ACS Medicinal Chemistry Letters

Viewpoint

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5-Amino-oxazepine and 5-Amino-thiazepine Compounds as β-Secretase Antagonists and Methods of Use

Patent Highlight

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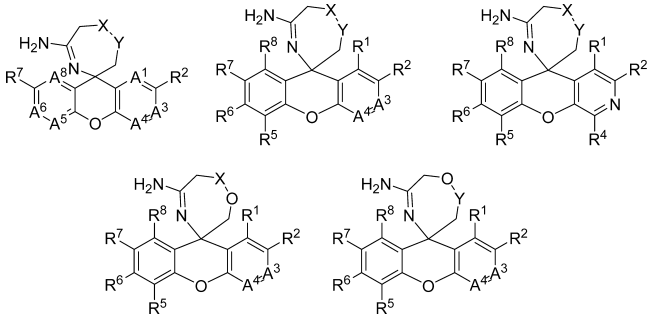
Title:	5-Amino-oxazepine and 5-Amino-thiazepine Compounds as β-Secretase Antagonists and Methods of Use		
Patent Application Number:	WO 2012/109165 A1	**Publication date:**	August 16th, 2012
Priority Application:	US 61/440,270	**Priority date:**	February, 7th, 2011
Inventors:	Dineen, T.; Weiss, M.; Patel, V. F.; Zheng, X. M.; White, R.		
Assignee Company:	Amgen Inc.		
Disease Area:	Alzheimer's disease	**Biological Target:**	β-secretase (BACE)

Summary:

It is estimated that over 12 million patients currently suffer from Alzheimer's disease worldwide and that the number of patients will continue to grow as the population ages. This disease accounts for the majority of clinically diagnosed dementia in patients over 60 years old, and it is characterized by progressive memory loss and decreased cognitive function. End stage patients generally suffer from severe cognitive impairment and are totally dependent on custodial care. The societal and economic impact of Alzheimer's disease is measured both in the billions of dollars in projected costs and the millions of lives that will be impacted as the disease progresses.

Although the cause of Alzheimer's disease has not been determined, there is significant evidence to support the "amyloid cascade hypothesis". This hypothesis proposes that Alzheimer's disease is caused by the overproduction of neurotoxic β amyloid peptides (Aβ1−40, Aβ1−42). These peptides are produced from amyloid precursor protein (APP) through the action of several aspartyl proteases, including β-secretase (BACE) and γ-secretase. It has been further suggested that BACE processing of APP is the rate limiting step of Aβ production in vivo (Sabbagh, M.; et al. *Alzheimer's Dis. Res.* 1997, *3*, 1−19), and as such inhibition of BACE would be an attractive therapeutic target for the treatment and prevention of Alzheimer's disease. This patent application describes a series of 5-amino-oxazepines and 5-amino-thiazepines that are useful as BACE inhibitors for the treatment of Alzheimer's disease.

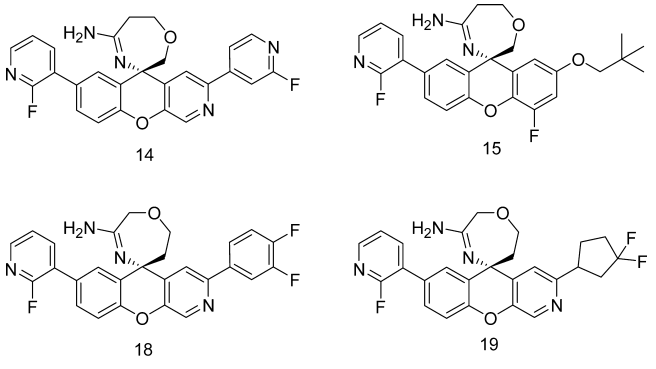
Important Compound Classes:



Definitions:

A^1 is CR^1 or N; A^3 is CR^3 or N; A^4 is CR^4 or N; A^5 is CR^5 or N; A^6 is CR^6 or N; A^8 is CR^8 or N, provided that no more than one of A^1, A^3, A^4, A^5, A^6, and A^8 is N

Key Structures:



Special Issue: Alzheimer's Disease

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Recent Review Articles:

β-site APP-cleaving enzyme 1 trafficking and Alzheimer's disease pathogenesis: Tan, J.; Evin, G. *J. Neurochem.* **2012**, *120* (5 and 6), 869−880.

Small-molecule BACE1 inhibitors: a patent literature review (2006−2011): Probst, G.; Xu, Y. *Expert Opin. Ther. Pat.*, 2012, *22* (5), 511−540.

The β-Amyloid Hypothesis in Alzheimer's Disease: Seeing Is Believing. Kung, H. F. *ACS Med. Chem. Lett.*, 2012, *3* (4), 265−267.

BACE inhibitors as potential drugs for the treatment of Alzheimer's disease: focus on bioactivity. Evin, G.; Lessene, G.; Wilkins, S. *Recent Pat. CNS Drug Discovery*, 2011, *6* (2), 91−106.

Biological Assay:

In vitro enzymatic BACE1 FRET assay.

In vitro BACE1 cell based assay (HEK cells).

Biological Data:

Example	BACE1 FRET assay IC_{50} (μM)	BACE1 cell based assay IC_{50} (μM)
14	0.0005	0.001
15	0.0005	0.007
18	0.002	0.019
19	0.003	0.004

Claims

17 claims total

12 composition of matter claims

4 method of use claims

1 process claim

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Notes

The authors declare no competing financial interest.