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Viewpoint

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BACE-Inhibitors: Potential Treatment of Alzheimer Disease, Dementia, and Related Neurodegenerative Diseases. C. Spiro-Heterocyclic Derivatives

Patent Highlight

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Title:	Heterocyclic Inhibitors of Beta-Secretase for the Treatment of Neurodegenerative Diseases		
Patent Application Number:	WO 2012/071458 A1	**Publication date:**	31 May 2012
Priority Application:	US 61/416,182	**Priority date:**	22 November 2010
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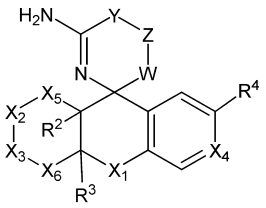
Assignee Company:	Array Biopharma Inc., 3200 Walnut Street, Boulder, CO 80301, United States Genentech, Inc., l DNA Way, South San Francisco, CA 94080-4990, United States		
Disease Area:	Alzheimer's disease and related neurodegenerative diseases	**Biological Target:**	β-Secretase [Beta site APP (or Amyloid) Cleaving Enzyme (BACE)]

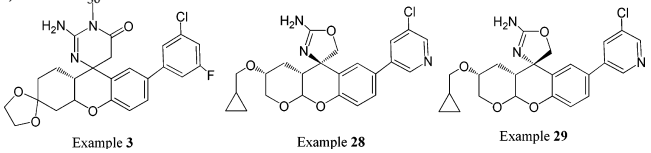
Summary: The invention in this patent application relates to compounds of formula (I) that are capable of inhibition of the enzyme β-secretase known as Beta site Amyloid Cleaving Enzyme (BACE or BAC-1) and that can potentially treat neurodegenerative diseases such as Alzheimer's disease (AD). The β-secretase enzyme (BACE) together with γ-secretase is responsible for the sequential cleavage at the *N*- and *C*-termini of the amyloid precursor protein (AAP) to form the amyloidogenic Aβ peptides, primarily Aβ 1−42. The Aβ peptides are responsible for formation of amyloid plaque in the brain and contribute to advancing of Alzheimer's disease in the patients. Additionally, the initial processing of AAP by β-secretase forms a soluble form named N-AAP. N-APP can bind to and activate the apoptotic death receptor 6 (DR6) and was recently implicated in neuronal cell death through a different pathway from that of amyloid plaque formation. Therefore, identifying effective inhibitors of BACE-1, such as the compounds of formula (I) claimed in this patent application, capable of potentially stopping or slowing the formation of both amyloid plaque and DR6-mediated apoptosis would provide a possible effective treatment for AD and other related neurodegenerative diseases.

Important Compound Classes:



Formula (**I**)

Key Structures: The patent application describes and lists 310 examples of compounds of formula (I). The following three compounds are representative examples; their IC_{50} data are listed below:



Example **3** Example **28** Example **29**

Biological Assay: **Cellular BACE-1 Inhibition Assay** (*in vitro* cellular Amyloidβ 1−40 production assay): cells incubated with test compound for 48 h; the level of Amyloidβ 1−40 was determined using homogeneous time-resolved fluorescence ("HTRF") immunoassay.

Special Issue: Alzheimer's Disease

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Biological Data: The patent application listed the IC_{50} data for 46 examples using the above assay. The highest value was obtained from example **3** while the lowest values were reported for the two diasteomeric compounds, examples **28** and **29**.

Example No.	IC_{50} (nM)
3	3083.85
28	7.8
29	8.9

Claims: Claims 1−47: composition of matter, variations of formula (I)

Claims 48−50: methods of inhibiting cleavage of AAP by β-secretase and treating Alzheimer's disease

Claims 51−55: pharmaceutical compositions and use of any of the claimed compounds in treatment of Alzheimer's disease

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Notes

The authors declare no competing financial interest.