

2002/0128319; Eriksen (2003) J. Clin. Invest. 112, 440). Potential limitations for the use of NSAIDs to prevent or treat AD are their inhibition activity of cyclooxygenase (COX) enzymes, which can lead to unwanted side effects, and their low CNS penetration (Peretto et al., 2005, J. Med. Chem. 48, 5705-5720). More recently the NSAID R-flurbiprofen, an enantiomer lacking
 5 Cox-inhibitory activity and related gastric toxicity, has failed in large phase III trial since the drug did not improve thinking ability or the ability of patients to carry out daily activities significantly more than those patients on placebo.

WO-2010/100606 discloses phenyl imidazoles and phenyl triazoles for use as gamma-secretase modulators.

10 US20090062529 relates to polycyclic compounds effective as therapeutic or prophylactic agents for a disease caused by A β .

WO-2010/070008 is concerned with novel substituted bicyclic imidazole derivatives useful as γ -secretase modulators.

WO-2010/089292 is concerned with novel substituted bicyclic heterocyclic compounds useful as
 15 γ -secretase modulators.

WO-2011/006903 is concerned with novel substituted triazole and imidazole derivatives useful as γ -secretase modulators.

WO-2012/131539 relates to novel bicyclic pyridinones useful as brain-penetrable γ -secretase modulators.

20 There is a strong need for novel compounds which modulate γ -secretase activity thereby opening new avenues for the treatment of AD. It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative. The compounds of the present invention or part of the compounds of the present invention may have improved metabolic stability properties, improved central brain availability, improved
 25 solubilities, or reduced CYP inhibition compared with the compounds disclosed in the prior art. It is accordingly an object of the present invention to provide such novel compounds.

Summary of the invention

It has been found that the compounds of the present ~~invention-disclosure~~ are useful as γ -secretase modulators. The compounds according to the ~~disclosure invention~~ and the pharmaceutically
 30 acceptable compositions thereof, may be useful in the treatment or prevention of AD.

The present ~~disclosure, in one aspect, invention~~ concerns novel compounds of Formula (I):

R¹ is hydrogen, C₁₋₄alkyl or Ar;

provided however that R¹ is C₁₋₄alkyl or Ar when L is a covalent bond;

- 5 R^2 is hydrogen, phenyl, cyclo C_{3-7} alkyl, tetrahydro-2H-pyranyl, tetrahydro-2H-thiopyranyl, piperidinyl, or C_{1-4} alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, hydroxyl, C_{1-4} alkyloxy and NR^7R^8 ; Z is methylene or 1,2-ethanediyl, wherein methylene or 1,2-ethanediyl is optionally substituted with one or two C_{1-4} alkyl substituents ;
- 10 L is a covalent bond, $-(CH_2)_m-Y-(CH_2)_n-$, 1,2-cyclopropanediyl, C_{1-6} alkanediyl optionally substituted with one or more substituents selected from the group consisting of tetrahydro-2H-pyranyl, phenyl and C_{1-4} alkyloxy C_{1-4} alkyl, or C_{1-6} alkanediyl wherein two geminal hydrogen atoms are replaced by C_{2-6} alkanediyl;
- 15 m represents 3, 4, 5, 6 or 7;
n represents 1, 2 or 3;
Y is O or NH;
- Ar is a ring system selected from the group consisting of phenyl, indolyl, oxazolyl, benzo[b]thienyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 3,4-dihydro-2H-1,5-benzodioxepinyl, pyridyl, indanyl, 1,2,3,4-tetrahydro-1-naphthalenyl, and naphthalenyl; wherein said ring system is optionally substituted with one or more substituents each independently selected from the group consisting of halo, Ar^2 , R^0 , C_{1-4} alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyloxy and cyclo C_{3-7} alkyl, and
- 25 C_{1-4} alkyloxy optionally substituted with one or more substituents each independently selected from the group consisting of halo and cyclo C_{3-7} alkyl;
- Ar^2 is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo and C_{1-4} alkyl optionally substituted with one or more halo substituents;
- 30 R^3 is hydrogen, halo or C_{1-4} alkyl;

R⁴ is hydrogen, halo or C₁₋₄alkyl;

R⁵ is hydrogen or C₁₋₄alkyl;

X is CR⁶ or N;

R⁶ is hydrogen or C₁₋₄alkyl;

5 R⁷ is hydrogen or C₁₋₄alkyl;

R⁸ is hydrogen or C₁₋₄alkyl;

R⁰ is a ring system selected from the group consisting of piperidinyl, morpholinyl, cycloC₃₋₇alkyl, pyrazolyl and pyrrolidinyl; wherein said ring system is optionally substituted with one or more substituents each independently selected from the group consisting of halo or C₁₋₄alkyl optionally substituted with one or more halo atoms;
10 and the pharmaceutically acceptable addition salts, and the solvates thereof.

The present ~~disclosure invention~~ also concerns methods for the preparation of compounds of Formula (I) and pharmaceutical compositions comprising them. In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as
15 active ingredient, a therapeutically effective amount of a compound as defined herein.

The present compounds were found to modulate the γ -secretase activity in vitro and in vivo, and therefore may be useful in the treatment or prevention of AD, traumatic brain injury (TBI), dementia pugilistica, mild cognitive impairment (MCI), senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia
20 associated with Parkinson's disease and dementia associated with beta-amyloid; preferably AD and other disorders with Beta-amyloid pathology (e.g. glaucoma). Hence, in a further aspect, there is provided a compound as defined herein for use in the treatment or prevention of a disease or condition selected from Alzheimer's disease, traumatic brain injury, mild cognitive impairment, y, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct
25 dementia, dementia pugilistica, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

In view of the aforementioned pharmacology of the compounds of Formula (I), it follows that they may be suitable for use as a medicament. Hence, in a third aspect, there is provided a compound as defined herein for use as a medicament.

30 More especially the compounds may be suitable in the treatment or prevention of AD, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica and Down syndrome.

The present ~~invention disclosure~~ also concerns the use of compounds according to the general Formula (I), the tautomers and the stereoisomeric forms thereof, and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a
35 medicament for the modulation of γ -secretase activity.

The present ~~disclosure invention~~ will now be further described. In the following passages, different aspects of the ~~disclosure invention~~ are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be