TETRAHYDROPYRROLOTHIAZINE COMPOUNDS

The present invention relates to novel tetrahydropyrrolothiazine compounds, to pharmaceutical compositions comprising the compounds, to methods of using the compounds to treat physiological disorders, and to intermediates and processes useful in the synthesis of the compounds.

The present invention is in the field of treatment of Alzheimer's disease and other diseases and disorders involving amyloid β (Abeta) peptide, a neurotoxic and highly aggregatory peptide segment of the amyloid precursor protein (APP). Alzheimer's disease is a devastating neurodegenerative disorder that affects millions of patients worldwide. In view of the currently approved agents on the market which afford only transient, symptomatic benefits to the patient, there is a significant unmet need in the treatment of Alzheimer's disease.

Alzheimer's disease is characterized by the generation, aggregation, and deposition of Abeta in the brain. Complete or partial inhibition of β-secretase (β-site amyloid precursor protein-cleaving enzyme; BACE) has been shown to have a significant effect on plaque-related and plaque-dependent pathologies in mouse models suggesting that even small reductions in Aβ peptide levels might result in a long-term significant reduction in plaque burden and synaptic deficits, thus providing significant therapeutic benefits, particularly in the treatment of Alzheimer's disease.

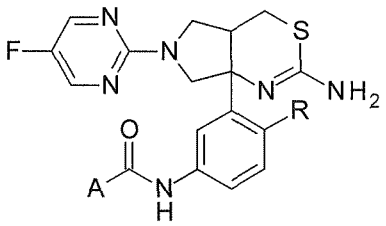
US 2009/0209755 discloses fused aminodihydrothiazine derivatives which possess BACE inhibitory activity and are further disclosed as useful therapeutic agents for a neurodegenerative disease caused by Aβ peptide, such as Alzheimer's type dementia. In addition, *J. Neuroscience*, 31(46), pages 16507-16516 (2011) discloses (S)-4-(2,4-difluoro-5-pyrimidin-5-yl-phenyl)-4-methyl-5,6-dihydro-4*H*-[1,3]thiazin-2-ylamine, an orally administered CNS-active BACE inhibitor.

Summary

BACE inhibitors that are potent with sufficient CNS penetration are desired to provide treatments for Abeta peptide-mediated disorders, such as Alzheimer's disease. The present ~~invention~~ disclosure provides certain novel compounds that are

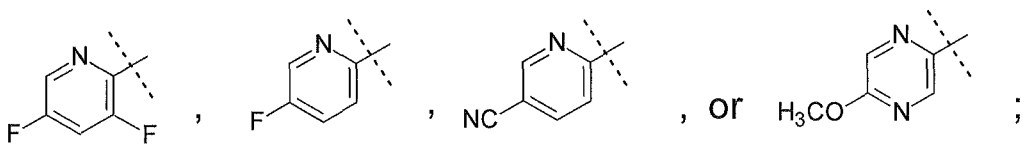
potent inhibitors of BACE. In addition, the present ~~invention~~ disclosure provides certain novel compounds with CNS penetration.

In one aspect, there is provided a compound of the formula:



wherein R is H or F; and

A is:



or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided use of a compound as disclosed above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of Alzheimer's disease.

In another aspect, there is provided use of a compound as disclosed above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention of the progression of developing Alzheimer's disease.

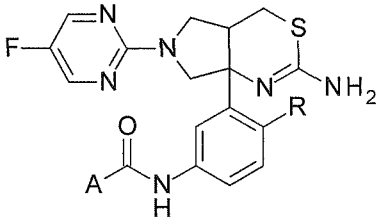
In another aspect, there is provided a compound or pharmaceutically acceptable salt thereof as disclosed above for use in therapy.

In another aspect, there is provided a compound or pharmaceutically acceptable salt thereof as disclosed above for use in the treatment of Alzheimer's disease.

In another aspect, there is provided a pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof as disclosed above with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Detailed Description

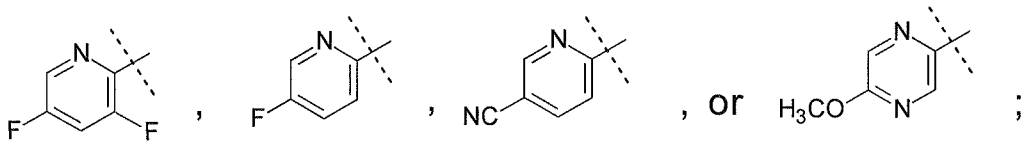
Accordingly, the present invention provides a compound of Formula I:



Formula I

wherein R is H or F; and

A is:



or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of treating Alzheimer's disease in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of preventing the progression of mild cognitive impairment to Alzheimer's disease in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of inhibiting BACE in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for inhibiting BACE-mediated cleavage of amyloid precursor protein, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The invention further provides a method for the inhibition of production of Abeta peptide, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

4. Use of a compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of ~~A method of treating~~ Alzheimer's disease ~~in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof~~.

5. Use of a compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention ~~A method of preventing~~ of the progression of ~~in a patient at risk for~~ developing Alzheimer's disease~~, comprising administering to a patient in need of such treatment an effective amount of a compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof~~.

6. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3 for use in therapy.

7. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3 for use in the treatment of Alzheimer's disease.

8. A pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-3 with one or more pharmaceutically acceptable carriers, diluents, or excipients.