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Viewpoint

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BACE Inhibitors: Potential Treatment of Alzheimer's Disease, Dementia, and Related Neurodegenerative Disorders (A): 5,6-Dihydroimidazo[1,2-*a*]pyrazin-8-yl-amine Derivatives

Patent Highlight

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Title:	5,6-Dihydroimidazo[1,2-*a*]pyrazin-8-ylamine Derivatives Useful as Inhibitors of *β*-Secretase (BACE)		
Patent Application Number:	WO 2012/085038 Al	**Publication Date:**	June 28, 2012
Priority Application:	EP 10196568.9	**Priority Date:**	December 22, 2010
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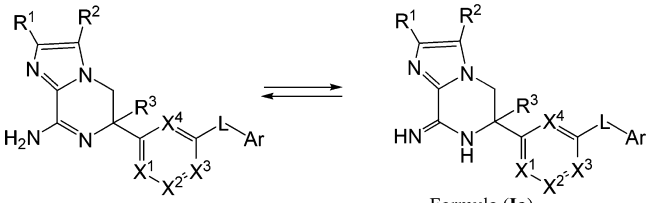
Disease Area:	Alzheimer's disease, mild cognitive impairment, senility, dementia, and related disorders	**Biological Target:**	*β*-Secretase [Beta-site Amyloid Cleaving Enzyme (BACE)]

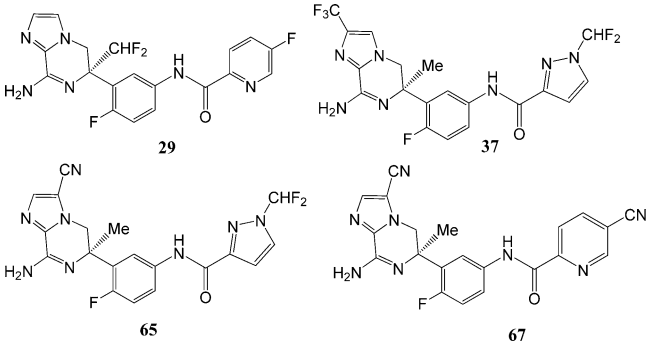
Summary: The invention in this patent application relates to novel 8-amino-5,6-dihydroimidazo[1,2-*a*]pyrazine derivatives represented by Formula (I), which inhibit the enzyme *β*-secretase, also known as *β*-site amyloid cleaving enzyme (BACE). The *β*-secretase (BACE) and *γ*-secretase enzymes cleave the amyloid precursor protein (APP) sequentially at the N and C termini to generate *β*-amyloid 1−42 [Abeta (or A*β*) 1−42] as well as A*β* 1−38 and A*β* 1−43 peptides. These peptides can aggregate to form oligomers, fibrils, and eventually amyloid plaques. The accumulation of amyloid plaques in the brain is a major characteristic pathological feature in Alzheimer's disease (AD) patients. Thus, the inhibition of the *β*-secretase (BACE) would be expected to prevent or slow the formation of A*β* 1−42 as well as A*β* 1−40, A*β* 1−38, and A*β* 1−43 peptides and consequently the amyloid plaque formation. BACE inhibitors, such as the compounds described in this patent application, would be potential therapeutic agents for the treatment of AD and related disorders. The patent application mentions the potential use of such inhibitors for the prevention and/or treatment of disorders in which *β*-secretase is involved, such as AD, mild cognitive impairment, senility, dementia, dementia with Lewy bodies, cerebrovascular amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with stroke, dementia associated with Parkinson's disease, or dementia associated with *β*-amyloid.

Important Compound Classes: The compounds represented by Formula (I) can coexist in a dynamic equilibrium with their tautomers of Formula (1a).



Formula (**I**) Formula (**Ia**)

Key Structures: The patent application describes 80 specific examples of the compounds of formula (I); four of these examples are shown below labeled by their reported numbers in the patent application:



29 **37** **65** **67**

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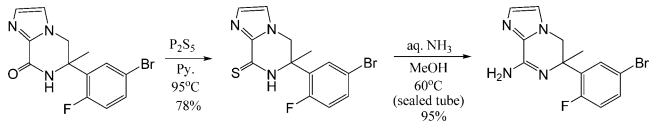
Biological Assay: The inhibition of BACE-1 by the compounds of formula (I) was tested using a biochemical fluorescence resonance energy transfer assay (FRET).

Biological Data: The inhibition data are given as pIC_{50} (higher values represent better inhibitors). The compounds with the highest and lowest values are selected as representatives; their structures are shown above.

Compound No.	Biochemical FRET based assay pIC_{50}
67	7.41
65	7.35
37	7.33
29	<4.52

Synthesis: The introduction of the NH_2 group to form the amidine, a common feature in all compounds of formula (I), was achieved from the corresponding amides via conversion to the thioamide followed by reaction with ammonia (or an ammonia source) as illustrated in the following example.



Claims: Claims 1−4: composition of matter, variations of formula (I)

Claims 5 and 6: pharmaceutical compositions

Claims 7: a compound for treating AD and a list of other related disorders associated with β-amyloid

Claim 8: a method for treating AD and a list of other related disorders associated with β-amyloid

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Notes

The authors declare no competing financial interest.