CRYSTALLINE BACE INHIBITORS

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

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.

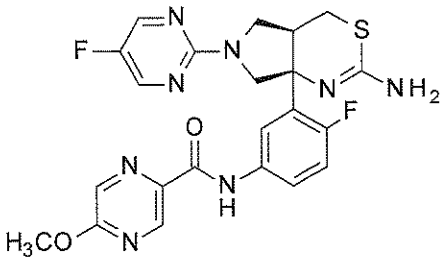
Alzheimer's disease is characterized by the generation, aggregation, and deposition of Abeta in the brain. Complete or partial inhibition of β-secretase (β-site amyloid precursor protein-cleaving enzyme; BACE) has been shown to have a significant effect on plaque-related and plaque-dependent pathologies in mouse models suggesting that even small reductions in Abeta 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.

United States Patent No. 8,158,620 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.

Crystalline forms of BACE inhibitors are desired to provide for ease of preparation of pharmaceutical formulations and for pharmaceutical compositions with improved stability.

Summary

In a first aspect of the present disclosure, there is provided a compound of formula:



which is crystalline.

In a second aspect of the present disclosure, there is provided a use of a compound of the first aspect in the manufacture of a medicament for treating Alzheimer's disease in a patient.

In a third aspect of the present disclosure, there is provided a use of a compound of the first aspect in the manufacture of a medicament for preventing the progression of mild cognitive impairment to Alzheimer's disease in a patient.

In a fourth aspect of the present disclosure, there is provided a compound according to the first aspect for use in therapy.

In a fifth aspect of the present disclosure, there is provided a compound according to the first aspect for use in the treatment of Alzheimer's disease.

In a sixth aspect of the present disclosure, there is provided a compound according to the first aspect for use in preventing the progression of mild cognitive impairment to Alzheimer's disease.

In a seventh aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound according to the first aspect with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Description

7. Use of a compound of any one of claims 1 to 6 in the manufacture of a medicament for treating Alzheimer's disease in a patient.
8. Use of a compound of any one of claims 1 to 6 in the manufacture of a medicament for preventing the progression of mild cognitive impairment to Alzheimer's disease in a patient.
9. A compound according to any one of claims 1 to 6 for use in therapy.
10. A compound according to any one of claims 1 to 6 for use in the treatment of Alzheimer's disease.
11. A compound according to any one of claims 1 to 6 for use in preventing the progression of mild cognitive impairment to Alzheimer's disease.
12. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 6 with one or more pharmaceutically acceptable carriers, diluents, or excipients.