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PATENT HIGHLIGHT

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4,6-Diarylaminothiazines as BACE1 Inhibitors and Their Use for the Reduction of Beta-Amyloid Production

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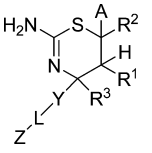
Title:	4,6-Diarylaminothiazines as BACE1 Inhibitors and Their Use for the Reduction of Beta-Amyloid Production		
Patent Application Number:	WO2014098831	**Publication date:**	June 26, 2014
Priority Application:	None	**Priority date:**	December 19, 2012
Inventors:	Wu, Yong-Jin; Guernon, Jason M.		
Assignee Company:	Bristol-Myers Squibb		
Disease Area:	Alzheimer's Disease	**Biological Target:**	BACE1

Summary: The progressive neurodegenerative disease known as Alzheimer's disease impacts approximately 36 million patients globally, and the number of afflicted individuals is expected to increase as the population ages. The first symptoms of this debilitating disease is memory loss, which eventually progresses to severe cognitive impairment, altered behavioral patterns, and decreased motor functions. It is the third leading cause of death and the most common form of dementia. The impact of Alzheimer's disease is measured in both the cost of treatment for the patients and the toll on caregivers, as patients eventually become unable to care for themselves.

Despite decades of research, clinical options and diagnostic biomarkers remain limited, and a full understanding of disease progression remains elusive. Post-mortem histopathological examination of patient brain tissue has, however, revealed a significant increase in neuritic plaques and neurofibrillary tangles. It has been demonstrated that these plaques consist primarily of β-amyloid peptides, which are formed in a stepwise process. Proteolytic cleavage of amyloid precursor protein (APP) by β-APP cleaving enzyme (BACE-1) is followed by γ-secretase processing. The resulting Aβ-42 amyloid segments then form the plaques typically observed in the brains of Alzheimer's disease patients. Although the presence of Aβ-42 amyloid plaques has as yet to be proven as causative, knowledge of this pathway has prompted significant research into the development of BACE-1 inhibitors as possible therapeutic agents. If the production of Aβ-42 amyloid plaques is indeed causative, then slowing or stopping their formation should slow disease progression. The present disclosure describes compounds capable of inhibiting BAC-1 that may be useful as therapeutic interventions capable of halting disease progression in Alzheimer's Disease patients.

Important Compound Classes:



Definitions:

R^1 and R^2 are independently hydrogen or CH_3;

or R^1 and R^2 can join together in a ring by adding $-(CH_2)_4-$;

R^3 is hydrogen or C_1-C_3 alkyl;

Y and Z are independently a C_6-C_{10} aryl group or a 5−10-membered heterocyclic group that can be further substituted with 0 to 3 substituents selected from the group of halogen, hydroxy, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, halo C_{1-4} alkyl, CN, C_1-C_6 alkyl or cycloalkyl, C_1-C_6 alkoxy, $-C{=}OC_{1-4}$ alkyl, $-SO_2C_{1-4}$ alkyl, and C_2-C_4 alkynyl;

A is selected from the groups of phenyl, benzyl, oxazolyl, thiazolyl, isoxazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, and pyrazinyl and groups that can be further substituted with 0 to 3 substituents selected from the group of halogen, hydroxy, amino, C_{1-4} alkylamino, C_{1-4} dialkylamino, halo C_{1-4} alkyl, hydroxy C_{1-6} alkyl, CN, C_1-C_6 alkyl or cycloalkyl, C_1-C_6 alkoxy, and C_2-C_4 alkynyl;

L is $-NHCO-$, or is a single bond; and

L and Z together can be absent.

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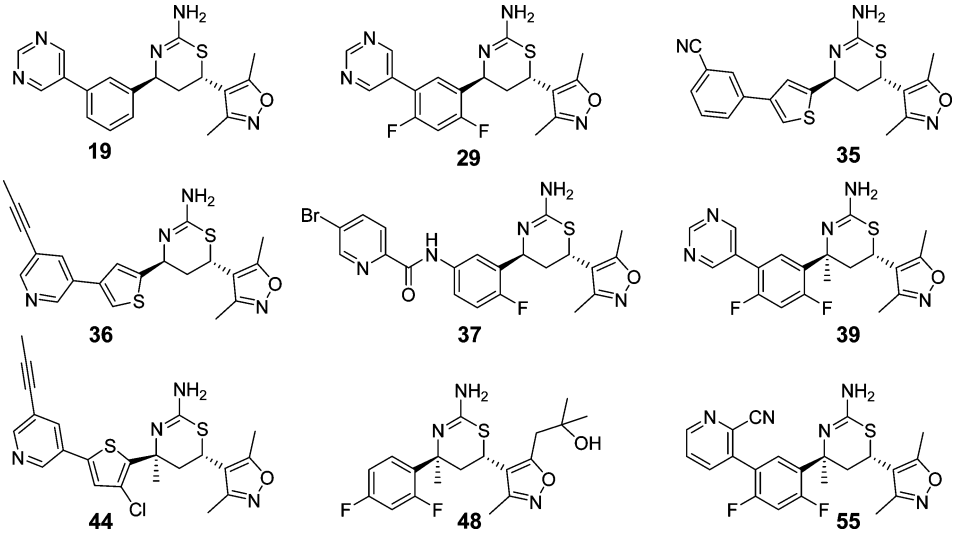
Key Structures:



Recent Review Articles:

1. Read, J.; Suphioglu, C. Dropping the BACE: Beta secretase (BACE1) as an Alzheimer's disease intervention target. *Neurodegener. Dis.* **2013**, 227−256.

2. Butini, S.; Brogi, S.; Novellino, E.; Campiani, G.; Ghosh, A. K.; Brindisi, M.; Gemma, S. The structural evolution of β-secretase inhibitors: A focus on the development of small-molecule inhibitors. *Curr. Top. Med. Chem.*,**2013**, *13* (15), 1787−1807.

3. Nino, H.; Garcia-Pintos, I.; Rodriguez-Borges, J. E.; Escobar-Cubiella, M.; Garcia-Mera, X.; Prado-Prado, F. Review of synthesis, biological assay and QSAR studies of β-secretase inhibitors. *Curr. Comput.-Aided Drug Des.* **2011**, *7* (4), 263−275.

Biological Assay: Cellular assay for inhibition of Aβ1−40 and Aβ1−42 production in H4 cell stably transfected with APP751 containing the Swedish mutation.

Biological Data:

Entry	nM	Entry	nM	Entry	nM
19	230	36	60	44	30
29	200	37	22	48	110
35	300	39	8	55	87

Claims:

18 Total claims

15 Composition of matter claims

3 Method of use claims

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Notes

The authors declare no competing financial interest.