

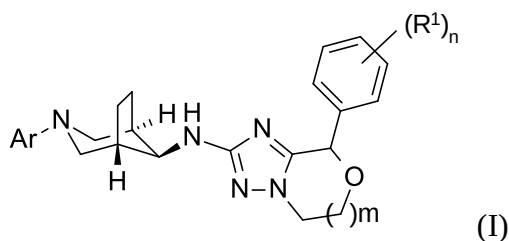
Clarke *et al.*, *J. Biol. Chem.*, 281 (2006) 31279-89
Stock *et al.*, *Bioorg. Med. Chem. Lett.*, 16 (2006) 2219–2223
Narlawar *et al.*, *J. Med. Chem.*, 49 (2006) 7588-91
Ebke *et al.*, *J. Biol. Chem.*, 286 (2011) 37181-86
5 Oehlich, Gijzen *et al.*, *J. Med. Chem.*, 54 (2011), 669 – 698
Li *et al.*, *Biochemistry*, 52 (2013), 3197 - 3216
Hall *et al.*, *Progress in Med. Chem.*, 53 (2014) 101-145
Bursavich *et al.*, *J. Med. Chem.*, 59 (2016).

10 Therefore, modulating the γ -secretase activity is a promising therapeutic strategy for the treatment or prevention of diseases associated with the deposition of β -amyloid in the brain, such as Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

15 There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with the deposition of β -amyloid in the brain. It is, therefore, an object of this invention to provide compounds useful for the treatment or prevention or amelioration of such diseases and disorders with improved therapeutic properties.

20 Summary of the invention

A first object of the present ~~invention~~disclosure is a compound of formula (I)



wherein

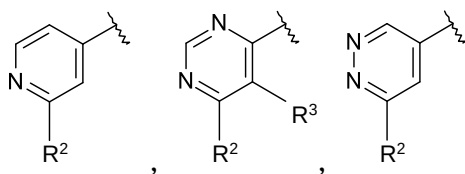
R¹ is halogen, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, or lower alkoxy substituted by halogen,

and R¹ may be different if n = 2 or 3;

m is 1 or 2;

n is 1, 2 or 3;

Ar is a six membered heteroaryl group, selected from



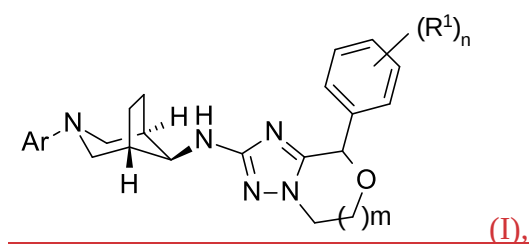
wherein

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, or lower alkoxy;

R^3 is hydrogen or halogen;

5 or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure provides a compound of formula (I)



wherein

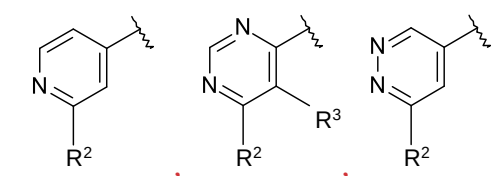
10 R^1 is halogen, C_{1-7} -alkyl, C_{1-7} -alkyl substituted by halogen, C_{1-7} -alkoxy, or C_{1-7} -alkoxy substituted by halogen,

and R^1 may be different if $n = 2$ or 3 ;

m is 1 or 2;

n is 1, 2 or 3;

15 Ar is a six membered heteroaryl group, selected from



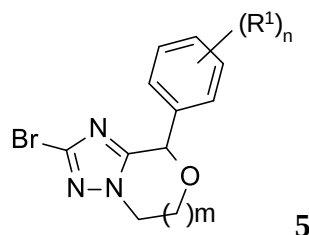
wherein

R^2 is hydrogen, halogen, C_{1-7} -alkyl, C_{1-7} -alkyl substituted by halogen, or C_{1-7} -alkoxy;

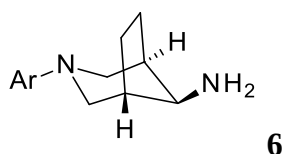
R^3 is hydrogen or halogen;

20 or a pharmaceutically acceptable salt thereof.

~~A further object of the invention is~~In another aspect, the present disclosure provides a process for the preparation of a compound ~~of formula (I)~~ as described herein, comprising reacting a compound 5



5 with an amine 6



wherein Ar, R¹, n and m are as defined herein,
to form said compound of formula (I), and if desired, converting the compounds obtained into a pharmaceutically acceptable salt thereof.

10

A further object of the present ~~invention~~disclosure is a compound of formula (I) as described herein, when manufactured according to the process as described above.

15

~~A further object of the present invention is~~In another aspect, the present disclosure provides a compound ~~of formula (I)~~ as described herein for use as a therapeutically active substance.

20

~~A further object of the present invention is~~In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound ~~of formula (I)~~ as described herein and a therapeutically inert carrier.

~~A further object of the present invention is~~In another aspect, the present disclosure provides a compound ~~of formula (I)~~ as described herein for use in the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid

angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type (~~HCHWA-D~~), multi-infarct dementia, dementia pugilistica, or Down syndrome.

A further object of the present ~~invention~~disclosure is the use of a compound of formula (I) as described herein for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), multi-infarct dementia, dementia pugilistica, or Down syndrome.

~~A further object of the present invention is~~In another aspect, the present disclosure
provides the use of a compound ~~of formula (I)~~ as described herein ~~for~~in the preparation of a medicament for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type (~~HCHWA-D~~), multi-infarct dementia, dementia pugilistica, or Down syndrome.

A further object of the present ~~invention~~disclosure is a method for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), multi-infarct dementia, dementia pugilistica, or Down syndrome, which method comprises administering an effective amount of a compound of formula (I) as described herein.

Detailed description of the invention

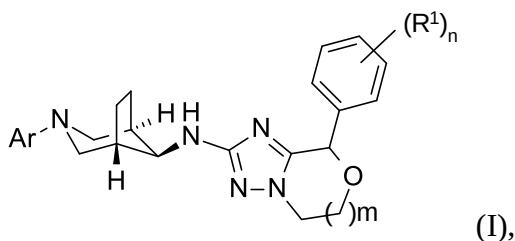
The following definitions of the general terms used in the present description apply irrespectively of whether the terms in question appear alone or in combination with other groups.

The term "lower alkyl", alone or in combination with other groups, refers to saturated straight- or branched-chain alkyl group, with single or multiple branching, wherein the alkyl group in general comprises 1 to 7 carbon atoms ("C₁₋₇-alkyl"), for example, methyl (Me), ethyl (Et), propyl, isopropyl (i-propyl), n-butyl, i-butyl (isobutyl), 2-butyl (sec-butyl), t-butyl (tert-butyl), isopentyl, 2-ethyl-propyl, 1,2-dimethyl-propyl and the like. Particular lower alkyl groups have 1 to 4 carbon atoms ("C₁₋₄-alkyl").

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 CF₃, CHF₂, CH₂F, CHF₂CF₃,

Claims

1. A compound of formula (I)



5

(I),

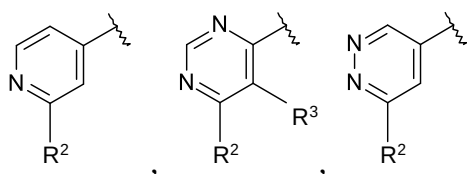
wherein

R¹ is halogen, ~~lower C₁₋₇-alkyl~~, ~~C₁₋₇-lower~~alkyl substituted by halogen, ~~C₁₋₇-lower~~alkoxy, or ~~C₁₋₇-lower~~alkoxy substituted by halogen, and R¹ may be different if n = 2 or 3;

10 m is 1 or 2;

n is 1, 2 or 3;

Ar is a six membered heteroaryl group, selected from



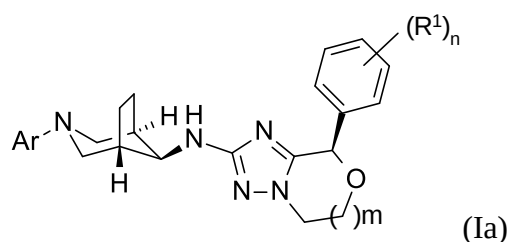
wherein

15 R² is hydrogen, halogen, ~~C₁₋₇-lower~~alkyl, ~~C₁₋₇-lower~~alkyl substituted by halogen, or ~~C₁₋₇-lower~~alkoxy;

R³ is hydrogen or halogen;

or a pharmaceutically acceptable salt thereof.

- 20 2. The compound of formula (I) according to claim 1, wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein R¹, m, n and Ar are as defined in claim 1.

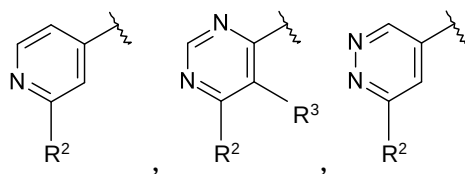
- 10



- 20

R^3 is hydrogen.

- 25 8. The compound of formula (I) according to any one of claims 1 to 7, wherein Ar is a
six membered heteroaryl group, selected from



wherein

R² is methyl or methoxy;

R³ is hydrogen.

5

9. The compound of formula (I) according to any one of claims 1 to 3, wherein:

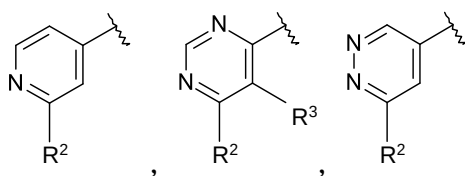
R¹ is halogen;

m is 1 or 2;

n is 2 or 3;

10

Ar is a six membered heteroaryl group, selected from



wherein

R² is ~~C₁₋₇-lower~~alkyl or ~~C₁₋₇-lower~~alkoxy;

R³ is hydrogen.

15

10. The compound of formula (I) according to any one of claims 1 to 3, wherein:

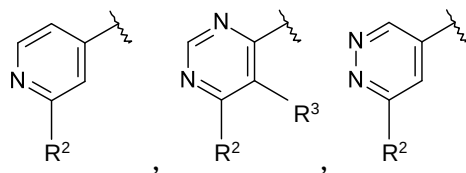
R¹ is fluorine or chlorine,

m is 1 or 2;

n is 2 or 3;

20

Ar is a six membered heteroaryl group, selected from



wherein

R² is methyl or methoxy;

R³ is hydrogen.

25

11. A compound according to any one of claims 1 to 10, selected from

- (9R)-9-(2,3-difluorophenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 5 (9S)-9-(2,3-difluorophenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9R)-9-(2,4-difluorophenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 10 (9S)-9-(2,4-difluorophenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9R)-9-(2,3-difluorophenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 15 (9S)-9-(2,3-difluorophenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9R)-9-(3,5-difluorophenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 20 (9S)-9-(3,5-difluorophenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9R)-9-(2,4-difluorophenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 25 (9S)-9-(2,4-difluorophenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 30 (9R)-9-(3,5-difluorophenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

- (9S)-9-(3,5-difluorophenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 5 (9R)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 10 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 15 (9R)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 20 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 25 (8R)-8-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 30 (8S)-8-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;

- (8R)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8S)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 5 (8R)-8-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8S)-8-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 10 (8R)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8S)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 15 (8R)-8-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8S)-8-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 20 (8R)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8S)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 25 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 30 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

(9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

5 (9R)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

(9S)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

10 (9R)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

(9S)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

or a pharmaceutically acceptable salt thereof.

15

12. A compound according to any one of claims 1 to 10, selected from

(9R)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

20 (9S)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

25 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

(9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

30 (9R)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

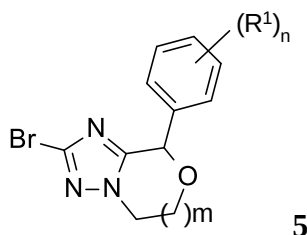
(9S)-N-[(1R,5S)-3-(6-methylpyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

- (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 5 (9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (8R)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 10 (8S)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8R)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- (8S)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-8-(2,3,4-trifluorophenyl)-6,8-dihydro-5H-[1,2,4]triazolo[5,1-c][1,4]oxazin-2-amine;
- 15 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 20 (9R)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-9-(3-chloro-5-fluoro-phenyl)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 25 (9R)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- (9S)-N-[(1R,5S)-3-(2-methoxy-4-pyridyl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
- 30 (9R)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;

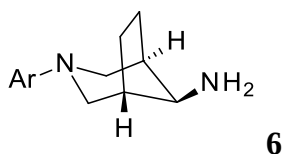
(9S)-N-[(1R,5S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-9-(2,3,4-trifluorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-c][1,4]oxazepin-2-amine;
or a pharmaceutically acceptable salt thereof.

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13. A process for the preparation of a compound according to any one of claims 1 to 12, comprising reacting a compound 5



with an amine 6



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wherein Ar, R¹, n and m are as defined in any one of claims 1 to 12, to form said compound of formula (I), and if desired, converting the compounds obtained into a pharmaceutically acceptable salt thereof.

15 ~~14.~~ A compound according to any one of claims 1 to 12, when manufactured according to the process of claim 13.

~~15.~~ 14. A compound according to any one of claims 1 to 12 and 14 for use as a therapeutically active substance.

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~~16.~~ 15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 and 14 and a therapeutically inert carrier.

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~~17.~~ 16. A compound according to any one of claims 1 to 12 and 14 for use in the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type, multi-infarct dementia, dementia pugilistica, or Down syndrome.

~~18. The use of a compound according to any one of claims 1 to 12 and 14 for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type, multi-infarct dementia, dementia pugilistica, or Down syndrome.~~

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~~19.~~17. The use of a compound according to any one of claims 1 to 12 ~~and 14~~ ~~for~~ in the preparation of a medicament for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type, multi-infarct dementia, dementia pugilistica, or Down syndrome.

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~~20. A method for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis-Dutch type, multi-infarct dementia, dementia pugilistica, or Down syndrome, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 12 and 14.~~

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~~21. The invention as hereinbefore described.~~

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