

β -Secretase Inhibitors for the Treatment of Alzheimer's Disease and Down's Syndrome

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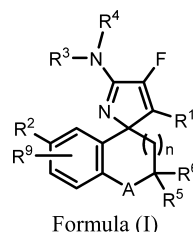
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Patent Application Title:	Monofluoro beta-secretase inhibitors		
Patent Application Number:	WO 2013/054108 A1	Publication date:	18 April 2013
Priority Application:	US 61/545334	Priority date:	10 October 2011
Inventors:	Minidis, A.; Rahm, F.; Viklund, J.		
Assignee Company:	Astrazeneca UK Limited; 2 Kingdom Street, London, Greater London W2 6BD, U.K.		
Disease Area:	$A\beta$ -related pathologies and β -amyloid angiopathy such as Alzheimer's disease and Down's syndrome	Biological Target:	β -secretase (BACE-1)

Summary: The invention in this patent application relates to monofluoro compounds represented generally by formula I that are inhibitors of β -secretase [also known as beta site amyloid cleaving enzyme (BACE or BACE-1)]. These compounds may potentially be used for treatment and/or prevention of amyloid β ($A\beta$)-related pathologies and β -amyloid angiopathy such as Down's syndrome, Alzheimer's disease, and other related disorders.

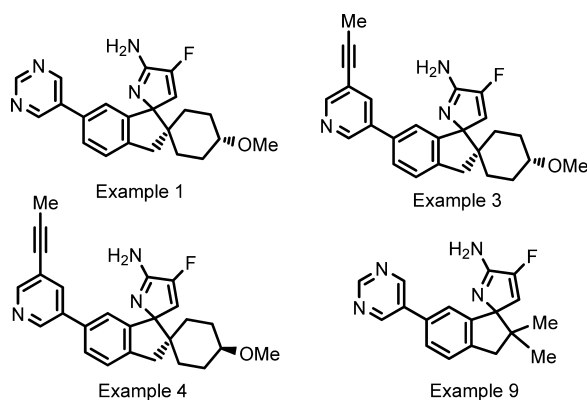
BACE is a membrane bound type 1 protein that is abundantly expressed in brain tissue. Its activity is implicated in the generation of $A\beta$ peptide from APP, and it is believed to be the rate-limiting step in the production of $A\beta$. Thus, inhibition of BACE activity with molecules such as those described in this patent application could reduce the production of $A\beta$ and may potentially slow formation of amyloid plaques and the progression of Alzheimer's disease and other related disorders involving deposition of $A\beta$ or its fragments.

Important Compound Classes:



Key Structures:

Four representative structures of the compounds of formula I:



Received: May 12, 2013

Published: May 17, 2013

Biological Assay:

- TR-FRET assay
- diluted TR-FRET assay
- sAPP β release assay
- ATP assay

Biological Data:

The inventors stated that typical IC₅₀ values for the tested compounds are in the range of about 0.01 to about 100 000 nM. The reported values for the four examples above are listed in the following table:

Compound	TR-FRET assay IC ₅₀ (nM)	sAPP β release assay IC ₅₀ (nM)
Example 1	22 (from diluted TR-FRET assay)	1.1
Example 3	18	0.031
Example 4	258	1.1
Example 9	3790	168

Claims:

Claims 1–8: composition of matter, variations of formula I
Claim 9–10: composition of matter, specific examples of the compounds of formula I listed by chemical name
Claim 11: pharmaceutical composition
Claims 12–15: claiming compounds for use as medicament and treating applicable conditions and diseases
Claims 16–19: methods of treatment or preventing relevant conditions and diseases

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Notes

The authors declare no competing financial interest.