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Patent Highlight

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Dihydrooxazines As Inhibitors of BACE-1 or BACE-2

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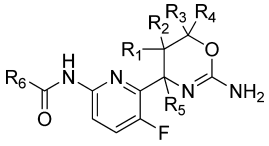
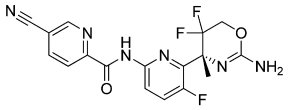
Title:	Dihydrooxazines As Inhibitors of BACE-1 or BACE-2		
Patent/Patent Application Number:	WO 2013/027188 A1	**Publication Date:**	February 28, 2013
Priority Application:		**Priority Date:**	August 23, 2012
Inventors:	Lueoend, R. M.; Machauer, R.; Rueeger, H.; Veenstra, S. J.		
Assignee Company:	Novartis AG, Basel, Switzerland		
Disease Area:	Alzheimer's disease, mild cognitive impairment, insulin intolerance, type 2 diabetes, obesity	**Biological Target:**	BACE-1, BACE-2

Summary: The patent application claims dihydrooxazine derivatives as inhibitors for the treatment of Alzheimer's disease or diabetes.

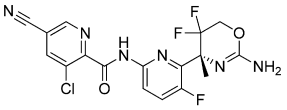
Important Compound Classes:



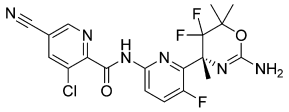
Key Structures:



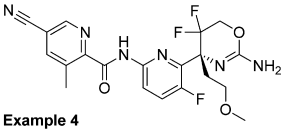
Example 1



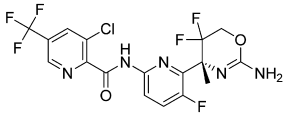
Example 2



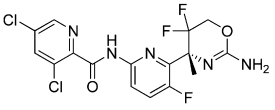
Example 3



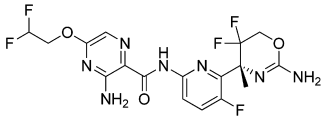
Example 4



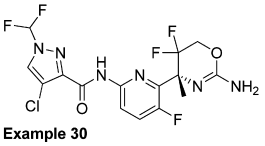
Example 7



Example 9



Example 11



Example 30

Biological Assays: Thirty-seven compounds described in this invention were evaluated for their inhibition properties against human BACE-1, BACE-2, and cellular release of amyloid peptide 1−40. Seven compounds were tested in vivo for their ability to lower Abeta in rat brain and CSF.

Pharmacological Data: Inhibition of BACE-1, BACE-2, or cellular release of amyloid peptide 1−40.

Example	BACE-1 (IC_{50}, μM)	BACE-2 (IC_{50}, μM)	Amyloid-β1-40 release (IC_{50}, μM)
1	0.012	0.066	0.007
2	0.012	0.071	0.008
3	0.029	0.071	0.007
4	0.100	0.580	0.049
7	0.035	0.290	0.027
9	0.018	0.004	0.012
11	0.830	2.900	0.440
30	0.019	0.007	0.013

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Example	Abeta lowering in rat forebrain	Abeta lowering in rat CSF
2	-67.1%	-70.7%
3	-20.0%	-35.3%
7	-63.6%	-67.9%
30	46.6%	-55.2%

Synthesis: Synthesis of 37 examples is described.

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Notes

The author declares no competing financial interest.