URACIL-BASED HYDROXY-AMIDES (UBHAs) AS A NEW CLASS OF PICOMOLAR HDAC INHIBITORS

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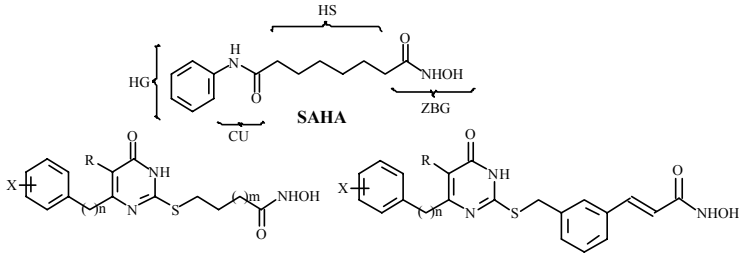
Histone deacetylase (HDAC) enzymes play an important role in the epigenetic regulation of gene expression. Since HDAC inhibitors have been reported to induce cell cycle arrest, differentiation and/or apoptosis, they are considered a promising class of new generation anticancer agents. Most of HDAC inhibitors generally consist of a zinc-binding group (ZBG) and a five- or six-carbon hydrocarbon spacer (HS) attached to a hydrophobic group (HG) via a connection unit (CU). Suberoylanilide hydroxamic acid (SAHA), a well-known HDAC inhibitor, shows a hydroxamate moiety (ZBG), a six-carbon linear aliphatic chain (HS), and an amide function (CU) connected to a benzene ring (HG), so perfectly exemplifying this general model for HDAC inhibition [1].

A comparison of amino acid sequences of the HDAC active site showed that its structural features are well conserved across all the HDACs, except for the rim of the catalytic pocket. Therefore, it has been reasoned that changes of the CU and/or HG, assumed to interact with the entry area of the catalytic pocket, could provide potent and possibly selective HDAC inhibitors. However, only a few connection units, such as amide, sulphonamide, ketone, ether, oxazole and thiazole have been reported [2]. Prompted by these evidences, we planned the synthesis and anti-HDAC evaluation of a new series of hydroxamates carrying an uracil moiety as CU, differently sized thioalkyl aliphatic and cinnamyl chains as HS, and several differently hindered (un)substituted aryl and arylalkyl moieties at the C6-position of the uracil ring as HG. Preliminary results showed that some of these derivatives are very potent HDAC inhibitors, with IC_{50} values in the subnanomolar range (600-800 pM), and are also endowed with promising class II HDAC selectivity and very interesting antiproliferative and cytodifferentiating activities.



R = H, alkyl, aryl, halogen, NHCOR, etc. X = H, eldonor and el-withdrawing groups n = 0-3; m = 0-5.

[1] Mai A, Massa S, Rotili D, Cerbara I, Valente S, Pezzi R, Simeoni S, Ragno R. Histone deacetylation in epigenetics: an attractive target for anticancer therapy. *Med. Res. Rev*. **2005**, in press.
[2] Dai Y, Guo Y, Curtin ML, Li J, Pease LJ, Guo J, et al. A novel series of histone deacetylase inhibitors incorporating hetero aromatic ring systems as connection units. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3817-3820.