(ARYLOXOPROPENYL)PYRROLYL HYDROXYAMIDES AS NOVEL HUMAN CLASS II HISTONE DEACETYLASE INHIBITORS

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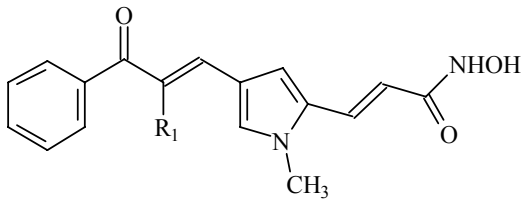
Histone deacetylase (HDAC) is a family of enzymes playing an important role in the control of gene expression. Because it has been reported that its inhibition brought about cell-cycle arrest and induced apoptosis and/or differentiation, HDAC is considered a promising target for new types of pharmaceuticals.

Recently, we reported a new series of hydroxamic acid-containing compounds, *ie* aroyl-pyrrolyl-hydroxyamides (APHAs), as HDAC inhibitors [1]. Various chemical modifications on different portions of APHA lead compound have been performed, with the aim to define structure-activity relationships and to improve its HDAC inhibitory activity. Among them, the insertion of an alkyl/alkenyl chain between the benzoyl portion and the pyrrole C4-position of the lead compound has been produced. All the newly synthesized derivatives were tested against maize HD2 and maize HD1-B and HD1-A, two deacetylase enzymes homologues of mammalian class I and class II HDACs, respectively. Interestingly, properly substituted (aryloxopropenyl)pyrrolyl hydroxyamides **1** were not very potent against HD2, slightly active against HD1-B, and endowed with high inhibitory activity against HD1-A enzyme [2]. IC_{50} values of such compounds against HD1-A are in the range 12-200 nM, the class II selectivity ratio is 30-180 depending on the type and the position of substituents on the benzene ring. Tested on human HDACs to confirm their class II HDAC selectivity in mammals, our selective pyrrole derivatives showed no activity against human HDAC1 (0% of inhibition at 5 μM) whilst were able to inhibit human HDAC4 (55% of inhibition at 5 μM). In functional assays, such compounds failed in p21 induction, whereas produced hyperacetylation of α-tubulin in ZRT5.1 breast cancer cells.



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[1] Mai A, Massa S, Rotili D, Cerbara I, Valente S, Pezzi R, Simeoni S, Ragno R. *Med. Res. Rev.* **2005**, in press.
[2] Mai, A.; Massa, S.; Pezzi, R.; Rotili, D.; Loidl, P.; Brosch, G. *J. Med. Chem*. **2003**, *46*, 4826-4829.