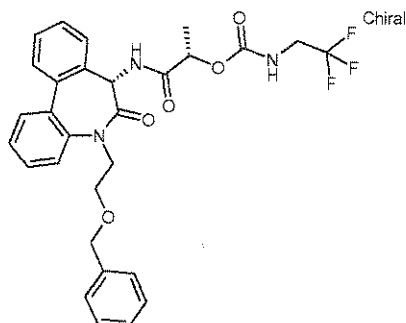


Using carbonic acid (*S*)-1-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester and 3,3,4,4,4-pentafluorobutylamine, the title compound was prepared in the same manner as described for example 5c. White solid (97%). MS: $m/e = 620(M+H^+)$.

20

Example 37

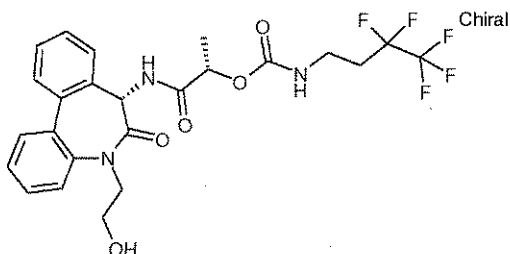
(2,2,2-Trifluoro-ethyl)-carbamic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester



- 5 Using carbonic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester and 2,2,2-trifluoroethylamine, the title compound was prepared in the same manner as described for example 5c. Colorless, waxy solid (94%). MS: $m/e = 556(M+H^+)$.

Example 38

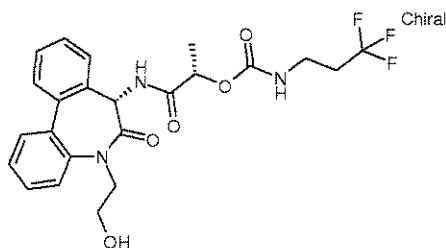
- 10 (3,3,4,4,4-Pentafluoro-butyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester



- Using (3,3,4,4,4-pentafluoro-butyl)-carbamic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester, the title compound
15 was prepared in the same manner as example 3 (70%). Yellow, crystals, mp 181-184°C. MS: $m/e = 530(M+H^+)$.

Example 39

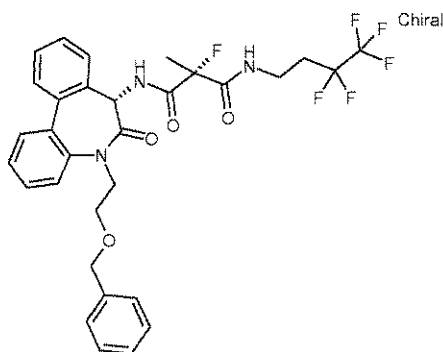
(3,3,3-Trifluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester



- Using (3,3,3-trifluoro-propyl)-carbamic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester, the title compound was prepared in the same manner as example 3 (72%). Colorless, waxy solid. MS: $m/e = 480(M+H^+)$.

Example 40

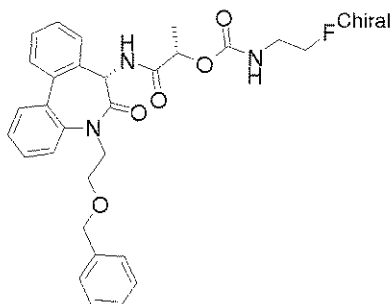
(R)-N-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide



- 10 Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 3,3,4,4,4-pentafluoro-butylamine, the title compound was prepared in the same manner as described for example 1c. White solid (85%). MS: $m/e = 622(M+H^+)$.

Example 41

- 15 (2-Fluoro-ethyl)-carbamic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester

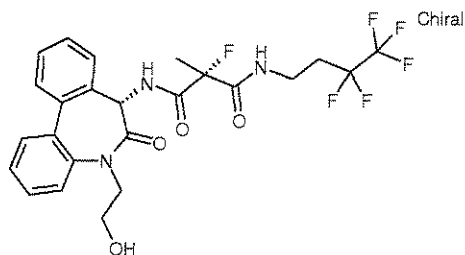


Carbonic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester 4-nitro-phenyl ester (80 mg, 0.13 mmol), 2-fluoroethylamine hydrochloride (40 mg, 0.40 mmol) and pyridine (2 ml) were stirred in a sealed tube for 18 h at ambient temperature. After evaporation of the volatile components under reduced pressure, the residue was taken up in water/ethyl acetate, the phases separated and the organic layer extracted 5-times with saturated aqueous sodium carbonate, twice with 10% citric acid and once with saturated aqueous sodium chloride. After drying over magnesium sulfate and evaporation of the solvent, the title compound is obtained as white solid (>98%). MS: $m/e = 520(M+H^+)$.

10

Example 42

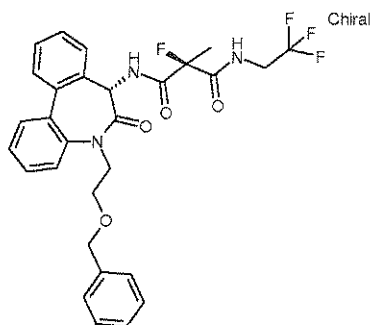
(R)-2-Fluoro-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide



Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-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, the title compound was prepared in the same manner as example 3. Final chromatography on silica (heptane/ethyl acetate gradient from 20 to 80%) afforded the title compound as white solid (56%). MS: $m/e = 532(M+H^+)$.

Example 43

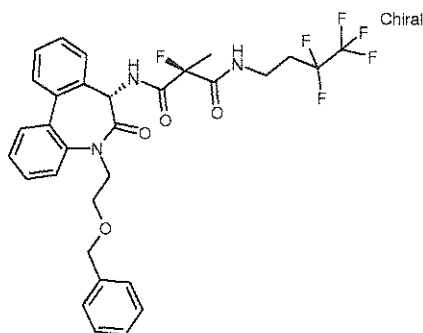
(S)-*N*-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide



Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 2,2,2-trifluoro-ethylamine, the title compound was prepared in the same manner as described for example 1c. Final chromatography on silica (heptane/ethyl acetate gradient from 5 to 100%) afforded the title compound as white solid (58%). MS: $m/e = 558(M+H^+)$.

Example 44

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



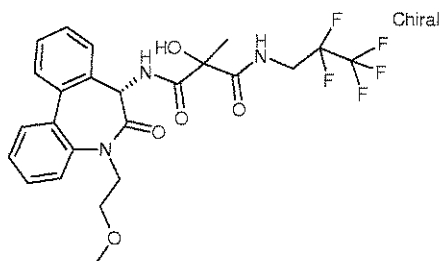
10

Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 3,3,4,4,4-pentafluoro-butylamine, the title compound was prepared in the same manner as described for example 1c. White solid (68%). MS: $m/e = 622(M+H^+)$.

15

Example 45

2-Hydroxy-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A

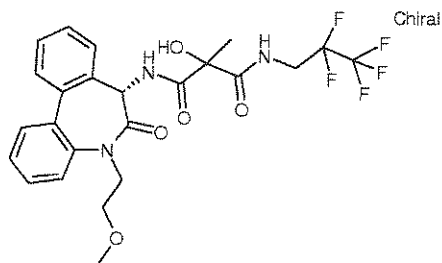


20

Separation of 2-hydroxy-*N*-[(S)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide by chiral HPLC (Chiralpak AD) afforded the title compound as first eluting material with negative rotation. White solid (33%). MS: $m/e = 530(M+H^+)$.

Example 46

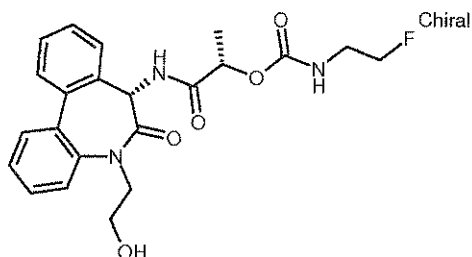
2-Hydroxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer B



- 5 Separation of 2-hydroxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide by chiral HPLC (Chiralpak AD) afforded the title compound as second eluting material with negative rotation. White solid (39%). MS: $m/e = 530(M+H^+)$.

Example 47

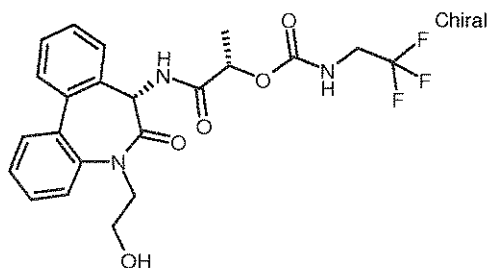
- 10 (2-Fluoro-ethyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester



- Using (2-fluoro-ethyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester, the title compound was prepared in the same manner as example 3 (>98%). Light yellow solid. MS: $m/e = 430(M+H^+)$.

Example 48

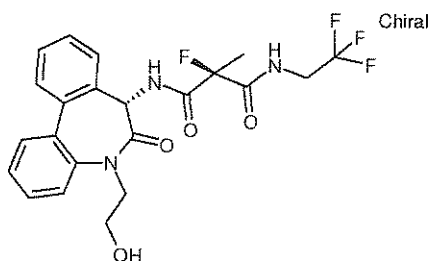
(2,2,2-Trifluoro-ethyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbonyl]-ethyl ester



Using (2,2,2-trifluoro-ethyl)-carbamic acid (S)-1-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-ylcarbonyl]-ethyl ester, the title compound was prepared in the same manner as example 3. Final chromatography (silica, gradient of ethyl acetate in heptane 5-90%) afforded the title compound as white solid (70%). MS: $m/e = 466(M+H^+)$.

Example 49

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



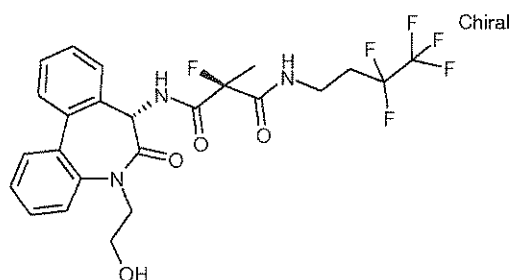
10

Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-2-fluoro-2-methyl-N'-(2,2,2-trifluoro-ethyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). Light yellow solid. MS: $m/e = 468(M+H^+)$.

15

Example 50

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

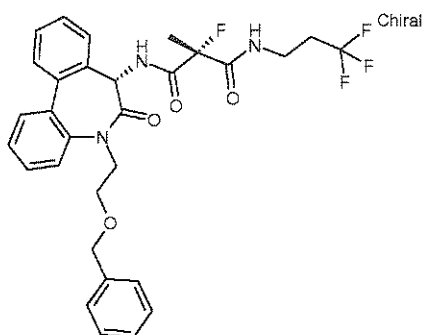


Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). White solid. MS: m/e= 532(M+H⁺).

5

Example 51

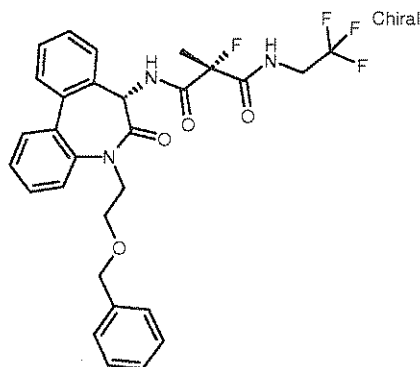
(R)-N-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-N'-(3,3,3-trifluoro-propyl)-malonamide



- 10 Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 3,3,3-trifluoropropylamine, the title compound was prepared in the same manner as described for example 1c. Colorless, viscous oil (72%). MS: m/e= 572(M+H⁺).

Example 52

- 15 (R)-N-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-N'-(2,2,2-trifluoro-ethyl)-malonamide

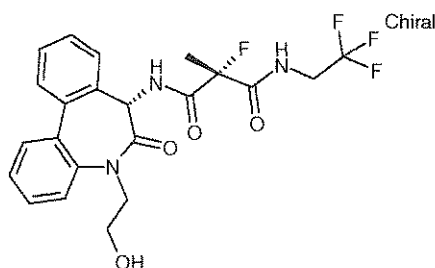


Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-malonamic acid and 2,2,2-trifluoroethylamine, the title compound

was prepared in the same manner as described for example 1c. Colorless, viscous oil (73%). MS: $m/e = 558(M+H^+)$.

Example 53

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

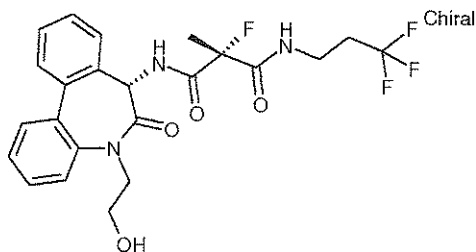


Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide, the title compound was prepared in the same manner as example 3 (91%). White solid. MS: $m/e = 468(M+H^+)$.

10

Example 54

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



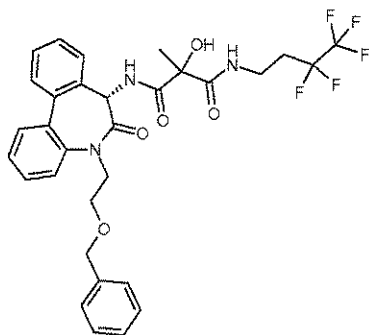
Using (R)-*N*-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-fluoro-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, the title compound was prepared in the same manner as example 3 (95%). Off-white solid. MS: $m/e = 482(M+H^+)$.

15

Example 55

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

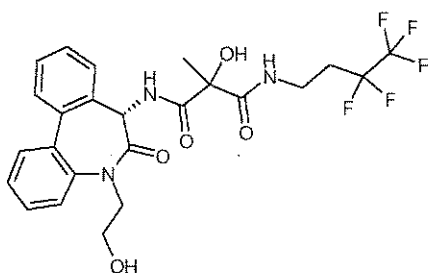
20



- Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-malonamic acid and 3,3,4,4,4-pentafluorobutylamine, the title compound was prepared in the same manner as described for example 1c. Light yellow, viscous oil (88%). MS: $m/e = 620(M+H^+)$.

Example 56

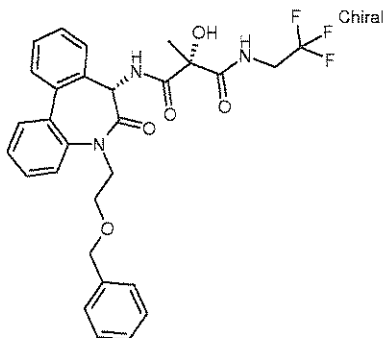
2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide



- Using *N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide, the title compound was prepared in the same manner as example 3 (92%). Off-white solid. MS: $m/e = 530(M+H^+)$.

Example 57

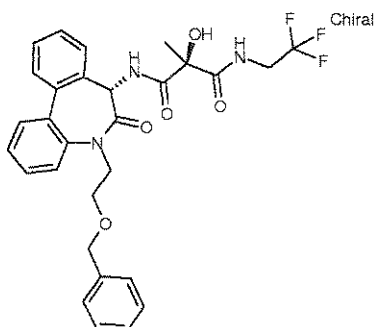
- (*R*)-*N*-[(*S*)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide



- Using (S)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and (R)-2-hydroxy-2-methyl-*N*-(2,2,2-trifluoro-ethyl)-malonamic acid, the title compound was prepared in the same manner as described for example 1c. Colorless, amorphous solid
 5 (96%). MS: $m/e = 556(M+H^+)$.

Example 58

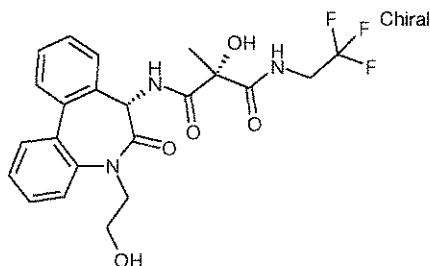
(S)-*N*-[(S)-5-(2-Benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide



- 10 Using (S)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and (S)-2-hydroxy-2-methyl-*N*-(2,2,2-trifluoro-ethyl)-malonamic acid, the title compound was prepared in the same manner as described for example 1c. Colorless, amorphous solid (91%). MS: $m/e = 556(M+H^+)$.

Example 59

- 15 (R)-2-Hydroxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide

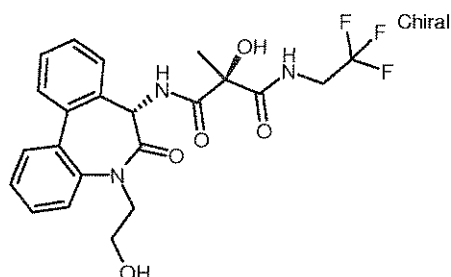


Using (R)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-2-hydroxy-2-methyl-N'-(2,2,2-trifluoro-ethyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). White solid. MS: m/e= 466(M+H⁺).

5

Example 60

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



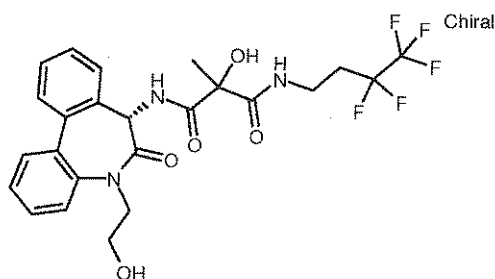
Using (S)-N-[(S)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-2-hydroxy-2-methyl-N'-(2,2,2-trifluoro-ethyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). White solid. MS: m/e= 466(M+H⁺).

10

Example 61

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

15

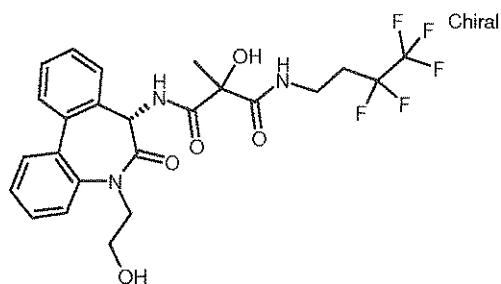


Separation of 2-hydroxy-N-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-2-methyl-N'-(3,3,4,4,4-pentafluoro-butyl)-malonamide (HPLC

on Chiralpak AD, eluent 20% ethanol in heptane) afforded the title compound as first eluting material with negative rotation. White solid (65% of th.). MS: $m/e = 530 (M+H^+)$.

Example 62

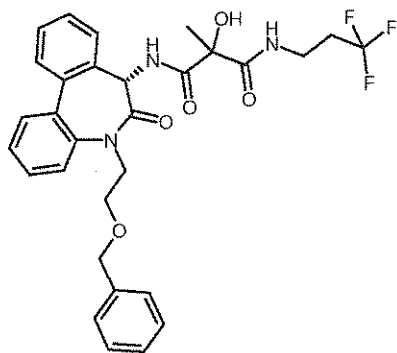
(S or R)-2-Hydroxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-
5 dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
epimer B



Separation of 2-hydroxy-*N*-[(S)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-
dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide (HPLC
10 on Chiralpak AD, eluent 20% ethanol in heptane) afforded the title compound as second
eluting material with negative rotation. White solid (72% of th.). MS: $m/e = 530 (M+H^+)$.

Example 63

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

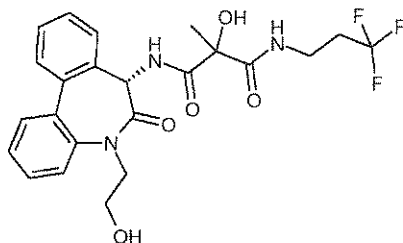


15

Using (S)-7-amino-5-(2-benzyloxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-
hydroxy-2-methyl-*N*-(3,3,3-trifluoro-propyl)-malonamic acid, the title compound was
prepared in the same manner as described for example 1c. Colorless, viscous oil (73%).
MS: $m/e = 570 (M+H^+)$.

Example 64

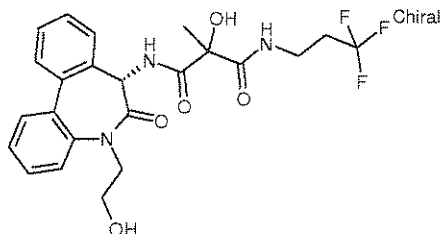
2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide



- 5 Using *N*-[(*S*)-5-(2-benzyloxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-hydroxy-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, the title compound was prepared in the same manner as example 3 (>98%). White solid, mp. 59-62°C. MS: $m/e = 480(M+H^+)$.

Example 65

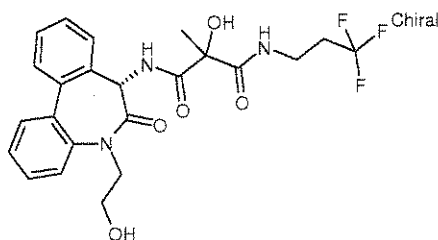
- 10 (*R* or *S*)-2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, epimer A



- Separation of 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide (HPLC on Chiralpak AD, eluent 20% ethanol in heptane) afforded the title compound as second eluting material with negative rotation. Off-white solid, mp. 61-69°C (76% of th.). MS: $m/e = 480(M+H^+)$.
- 15

Example 66

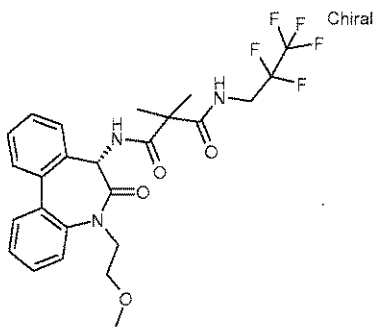
- (*S* or *R*)-2-Hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, epimer B
- 20



Separation of 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide (HPLC on Chiralpak AD, eluent 20% ethanol in heptane) afforded the title compound as second
 5 eluting material with negative rotation. Off-white solid, mp 64-71°C (79% of th.). MS: $m/e = 480(M+H^+)$.

Example 67

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

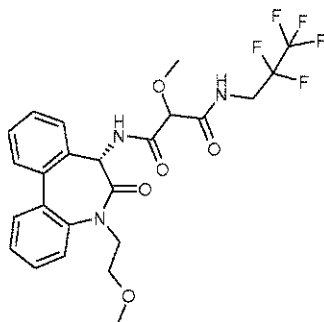


10

Using (*S*)-7-amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2,2-dimethyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid, the title compound was prepared in the same manner as example 1c (74%). White solid. MS: $m/e = 528(M+H^+)$.

Example 68

15 2-Methoxy-*N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

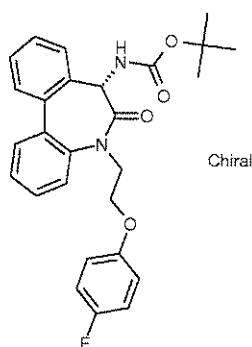


Using (S)-7-amino-5-(2-methoxy-ethyl)-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one and 2-methoxy-*N*-(2,2,3,3,3-pentafluoro-propyl)-malonamic acid, the title compound was prepared in the same manner as example 1c (84%). White solid. MS: $m/e = 530(M+H^+)$.

Example 69

- 5 *N*-{(S)-5-[2-(4-Fluoro-phenoxy)-ethyl]-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl}-2,2-dimethyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

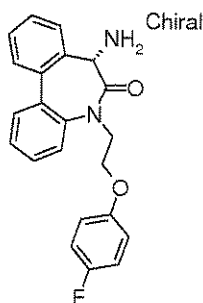
a) [(S)-5-[2-(4-fluoro-phenoxy)-ethyl]-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-carbamic acid *tert*-butyl ester



10

Using ((S)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl ester and 4-fluorophenoxy-ethylbromide, the title product was prepared in the same manner as described for example 1a (84%). White solid. MS: $m/e = 463(M+H^+)$.

b) (S)-7-Amino-5-[2-(4-fluoro-phenoxy)-ethyl]-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one

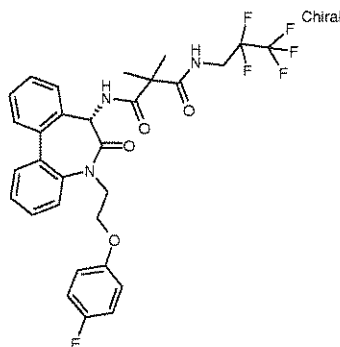


15

Using [(S)-5-[2-(4-fluoro-phenoxy)-ethyl]-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-carbamic acid *tert*-butyl ester, the title product was prepared in the same manner as described for example 24b (>98%). Light yellow solid. MS: $m/e = 363(M+H^+)$.

- c) *N*-{(S)-5-[2-(4-Fluoro-phenoxy)-ethyl]-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl}-2,2-dimethyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide

20



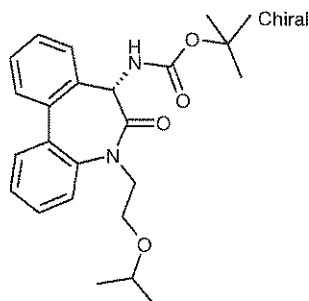
Using (S)-7-Amino-5-[2-(4-fluorophenoxy)-ethyl]-5H,7H-dibenzo[b,d]azepin-6-one and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoropropyl)-malonamic acid, the title compound

5 608(M+H⁺).

Example 70

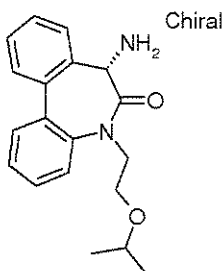
N-[(S)-5-(2-Isopropoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-2,2-dimethyl-N'-(2,2,3,3,3-pentafluoropropyl)-malonamide

10 a) [(S)-5-(2-Isopropoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-carbamic acid *tert*-butyl ester



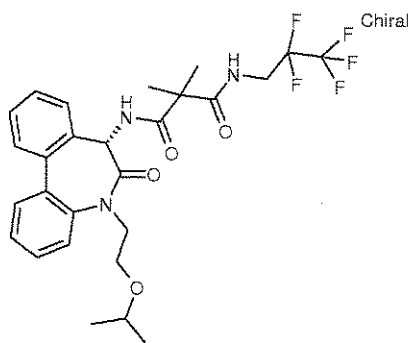
Using ((S)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-carbamic acid *tert*-butyl ester and 2-(2-bromo-ethoxy)-propane, the title product was prepared in the same manner as described for example 1a (69%). Pink, viscous oil. MS: m/e= 411(M+H⁺).

15 b) (S)-7-Amino-5-(2-isopropoxy-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one



Using [(S)-5-(2-Isopropoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-carbamic acid *tert*-butyl ester, the title product was prepared in the same manner as described for example 24b (>98%). Light yellow oil. MS: $m/e = 311(M+H^+)$.

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



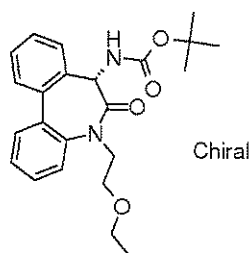
Using (S)-7-Amino-5-(2-isopropoxy-ethyl)-5H,7H-dibenzo[*b,d*]azepin-6-one and 2,2-dimethyl-*N*-(2,2,3,3,3-pentafluoro-propyl)-malonic acid, the title compound was prepared in the same manner as example 1c (78%). White solid. MS: $m/e = 556(M+H^+)$.

10

Example 71

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

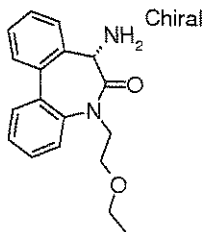
- a) [(S)-5-(2-Ethoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl]-carbamic acid *tert*-butyl ester



15

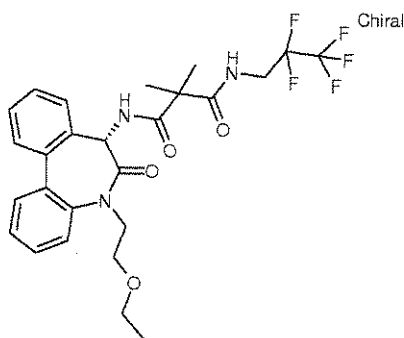
Using ((S)-6-oxo-6,7-dihydro-5H-dibenzo[*b,d*]azepin-7-yl)-carbamic acid *tert*-butyl ester and 2-bromomethyl-ethyl ether, the title product was prepared in the same manner as described for example 1a (83%). Pink, viscous oil. MS: $m/e = 397(M+H^+)$.

- b) (S)-7-Amino-5-(2-ethoxy-ethyl)-5H,7H-dibenzo[*b,d*]azepin-6-one



Using [(S)-5-(2-ethoxy-ethyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-carbamic acid *tert*-butyl ester, the title product was prepared in the same manner as described for example 24b (98%). Yellow oil. MS: $m/e = 297(M+H^+)$.

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

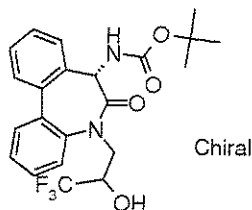


- Using (S)-7-amino-5-(2-ethoxy-ethyl)-5H,7H-dibenzo[b,d]azepin-6-one and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonic acid, the title compound was
10 prepared in the same manner as example 1c (80%). White solid. MS: $m/e = 542(M+H^+)$.

Example 72

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

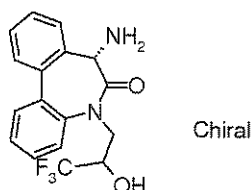
- 15 a) [(S)-5-(3,3,3-Trifluoro-2-hydroxy-propyl)-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-carbamic acid *tert*-butyl ester



((S)-6-Oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-carbamic acid *tert*-butyl ester (108 mg, 0.33 mmol) and 1,1,1-trifluoro-2,3-epoxypropane (762 mg, 6.7 mmol) were dissolved in DMF (2 ml) and heated to 90°C for 4 h in a sealed tube. After addition of

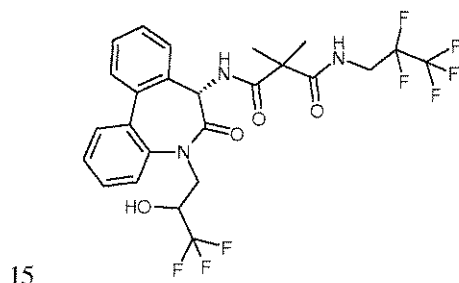
- another 500 mg of 1,1,1-trifluoro-2,3-epoxypropane, heating was continued for 18 h. The mixture was diluted with ethyl acetate and water (10 ml each), separated and the aqueous phase extracted twice with each 10 ml ethyl acetate. The combine organic phases are dried over magnesium sulfate and evaporated to dryness. Chromatography (silica, eluent
- 5 heptanes/ethyl acetate gradient from 1 to 30%) afforded the title compound as white solid (76%). MS: $m/e = 437(M+H^+)$.

b) (S)-7-Amino-5-(3,3,3-trifluoro-2-hydroxy-propyl)-5H,7H-dibenzo[b,d]azepin-6-one



- Using [(S)-5-(3,3,3-trifluoro-2-hydroxy-propyl)-6-oxo-6,7-dihydro-5H-
- 10 dibenzo[b,d]azepin-7-yl]-carbamic acid *tert*-butyl ester, the title product was prepared in the same manner as described for example 24b (>98%). White solid, mp 192-194°C. MS: $m/e = 337(M+H^+)$.

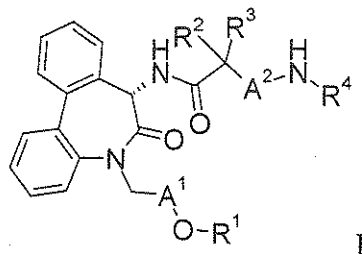
c) 2,2-Dimethyl-N'-[(S)-6-oxo-5-(3,3,3-trifluoro-2-hydroxy-propyl)-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-N'-(2,2,3,3,3-pentafluoro-propyl)-malonamide



Using (S)-7-amino-5-(3,3,3-trifluoro-2-hydroxy-propyl)-5H,7H-dibenzo[b,d]azepin-6-one and 2,2-dimethyl-N-(2,2,3,3,3-pentafluoro-propyl)-malonic acid, the title compound was prepared in the same manner as example 1c (87%). White solid. MS: $m/e = 582(M+H^+)$.

Claims

1. Compounds of the general formula



wherein

A¹ is -CHR- or -C(O)-;

A² is -C(O)- and

R²/R³ are independently from each other hydrogen, C₁ to C₇ alkyl, halogen, hydroxy or C₁ to C₇ alkoxy;

or

A² is -O-C(O)- and

R²/R³ are independently from each other hydrogen or C₁ to C₇ alkyl;

R is hydrogen or C₁ to C₇ alkyl substituted by halogen;

R¹ is hydrogen, C₁ to C₇ alkyl or -(CH₂)_n-aryl, optionally substituted by halogen;

R⁴ is C₁ to C₇ alkyl substituted by halogen

n is 0, 1 or 2;

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

2. Compounds of formula I according to claim 1, wherein A¹ is CH₂, A² is CO, R¹ is hydrogen or C₁ to C₇ alkyl.

3. Compounds according to claim 2, which compounds are

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

- N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2,2-dimethyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- 5 *N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methoxy-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- 2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-
- 10 methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- 2-ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- (*S* or *R*)-2-ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A,
- 15 [*R* or *S*] 2-ethoxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer B,
- 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide, epimer A,
- 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-
- 20 2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide epimer B,
- N*-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- 25 (*S*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide,
- N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-(3,3,3-trifluoro-propyl)-malonamide,
- N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-*N'*-
- 30 (3,3,4,4,4-pentafluoro-butyl)-malonamide,
- (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
- (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide,
- 35 (*R*)-2-fluoro-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide,
- 2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-

2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide,
(*R*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide,
(*S*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(2,2,2-trifluoro-ethyl)-malonamide,
(*R* or *S*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide, epimer A,
(*S* or *R*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,4,4,4-pentafluoro-butyl)-malonamide, epimer B,
2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide,
(*R* or *S*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, epimer A and
(*S* or *R*)-2-hydroxy-*N*-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-yl]-2-methyl-*N'*-(3,3,3-trifluoro-propyl)-malonamide, epimer B.

4. Compounds of formula I according to claim 1, wherein A¹ is CH₂, A² is O-CO and R¹ is hydrogen or C₁ to C₇ alkyl.

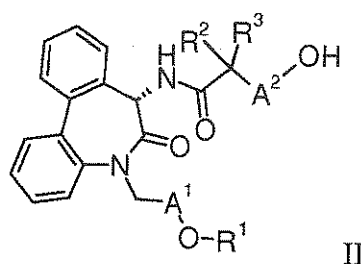
5. Compounds according to claim 4, which compounds are
(2,2,3,3,3-pentafluoro-propyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester,
(2,2,3,3,3-pentafluoro-propyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-methoxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester,
(3,3,4,4,4-pentafluoro-butyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester,
(3,3,3-trifluoro-propyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester,
(2-fluoro-ethyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester or
(2,2,2-trifluoro-ethyl)-carbamic acid (*S*)-1-[(*S*)-5-(2-hydroxy-ethyl)-6-oxo-6,7-dihydro-5*H*-dibenzo[*b,d*]azepin-7-ylcarbamoyl]-ethyl ester.

6. Compounds of formula I according to claim 1, wherein A¹ is CHCF₃, A² is CO and R¹ is hydrogen or C₁ to C₇ alkyl.

7. Compounds according to claim 6, which compound is
2,2-dimethyl-*N*-[(*S*)-6-oxo-5-(3,3,3-trifluoro-2-hydroxy-propyl)-6,7-dihydro-5*H*-
dibenzo[*b,d*]azepin-7-yl]-*N'*-(2,2,3,3,3-pentafluoro-propyl)-malonamide.

- 5 8. A process for preparing a compound of formula I as defined in claims 1 – 7, which
process comprises

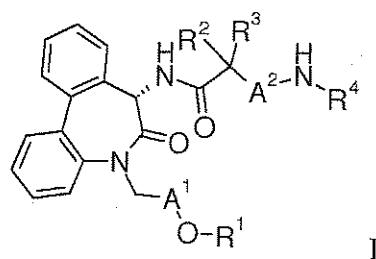
a) reacting a compound of formula



with a compound of formula



to a compound of formula



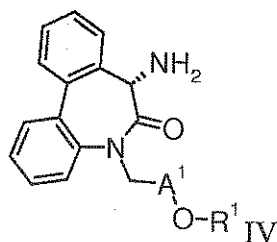
wherein A^1 and $\text{R}^1 - \text{R}^4$ have the meaning as described above and A^2 depicts CO,
and

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

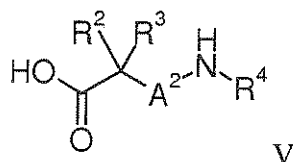
or

b) reacting a compound of formula

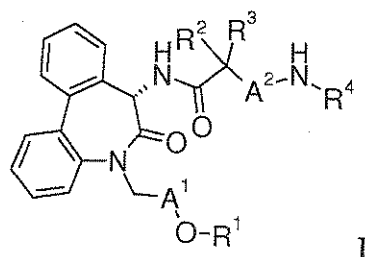
- 69 -



with a compound of formula



to a compound of formula



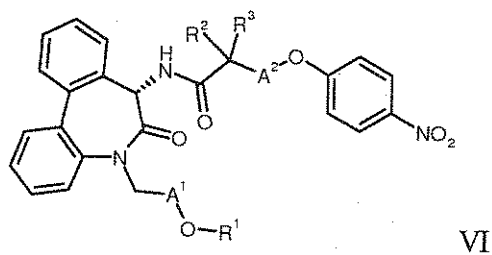
5

wherein A^1 and $R^1 - R^4$ have the meaning as described above and A^2 depicts CO, and

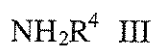
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

10 or

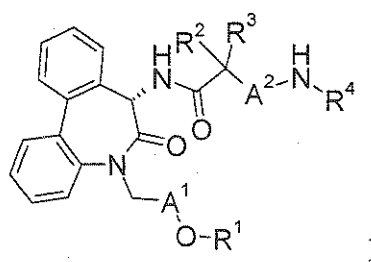
c) reacting a compound of formula



with a compound of formula



to a compound of formula



wherein A¹ and R¹–R⁴ have the meaning as described above and A² depicts O-CO,
and

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

9. A medicament containing one or more compounds as claimed in any one of claims 1 – 7 and pharmaceutically acceptable excipients.
10. A medicament according to claim 9 for the treatment of Alzheimer's disease.
11. The use of a compound in any one of claims 1 – 7 for the manufacture of medicaments for the treatment of Alzheimer's disease.
