ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Histone Deacetylase 4 (HDAC4) Inhibitors: A Promising Treatment for Huntington's Disease

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Title:	Novel Trifluoromethyl-Oxadiazole Derivatives and Their Use in the Treatment of Disease		
Patent Application Number:	WO 2013/080120 A1	**Publication date:**	6 June 2013
Priority Application:	US 61/564,031	**Priority date:**	28 November 2011
Inventors:	Hebach, C.; Kallen, J.; Nozulak, J.; Tintelnot-Blomley, M.; Widler, L.		
Assignee Company:	Novartis AG; Lichtstrasse 35, CH-4056 Basel (CH)		
Disease Area:	Huntington's disease, muscle atrophy, and diabetes/metabolic syndrome	**Biological Target:**	Histone deacetylase 4 (HDAC4)

Summary:

The invention in this patent application relates to trifluoromethyl-1,2,4-oxadiazole derivatives represented generally by formula (I). These derivatives possess selective HDAC4 inhibitory activity and may potentially be used as a treatment for Huntington's disease, muscle atrophy, and diabetes/metabolic syndrome.

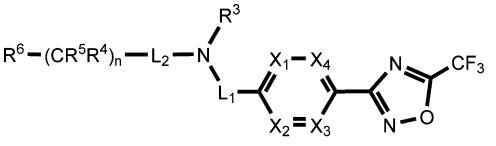
Huntington's disease (HD) is an autosomal dominant neurodegenerative genetic disorder that affects muscle coordination and leads to mental deterioration and psychiatric problems. It typically becomes noticeable in midadult life (30−50 years) and continues without remission over 10 to 25 years. It is believed to be caused by an expansion of C−A−G trinucleotide repeats within the *huntingtin* gene that results in the formation of a mutant form of the protein huntingtin (mHTT) with a polyglutamine repeat within the amino terminus. mHTT and its proteolytic N-terminal fragments accumulate in intracellular aggregates and have been shown to interfere with the transcriptional machinery of the cell.

Histone deacetylases (HDACs) are a family of enzymes that cleave acetyl groups from ε-*N*-acetyl lysine residues on histone proteins. The enzyme family is classified into subfamilies: class I (HDAC1,2,3,8), class IIa (HDAC4,5,7,9), class IIb (HDAC6,10), and class IV (HDAC11). Some known nonselective HDAC inhibitors (pan-inhibitors) such as suberoylanilide hydroxamic acid (SAHA) were found effective in drosophila and mouse assays for Huntington's pathology. Recent research has shown that the reduction in HDAC4 expression levels improved the motor impairment phenotype of the R6/2 mice. Therefore, the inhibition of HDAC4 may potentially provide a treatment for Huntington's disease.

It was also found that class IIa HDACs are expressed in skeletal muscle and that their expression is at a lower level in slow-twitching muscle compared to fast-twitching muscle. Recent studies have shown that denervated mice lacking both HDAC4 and HDAC5 demonstrated only 10% loss in muscle weight compared to 30% loss in those lacking either HDAC4 or HDAC5 and 50% loss in wild-type mice. Thus, inhibition of HDAC4 may also provide a potential treatment for muscle atrophy.

Another recent study has revealed a pivotal role for class IIa HDACs in the regulation of glucose homeostasis. Mouse studies have also shown that reduction of class IIa HDACs lowers blood glucose, increases glycogen storage, and improves hyperglycemia. Inhibitors of HDAC4 may thus provide a treatment for diabetes/metabolic syndrome.

Important Compound Classes:



Formula (I)

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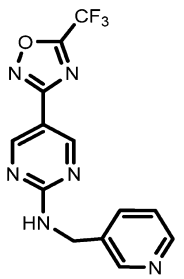
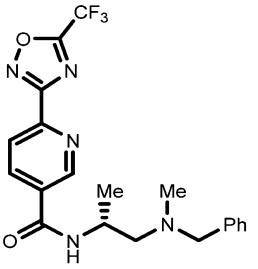
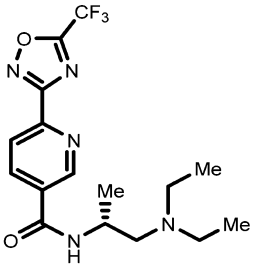
Key Structures: The inventors describe the synthesis of 46 examples of formula (I) compounds including the following examples:



Example **10**



Example **21**



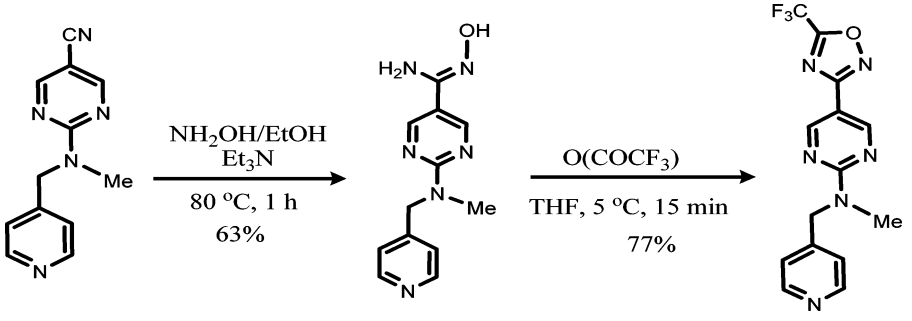
Example **23**

Biological Assays: HDAC1 Assay HDAC4 Assay HDAC6 Assay

Biological Data: The inventors reported the IC_{50} values for 46 examples of formula (I) compounds. The values for examples **10**, **21**, and **23** are shown here:

Compound	HDAC1 IC_{50} (μM)	HDAC4 IC_{50} (μM)	HDAC6 IC_{50} (μM)
Example **10**	6.6	0.14	1.1
Example **21**	>10	0.018	>10
Example **23**	>10	0.028	>10

Synthesis: The 5-trifluoromethyl-1,2,4-oxadiazole ring is common in all compounds; it was synthesized from the corresponding nitrile using a two step conversion sequence illustrated with one of the examples:



Claims: Claims 1−9: composition of matter, definitions of formula (I)
Claim 10: composition of matter, 44 examples of formula (I) listed by chemical names
Claim 11: pharmaceutical composition
Claims 12−15: use of compounds as medicaments
Claim 16: pharmaceutical composition, a combination with a second drug substance

Recent Review Articles:
1. Kumar, A.; Rinwa, P. *World J. Pharm. Pharm. Sci.* **2012**, *1* (2), 486−498.
2. Debacker, K.; Frizzell, A.; Gleeson, O.; Kirkham-McCarthy, L.; Mertz, T.; Lahue, R. S. *PLoS Biol.* **2012**, *10* (2), e1001257.
3. Gray, S. G. *Clin. Epigenet.* **2011**, *2* (2), 257−277.

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Notes

The authors declare no competing financial interest.