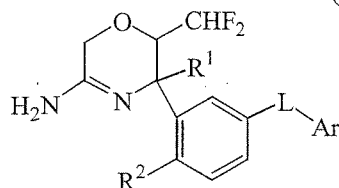


1-42 is generated from the amyloid precursor protein (APP), comprised of 770 amino acids. The N-terminus of Abeta 1-42 is cleaved by beta-secretase (BACE), and then gamma-secretase cleaves the C-terminal end. In addition to Abeta 1-42, gamma-secretase also liberates Abeta 1-40 which is the predominant 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 BACE 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-2011/009943 (Novartis) discloses unsubstituted and 2-substituted oxazine derivatives and their use as BACE inhibitors for the treatment of neurological disorders. WO-2011/020806 (Hoffmann-LaRoche) discloses 2,6-unsubstituted 3-amino-5-phenyl-5,6-dihydro-2H-[1,4]oxazine derivatives having BACE1 and/or BACE2 inhibitory properties.

SUMMARY

The present disclosure, in one aspect, is directed to compound such as a 5,6-dihydro-2H-[1,4]oxazin-3-amine derivative of Formula (I)



or a tautomer or a stereoisomeric form thereof, wherein

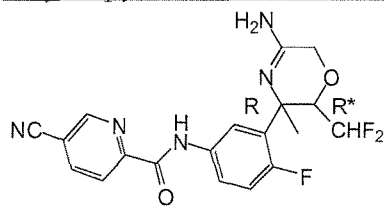
R¹ is C₁₋₃alkyl;

R² is hydrogen or fluoro;

L is a bond or -NHCO-;

Ar is selected from the group consisting of pyridinyl, pyrimidinyl and pyrazinyl, each optionally substituted with halo or C₁₋₃alkoxy; and the pharmaceutically acceptable addition salts thereof.

In another aspect, there is provided a compound defined as *N*-{3-[(2*R**,3*R*)-5-Amino-2-(difluoromethyl)-3-methyl-3,6-dihydro-2*H*-1,4-oxazin-3-yl]-4-fluorophenyl}-5-cyanopyridine-2-carboxamide

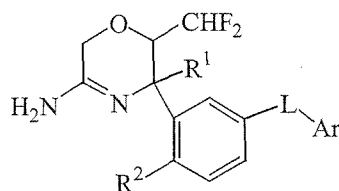


5 or a pharmaceutically acceptable addition salt thereof

In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of any of the compounds described above. An illustration of the disclosure is a pharmaceutical
10 composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. In another aspect, there is provided

Claims

1. A compound of Formula (I)



or a tautomer or a stereoisomeric form thereof, wherein

R¹ is C₁₋₃alkyl;

R² is hydrogen or fluoro;

L is a bond or -NHCO-;

Ar is selected from the group consisting of pyridinyl, pyrimidinyl and pyrazinyl, each optionally substituted with halo or C₁₋₃alkoxy; or a pharmaceutically acceptable addition salt thereof.

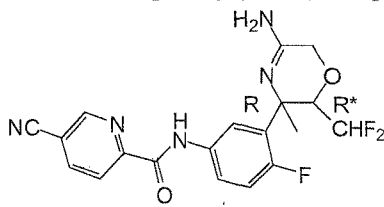
2. The compound of claim 1 wherein R¹ is methyl or ethyl.

3. The compound of claim 2 wherein Ar is selected from 5-methoxy-pyridinyl, 5-pyrimidinyl and 5-fluoropyrazinyl.

4. The compound of claim 1 wherein R² is hydrogen or fluoro.

5. The compound of claim 1 wherein the quaternary carbon atom substituted with R¹ has the *R*-configuration.

6. A compound defined as *N*-{3-[(2*R**,3*R*)-5-Amino-2-(difluoromethyl)-3-methyl-3,6-dihydro-2*H*-1,4-oxazin-3-yl]-4-fluorophenyl}-5-cyanopyridine-2-carboxamide



or a pharmaceutically acceptable addition salt thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

78. A process for preparing a pharmaceutical composition as defined in claim 67, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 56.

89. A compound as defined in any one of claims 1 to ~~5~~6 for use in the treatment or prevention of Alzheimer's disease (AD), mild cognitive impairment, senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease or dementia associated with beta-amyloid.

910. Use of a compound as defined in any one of claims 1 to ~~5~~6 or a pharmaceutical composition as defined in claim ~~6~~7 in the manufacture of a medicament for the treatment of a disorder selected from the group consisting of Alzheimer's disease, mild cognitive impairment, senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

15