

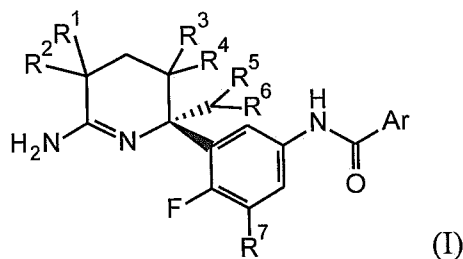
symptoms of the disease and include acetylcholinesterase inhibitors to improve cognitive properties as well as anxiolytics and antipsychotics to control the behavioral problems associated with this ailment.

The hallmark pathological features in the brain of AD patients are neurofibrillary tangles which are generated by hyperphosphorylation of tau protein and amyloid plaques which form by aggregation of beta-amyloid 1-42 (Abeta 1-42) peptide. Abeta 1-42 forms oligomers and then fibrils, and ultimately amyloid plaques. The oligomers and fibrils are believed to be especially neurotoxic and may cause most of the neurological damage associated with AD. Agents that prevent the formation of Abeta 1-42 have the potential to be disease-modifying agents for the treatment of AD. Abeta 1-42 is generated from the amyloid precursor protein (APP), comprised of 770 amino acids. The N-terminus of Abeta 1-42 is cleaved by beta-secretase (BACE1), and then gamma-secretase cleaves the C-terminal end. In addition to Abeta 1-42, gamma-secretase also liberates Abeta 1-40 which is the predominant cleavage product as well as Abeta 1-38 and Abeta 1-43. These Abeta forms can also aggregate to form oligomers and fibrils. Thus, inhibitors of BACE1 would be expected to prevent the formation of Abeta 1-42 as well as Abeta 1-40, Abeta 1-38 and Abeta 1-43 and would be potential therapeutic agents in the treatment of AD.

WO-2015/124576 (Lundbeck & Co AS H) discloses 2-amino-3,5,5-trifluoro-3,4,5,6-tetrahydropyridine derivatives and their use as BACE inhibitors for the treatment of neurodegenerative disorders. WO-2011/009943 (Novartis AG) discloses dihydrooxazine derivatives having BACE inhibitory properties. WO-2014/059185 (Amgen Inc) discloses dihydrothiazine derivatives as BACE inhibitors.

SUMMARY

The present disclosure, in one aspect, is directed to compounds of Formula (I)



and the tautomers and the stereoisomeric forms thereof, wherein

R¹ is selected from the group consisting of -C₁₋₃alkyl, -C₁₋₃alkyl-F and fluoro;

R² is selected from the group consisting of -SO₂C₁₋₃alkyl, -SO₂cyclopropyl, -CN, -OC₁₋₃alkyl, CF₃, and -SO(NCH₃)CH₃;

Ar is homoaryl or heteroaryl;

5 wherein homoaryl is phenyl or phenyl substituted with one, two or three substituents each independently selected from the group consisting of halo, cyano, C₁₋₃alkyl, cyclopropyl, C₁₋₃alkyloxy, cyclopropyloxy, (cyclopropyl)C₁₋₃alkyloxy, monohalo-C₁₋₃alkyl, polyhalo-C₁₋₃alkyl, monohalo-cyclopropyl, polyhalo-cyclopropyl, monohalo-C₁₋₃alkyloxy, polyhalo-C₁₋₃alkyloxy, monohalo-cyclopropyloxy, polyhalo-cyclopropyloxy, (C₁₋₃alkyloxy)C₁₋₃alkyloxy, (cyclopropyloxy)C₁₋₃alkyloxy, and HC≡CCH₂O;

10 heteroaryl is selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, and oxadiazolyl, each optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, cyano, C₁₋₃alkyl, cyclopropyl, C₂₋₃alkynyl, C₁₋₃alkyloxy, cyclopropyloxy, (cyclopropyl)C₁₋₃alkyloxy, monohalo-C₁₋₃alkyl, polyhalo-C₁₋₃alkyl, monohalo-cyclopropyl, polyhalo-cyclopropyl, monohalo-C₁₋₃alkyloxy, polyhalo-C₁₋₃alkyloxy, monohalo-cyclopropyloxy, polyhalo-cyclopropyloxy, (C₁₋₃alkyloxy)C₁₋₃alkyloxy, (cyclopropyloxy)C₁₋₃alkyloxy, and HC≡CCH₂O;

15 R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of H, fluoro, methyl and methoxy; and

20 R⁷ is hydrogen or fluoro;

and the pharmaceutically acceptable addition salts and the solvates thereof.

25 Illustrative of the disclosure is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound described above and a pharmaceutically acceptable carrier. An illustration of the disclosure is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the disclosure is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. In another

aspect, there is provided a process for preparing a pharmaceutical composition described above comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound described above.

Exemplifying the disclosure are methods of treating a disorder mediated by the
5 beta-secretase enzyme, comprising administering to a subject in need thereof a

therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Further exemplifying the disclosure are methods of inhibiting the beta-secretase enzyme, comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

An example of the disclosure is a method of treating a disorder selected from the group consisting of Alzheimer's disease, mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease, and dementia associated with beta-amyloid, preferably Alzheimer's disease, comprising administering to a subject in need thereof, a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Another example of the disclosure is any of the compounds described above for use in treating: (a) Alzheimer's Disease, (b) mild cognitive impairment, (c) senility, (d) dementia, (e) dementia with Lewy bodies, (f) Down's syndrome, (g) dementia associated with stroke, (h) dementia associated with Parkinson's disease, or (i) dementia associated with beta-amyloid in a subject in need thereof.

In another aspect, there is provided a compound described above or a pharmaceutical composition described above for use as a medicament.

In another aspect, there is provided a compound described above or a pharmaceutical composition described above for use in the treatment or prevention of Alzheimer's disease (AD), mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease, or dementia associated with beta-amyloid.

In another aspect, there is provided a compound described above or a pharmaceutical composition described above for use in modulating beta-site amyloid cleaving enzyme activity.

In another aspect, there is provided use of a compound described above or a pharmaceutical composition described above for the manufacture of a medicament for treating or preventing Alzheimer's disease (AD), mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease, or dementia associated with beta-amyloid.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula (I) as defined hereinbefore, and pharmaceutically acceptable addition salts and solvates thereof. The compounds of formula (I) are inhibitors of the beta-secretase enzyme (also known as
5 beta-site cleaving enzyme, BACE, BACE1, Asp2 or memapsin 2, or BACE2), and may be useful in the treatment of Alzheimer's disease, mild cognitive impairment, senility, dementia, dementia associated with stroke, dementia with Lewy bodies, Down's syndrome, dementia associated with Parkinson's disease, and dementia associated with beta-amyloid, preferably Alzheimer's disease, mild cognitive impairment or dementia,
10 more preferably Alzheimer's disease.

In a particular embodiment, the invention is directed to compounds of Formula (I), wherein

R¹ is selected from the group consisting of -C₁₋₃alkyl, -C₁₋₃alkyl-F and fluoro;

R² is selected from the group consisting of -SO₂C₁₋₃alkyl, -SO₂cyclopropyl, -CN,
15 -OC₁₋₃alkyl, CF₃, and -SO(NCH₃)CH₃;

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier.
10. A process for preparing a pharmaceutical composition as defined in claim 9 comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound according to any one of claims 1 to 8.
11. A compound as defined in any one of claims 1 to 8 or a pharmaceutical composition as defined in claim 9 for use as a medicament.
12. A compound as defined in any one of claims 1 to 8 or a pharmaceutical composition as defined in claim 9 for use in the treatment or prevention of Alzheimer's disease (AD), mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease, or dementia associated with beta-amyloid.
13. A compound according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 9 for use in modulating beta-site amyloid cleaving enzyme activity.
14. Use of a compound as claimed in any one of claims 1 to 8 or a pharmaceutical composition as claimed in claim 9 for the manufacture of a medicament for treating or preventing Alzheimer's disease (AD), mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease, or dementia associated with beta-amyloid.