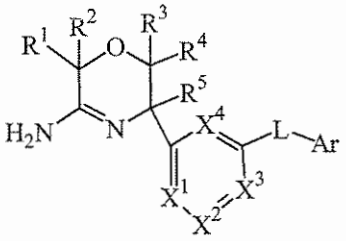
1-42 is generated from the amyloid precursor protein (APP), comprised of 770 amino acids. The N-terminus of Abeta 1-42 is cleaved by beta-secretase (BACE), and then gamma-secretase cleaves the C-terminal end. In addition to Abeta 1-42, gamma-secretase also liberates Abeta 1-40 which is the predominant 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 ~~OF THE INVENTION~~

In one aspect, t~~T~~he present ~~invention~~disclosure is directed to 5,6-dihydro-2*H*-[1,4]oxazin-3-ylamine derivatives of Formula



and the tautomers and the stereoisomeric forms thereof, wherein

R^1, R^2, R^3, R^4 are independently selected from the group consisting of hydrogen, fluoro, cyano, C_{1-3}alkyl, mono- and polyhalo-C_{1-3}alkyl, and C_{3-6}cycloalkyl; or R^1 and R^2, or R^3 and R^4 taken together with the carbon atom to which they are attached may form a C_{3-6}cycloalkanediyl ring;

R^5 is selected from the group consisting of hydrogen, C_{1-3}alkyl, cyclopropyl, mono- and polyhalo-C_{1-3}alkyl, homoaryl and heteroaryl;

X^1, X^2, X^3, X^4 are independently $C(R^6)$ or N, provided that no more than two thereof represent N; each R^6 is selected from the group consisting of hydrogen, halo, C_{1-3}alkyl, mono- and polyhalo-C_{1-3}alkyl, cyano, C_{1-3}alkyloxy, mono- and polyhalo-C_{1-3}alkyloxy;

L is a bond or $-N(R^7)CO-$, wherein R^7 is hydrogen or C_{1-3}alkyl;

Ar is homoaryl or heteroaryl;
wherein homoaryl is phenyl or phenyl substituted with one, two or three substituents selected from the group consisting of halo, cyano, C_{1-3}alkyl, C_{1-3}alkyloxy, mono- and polyhalo-C_{1-3}alkyl, mono-and polyhalo-C_{1-3}alkyloxy;
heteroaryl is selected from the group consisting of pyridyl, pyrimidyl, pyrazyl, pyridazyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, and oxadiazolyl, each optionally substituted with one, two or three substituents selected from the group consisting of halo, cyano, C_{1-3}alkyl, C_{2-3}alkynyl, C_{1-3}alkyloxy, mono- and polyhalo-C_{1-3}alkyl, mono- and polyhalo-C_{1-3}alkyloxy, and C_{1-3}alkyloxyC_{1-3}alkyloxy;
and the addition salts and the solvates thereof.

Illustrative of the ~~invention~~disclosure is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. In a second aspect, the present disclosure is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above and a pharmaceutically acceptable carrier. An illustration of the ~~invention~~disclosure is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the ~~invention~~disclosure is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. In a third aspect, the present disclosure is directed to a process for preparing a pharmaceutical composition as defined above, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined above.

Exemplifying the ~~invention~~disclosure are methods of treating a disorder mediated by 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.

Further exemplifying the ~~invention~~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.

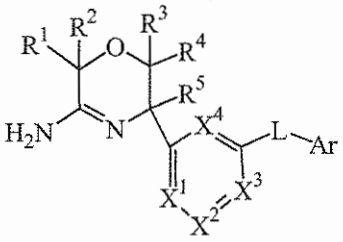
An example of the ~~invention~~disclosure is a method of treating a disorder selected from the group consisting of Alzheimer's disease, mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease 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 ~~invention~~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 and (i) dementia associated with beta-amyloid, in a subject in need thereof. Hence, in a fourth aspect, the present disclosure is directed to a compound as defined above for use in the treatment, prevention or prophylaxis 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.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula (I) as defined hereinbefore, and pharmaceutically acceptable salts thereof. The compounds of formula (I) are inhibitors of the beta-secretase enzyme (also known as beta-site cleaving enzyme, BACE, BACE1 , Asp2 or memapsin 2), and are 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, more preferably Alzheimer's disease.

In particular the present invention is directed to 6-substituted 5,6-dihydro-2*H*-[1,4]oxazin-3-ylamine derivatives of Formula (I)



and the tautomers and the stereoisomeric forms thereof, wherein

R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, fluoro, cyano, C_{1-3}alkyl, mono- and polyhalo-C_{1-3}alkyl, and C_{3-6}cycloalkyl;

R^4 is fluoro or trifluoromethyl; or

R^1 and R^2, or R^3 and R^4 taken together with the carbon atom to which they are attached may form a C_{3-6}cycloalkanediyl ring;

R^5 is selected from the group consisting of hydrogen, C_{1-3}alkyl, cyclopropyl, mono- and polyhalo-C_{1-3}alkyl, homoaryl and heteroaryl;

10. The compound according to claim 1 wherein R^1 and R^2 are hydrogen, R^3 is fluoro, R^4 is trifluoromethyl and L is $-N(R^7)CO-$ wherein R^7 is hydrogen.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

12. A process for preparing a pharmaceutical composition as defined in claim 11, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutic ally effective amount of a compound as defined in any one of claims 1 to 10.

13. A compound as defined in any one of claims 1 to 10 for use in the treatment, prevention or prophylaxis 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.

~~**14.** 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, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound as defined in any one of claims 1 to 10 or a pharmaceutical composition as defined in claim 11.~~