ACS Medicinal Chemistry Letters

Viewpoint

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Novel and Selective Inhibitors of Histone Deacetylase

Patent Highlight

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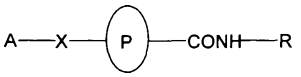
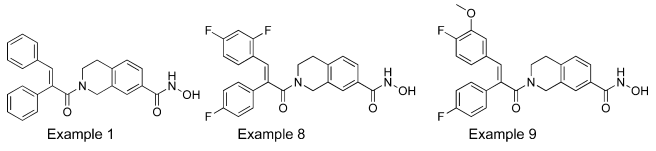
Title:	Novel and Selective Inhibitors of Histone Deacetylase		
Patent/Patent Application Number:	WO 2012/117421 A1	**Publication date:**	March 1, 2012
Priority Application:	IN 2011-CH613	**Priority date:**	March 2, 2011
Inventors:	Rajagopal, S.; Kilambi, N.; Kachadia, V.; Rathinasamy, S.; Balusubramanian, G.; Mani, U.; Rajagopalan, N.; Pushparaj, J. A.; Roy, A. M.; Vishwakarma, L.S.; Narayanan, S.; Kaliyamoorthy, V.; Thanasekaran, P.; Thatavarthy Krishna, R.; Kannan, K.; Mookkan, J.; Chidambaram Venkateswaran, S.; Ahamed Ali, F.		
Assignee Company:	Orchid Research Laboratories Ltd., India		
Disease Area:	CNS diseases, cancer	**Biological Target:**	HDAC6
Summary:	The patent application claims a series of hydroxamic acids as selective inhibitors of histone deacetylase 6 (HDAC6) for the treatment of various diseases, including Alzheimer's disease and cancer.		

Important Compound Classes: Compounds general formula:

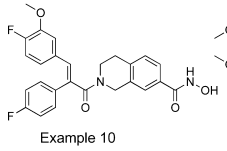


Key Structures:


Example 1

Example 8

Example 9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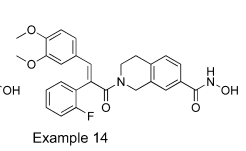
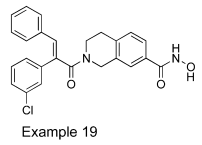
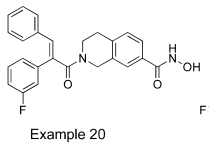

Example 14


Example 19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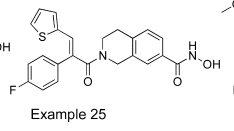
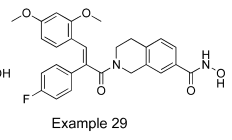
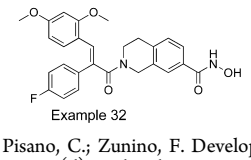

Example 25


Example 29


Example 32

Recent Review Articles:

1. Dallavalle, S.; Pisano, C.; Zunino, F. Development and therapeutic impact of HDAC6-selective inhibitors. *Bio. Pharm.* **2012**, *84* (6), 756−765.

2. d'Ydewalle, C.; Bogaert, E.; Van Den Bosch, L. HDAC6 at the intersection of neuroprotection and neurodegeneration. *Traffic* **2012**, *13*, (6), 771−779.

Biological Assay: Compounds were tested for HDAC6 and HDAC1 enzyme inhibitory activity, for anticancer activity by measuring cell viability in ten different cancer cell lines, and for CNS protection by measuring cytotoxicity by using lactate dehydrogenase assay.

Special Issue: Alzheimer's Disease

Published: October 24, 2012

Biological Data: Fifty-one compounds had IC_{50} values between <1 nM and 50 nM against HDAC6. A selectivity >100−2000 for HADC6 over HDAC1 is described but not exemplified. Forty compounds were screened for cell viability and decreased cell percent growth by 50% versus control at low micromolar concentration.

Examples 1, 8, 9, 10, 14, 19, 23, 25, 29, and 32 had an IC_{50} (HDAC6) = <1−50 nM.

Example	PC12 neuroprotection	Example	PC12 neuroprotection
1	36.6% @ 1 μM	19	77.8% @ 1 μM
8	56% @ 1 μM	23	68.7% @ 1 μM
9	67.2% @ 1 μM	25	71.8% @ 1 μM
10	100% @ 1 μM	29	38% @ 1 μM
14	100% @ 1 μM	32	55% @ 1 μM

Synthesis: Preparation of 162 compounds is described.

Claims: Claim 14 is for use of compounds in the treatment of Alzheimer's disease, Huntington's disease, Parkinson's disease, stroke, and Friedrich's Ataxia.

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Notes

The authors declare no competing financial interest.