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BACE Inhibitors: Potential Treatment of Alzheimer's Disease, Dementia, and Related Neurodegenerative Disorders (B): 3-Amino-4-fluoro-1*H*-isoindol Derivatives

Patent Highlight

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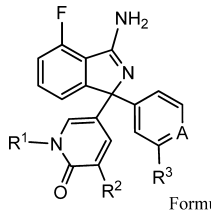
BACE Inhibitors: Potential Treatment of Alzheimer's Disease, Dementia, and Related Neurodegenerative Disorders (B): 3-Amino-4-fluoro-1*H*-isoindol Derivatives

Title:	Compounds and Their Use as BACE Inhibitors		
Patent Application Number:	WO 2012/087236 Al	**Publication Date:**	June 28, 2012
Priority Application:	US 61/425,853	**Priority Date:**	December 22, 2010
Inventors:	Kolmodin, K.; Swahn, B.-M.; Von Berg, S.; Kihlstrom, J.; Lindstrom, J.; Karlstrom, S.; Sundstrom, M.		
Assignee Company:	Astrazeneca AB; S-151 85 Siidertalje (SE)		
Disease Area:	Alzheimer's disease and related disorders	**Biological Target:**	β-Secretase [Beta-site APP Cleaving Enzyme (BACE)]

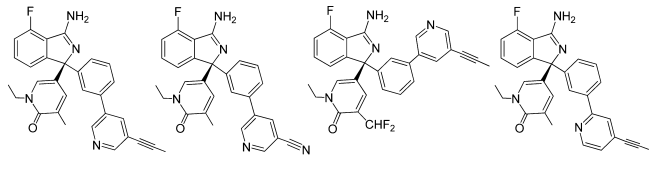
Summary: The invention in this patent application relates to the compounds represented by Formula (I) that inhibit the β-site amyloid cleaving enzyme (BACE). BACE is involved in the production of amyloid-β-proteins (Aβ), a major constituent of the brain plaques, which are characteristic of Alzheimer's disease (AD). Aβ may also deposit elsewhere, which may cause other disorders. Inhibition of BACE is therefore an attractive target for the treatment and/or prophylaxis of AD. Potent inhibitors of BACE activity would reduce the levels of Aβ in the brain, which would slow the formation of amyloid plaques and consequently would slow the progression of AD. Inhibition of BACE and slowing the production of Aβ may also be beneficial in the treatment of other related disorders that involve the deposition of Aβ. The patent application listed the following conditions that may potentially be treatable by BACE inhibitors: "Down's syndrome, β-amyloid angiopathy such as but not limited to cerebral amyloid angiopathy or hereditary cerebral hemorrhage, disorders associated with cognitive impairment such as but not limited to MCI ("mild cognitive impairment"), Alzheimer's disease, memory loss, attention deficit symptoms associated with Alzheimer's disease, neurodegeneration associated with diseases such as Alzheimer's disease or dementia including dementia of mixed vascular and degenerative origin, pre-senile dementia, senile dementia and dementia associated with Parkinson's disease, progressive supranuclear palsy or cortical basal degeneration."

Important Compound Classes:



Formula (I)

Key Structures: The patent application describes 26 specific examples of the compounds represented by formula (I) including the four compounds illustrated below:



Example **3** Example **8** Example **23** Example **28**

Biological Assay: The activities of the compounds were tested using:

- TR-FRET assay: compounds with high affinity were further tested in a diluted TR-FRET assay.
- sAAPβ release assay

Special Issue: Alzheimer's Disease

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Biological Data: The patent application stated: a typical IC_{50} value for the tested compounds ranged from 0.1 to about 10000 nM. Some of the lowest IC_{50} values were reported for the following four compounds (structures above):

Example No.	IC_{50} in (diluted) TR-FRET assay (nM)	IC_{50} in sAAPβ release assay (nM)
3	2	0.2
8	8	2
23	6	4
25	5	2

Claims: Claims 1−11: composition of matter; variations of formula (I)

Claim 12: a group of specific 25 compounds listed by chemical names

Claims 13: pharmaceutical composition

Claims 14−21: use of any of the claimed compounds and/or methods for treating AD and other Aβ-related pathologies

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Notes

The authors declare no competing financial interest.