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Patent Highlight

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Cyclopropyl-Fused 1,3-Thiazepines as BACE1 and BACE2 Inhibitors

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Title:	Cyclopropyl-Fused 1,3-Thiazepines as BACE1 and BACE2 Inhibitors		
Patent/Patent Application Number:	WO2013004676	**Publication date:**	January 10th, 2013
Priority Application:	EP11172784.8	**Priority date:**	July 6th, 2011
Inventors:	Woltering, T.		
Assignee Company:	Hoffmann-La Roche AG and Siena Biotech SPA		
Disease Area:	Alzheimer's disease (AD)	**Biological Target:**	B-secretase 1 (BACE1)
	Type 2 diabetes (T2D)		B-secretase 2 (BACE2)

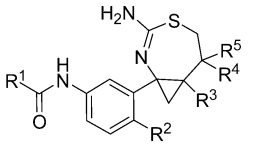
Summary:

Alzheimer's disease, the most common form of dementia, was originally described by German psychiatrist and neuropathologist Alois Alzheimer in 1906. Although the majority of cases are diagnosed in patients over 65, early onset Alzheimer's disease can occur much earlier. In 2010, there were over 35.6 million patients suffering from this disease, and it has been predicted that Alzheimer's disease will affect 1 in 85 people by 2050. Although the cause of Alzheimer's disease is unknown, disease progression has been linked to the formation of neurotoxic amyloid β peptides (Aβ1−40, Aβ1−42) in critical parts of the brain, which are produced as a result of the action of β-secretase (BACE1) on Aβ amyloid precursor protein (APP). BACE1 cleaves APP at the β-cleavage site, and further processing by γ-secretase generates the insoluble Aβ proteins, which in turn form oligomers and, ultimately, the plaques that are the hallmark of Alzheimer's disease. It has been suggested that inhibition of BACE1 processing of APP will decrease Aβ production, providing therapeutic relief.

Separately, type 2 diabetes (T2D) is associated with insulin resistance, inadequate insulin secretion, poor blood-glucose control, and hyperglycemia. It is estimated that over 171 million people have this condition, and this number is expected to double by 2030. The onset of β-cell failure and the associated dramatic decrease in insulin production occur at the onset of T2D, but current treatment regimens do not protect β-cells, nor do they promote β-cell proliferation. Recent literature has identified the protein Tmem27 as capable of promoting β-cell proliferation and insulin secretion. BACE2 is a membrane-bound aspartyl protease that is colocalized with Tmem27 in human pancreatic cells, and it has been suggested that BACE2 is responsible for degradation of TMEM27. Further, BACE2 inhibitors increase β-cell proliferation in in vitro studies, suggesting that inhibition of BACE2 may be a viable treatment mechanism for T2D patients.

The patent application WO2013004676 describes a series of compounds useful as BACE1 and BACE2 inhibitors for the treatment of Alzheimer's disease and type 2 diabetes

Important Compound Classes:



Definitions:

R^1 is selected from the group consisting of heteroaryl optionally substituted with 1−2 substituents individually selected from cyano, cyano-C_{1-6}-alkyl, halogen, halogen-C_{1-6}-alkoxy, halogen-C_{1-6}-alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{1-6} alkyl.

R^2 is selected from the group consisting of H and halogen.

R^3 is selected from the group consisting of H, C_{1-6} alkyl.

R^4 is selected from the group consisting of H, halogen, C_{1-6} alkyl.

R^5 is selected from the group consisting of H, halogen, C_{1-6} alkyl.

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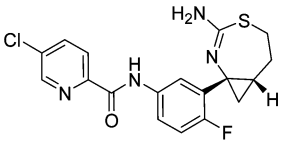
Key Structures: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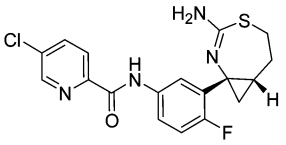
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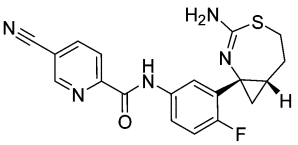
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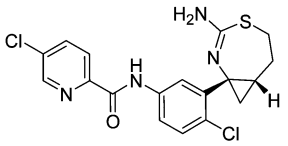
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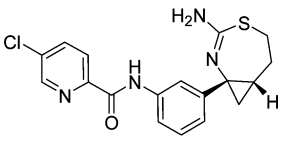
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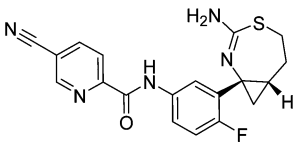
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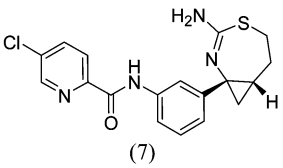
(7)

Recent Review Articles:

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

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

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

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

Biological Assay:

BACE1: Human HEK293 APP695 cellular assay.

BACE2: Inhibition of TMEM27 cleavage by endogenous cellular BACE2 in Ins1e rat cells.

Biological Data:

Entry	BACE1	BACE2	Entry	BACE1	BACE2
	IC_{50} (μM)			IC_{50} (μM)	
1	0.012	0.011	5	0.050	0.002
2	0.026	0.002	6	0.052	0.001
3	0.060	0.005	7	0.005	0.002
4	N/D	0.690			

Claims:

27 Total claims.

13 Composition of matter claims.

1 Process claim.

13 Method of use claims.

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Notes

The authors declare no competing financial interest.