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Viewpoint

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Compounds and Their Use as BACE Inhibitors

Patent Highlight

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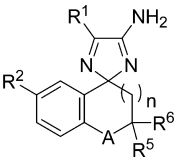
Title:	Compounds and Their Use as BACE Inhibitors		
Patent Application Number:	WO 2012/087237A1	**Publication date:**	June 28th, 2012
Priority Application:	US 61/425,852	**Priority date:**	December 22nd, 2010
	US 61/529,620		August 31st, 2011
Inventors:	Csjernyik, G.; Karlstrom, S.; Kers, A.; Kolmodin, K.; Nylof, M.; Ohberg, L.; Rakos, L.; Sandberg, L.; Sehgelmeble, F.; Soderman, P.; Swahn, B. M.; Von Berg, S.		
Assignee Company:	Astra Zeneca AB		
Disease Area:	Alzheimer's Disease	**Biological Target:**	β-secretase (BACE)

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 (BACE) on Aβ amyloid precursor protein (APP). BACE cleaves APP at the β-cleavage site, and further processing by γ-secretase generates the insoluble Aβ proteins, which in turn forms oligomers and, ultimately, the plaques that are the hallmark of Alzheimer's disease. It has been suggested that inhibition of BACE processing of APP will decrease Aβ production, providing therapeutic relief. This patent application discloses a series of 1,4-diazaspirocyclic-1,3-dien-2-ylamines that are useful as BACE inhibitors for the treatment of Alzheimer's disease.

Important Compound Classes:



Definitions:

A is O or CH_2; N = 0 or 1.

R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl.

R^2 is H, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{2-6}alkynyl, C_{2-6}alkenyl, C_{1-6}alkyl, halogen, cyano, C_{1-6}haloalkyl, NHC(O)R^9, or OR^8, wherein each is optionally substituted with one to three R^7.

R^5 and R^6 are independently H, heterocyclyl, C_{3-6}cycloalkyl, aryl, heteroaryl, or C_{1-6}alkyl, wherein each is optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, or OR^8.

R^5 and R^6 together with the carbon to which they are attached form a ring B which is a 3−14 membered cycloalkyl or heterocyclyl monocyclic ring or a 9−14 membered bicyclic cycloalkyl or heterocyclyl ring and wherein ring B is optionally substituted by one or two substituents independently selected from oxo, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, or OR^8; and ring B is optionally fused with an aryl or heteroaryl ring.

R^7 is independently C_{1-6}alkyl, halogen, cyano, C_{0-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}haloalkyl, C_{2-6}alkynyl, or C_{2-6}alkenyl, wherein each is optionally substituted with 1−3 substituents independently selected from halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, OC_{1-6}alkyl, OC_{1-6}haloalkyl.

R^8 is independently H, C_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, aryl, heteroaryl, wherein each is optionally substituted with a group selected from halogen, cyano, and C_{1-6}alkyl.

R^9 is a heteroaryl optionally substituted with halogen, cyano, OR^8, C_{1-6}haloalkyl or C_{1-6}alkyl.

Special Issue: Alzheimer's Disease

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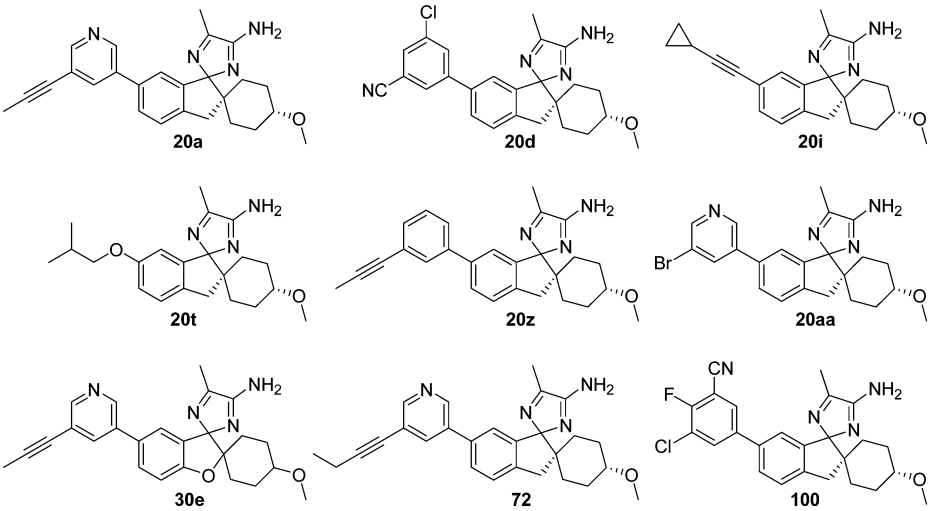
Key Structures:



Recent Review Articles:

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

Vassar, R.; Kandalepas, P. C. The *β*-secretase enzyme BACE1 as a therapeutic target for Alzheimer's disease. *Alzheimer's Res. Ther.* 2011, *3* (3), 20.

Biological Assay:

β-Secretase TR-FRET assay and sAPP*β* release assay.

Biological Data:

Example	β-Secretase TR-FRET IC_{50} (nM)	sAPPβ release assay IC_{50} (nM)
20a	2.2	0.28
20d	1.6	0.72
20i	4.8	4.6
20t	20	0.56
20z	1.4	5.2
20aa	1.6	0.72
30e	1.4	2.2
72	2.3	0.76
100	0.72	0.59

Claims:

25 Total claims.

17 Composition of matter claims.

8 Method of use claims.

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Notes

The authors declare no competing financial interest.