Secretases as therapeutics targets in Alzheimer's disease: patents 2000 – 2004. Expert Opin. Ther. Patents 14, 1403-1420).

Indeed, this finding was supported by biochemical studies in which an effect of certain Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on γ-secretase was shown (US 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 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-2009/032277 relates to heterocyclic compounds useful as gamma secretase modulators.

US 2008/0280948 A1 relates to aminophenyl derivatives which are modulators for amyloid beta.

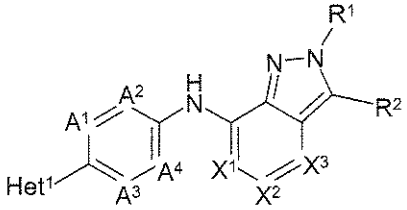
WO-2009/005729 relates to heterocyclic compounds and their use as gamma secretase modulators.

There is a strong need for novel compounds which modulate γ-secretase activity thereby opening new avenues for the treatment of Alzheimer´s disease. 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. 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 disclosure~~invention~~ are useful as gamma secretase modulators. The compounds according to the disclosure~~invention~~ and the pharmaceutically acceptable compositions thereof, may be useful in the treatment or prevention of Alzheimer´s disease.

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



(I)

and stereoisomeric forms thereof, wherein

R^{11} is hydrogen or C_{1-4}alkyl;

R^{12} is C_{1-4}alkyl;

G^1 is O or S;

G^2 is CH or N;

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 a second aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined herein.

The present compounds surprisingly were found to modulate the γ-secretase activity in vitro and in vivo, and therefore may be useful in the treatment or prevention of Alzheimer's disease (AD), traumatic brain injury (TBI), mild cognitive impairment (MCI), senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid, preferably AD and other disorders with Beta-amyloid pathology (e.g. glaucoma).

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. In a fourth 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, senility, dementia, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and dementia associated with beta-amyloid.

More especially the compounds may be suitable in the treatment or prevention of Alzheimer´s disease, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

The disclosure~~invention~~ also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for use in 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 combined with any other feature or features indicated as being preferred or advantageous.

Detailed description

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.

Whenever the term "substituted" is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more