3D-QSAR MODELS FOR SELECTIVE CLASS I (HD1-B) AND CLASS II (HD1-A) HDAC INHIBITORS

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Histone deacetylases (HDACs) are known to play an important role in the regulation of gene expression by catalyzing the deacetylation of the acetylated ε-amino groups of specific histone lysine residues. In eucaryotes, three deacetylase families have been identified so far (class I, class II and class III HDACs) with different sensitivity to different inhibitors, but no strongly selective compounds. Because of class I HDACs selective inhibitors may have great therapeutic potential as anticancer agents, and class II selective inhibitors can represent useful tools to explore or dissect the role of a given HDACs in different protein complexes, 3D-QSAR analyses have been conducted on a series of 25 (aryloxopropenyl)pyrrolyl hydroxyamides [1] active against both maize HD1-B (homologous of mammalian class I HDACs) and HD1-A (homologous of class II HDACs) enzymes, with the end of interpreting their HD1-B and/or HD1-A selectivity. The starting compound conformations have been performed using a molecular dynamic run with simulated annealing procedure as implemented in Macromodel 7.1 and the 3D-QSAR models have been built using the Grid Independent Descriptors (GRIND) calculated by Almond 3.2.0a software.
Satisfactory results have been obtained: the r^2 and q^2 have been 0.96 and 0.81 for the HD1-B model, and 0.98 and 0.85 for the HD1-A model.
The data analysis has revealed that the main characteristic for the HD1-A selectivity is the *shape* of compounds. In fact, the importance of shape description have been recognized by many authors and it is considered crucial for the ligand ability to bind to a receptor. In this case, the exactly shape has been calculated using one of the GRIND descriptors (TIP-descriptor), which selects the most descriptive molecular surface regions according a criterion based on the local curvature.
Molecules with a bowed shape and consequently with an exact distance (around 8.5 Å) between the H-bond acceptor region of the hydroxamic acid and the hydrophobic region of the cap group of the pyrrole compounds have high HD1-A activity and low HD1-B activity. It seems that when the molecules are bended, their caps can interact with an external hydrophobic region of the enzymes and that is relevant for the HD1-A activity, but not for the HD1-B one. Infact, all the most HD1-B-active pyrroles have a straight shape.

[1] Mai, A.; Massa, S.; Pezzi, R.; Rotili, D.; Loidl, P.; Brosch, G. *J. Med. Chem*. **2003**, *46*, 4826-4829.