ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Gamma Secretase Modulators

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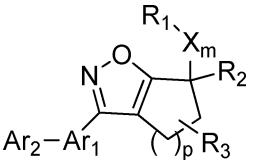
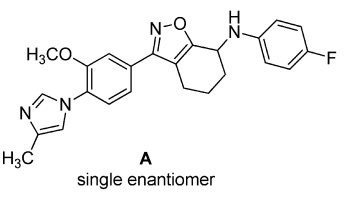
Title:	Gamma Secretase Modulators		
Application Number:	WO 2013066740A1	**Publication date:**	10 May 2013
Priority Application:	61/553,384	**Priority date:**	31 October 2011
Inventors:	W. Greenlee, D. Pissarnitski, Z. Zhao, Z. Zhu		
Assignee Company:	Merck Sharpe & Dohme		
Disease Area:	Neurodegeneration	**Biological Target:**	Gamma secretase

Summary: Gamma secretase is an aspartic protease complex involved in the biosynthesis of Aβ peptide, a potential neurotoxic contributor in the progression of Alzheimer's disease. Direct inhibition of enzymatic activity introduces potential selectivity issues associated with other biological functions of gamma secretase including Notch and Eph processing. As an alternative approach to gamma secretase inhibition, modulation of enzyme activity using, e.g., NSAIDs is a potentially druggable concept. This patent describes the synthesis and evaluation of a novel chemical series that demonstrates inhibition of gamma secretase activity in vitro and reduction of Aβ42 CSF levels following oral administration of a standard dose of 30 mg/kg.

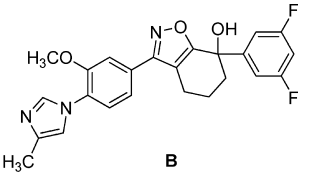
Primary Markush:



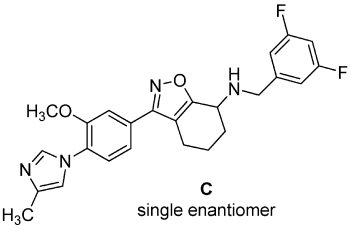
Notable Substructures:



A
single enantiomer



B



C
single enantiomer

Biological Data: Compound A: Aβ42 IC_{50} 39 nM; reduction CSF Aβ42 in vivo, 58%
Compound B: Aβ42 IC_{50} 190 nM; reduction CSF Aβ42 in vivo, 20%
Compound C: Aβ42 IC_{50} 29 nM; reduction CSF Aβ42 in vivo, 20%

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Notes

The authors declare no competing financial interest.

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