"New Drug Hits and Chemical Probes Targeting Histone Deacetylase 10 (HDAC10)"

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Abstract:
Despite its critical role in various fundamental aspects of cancer and its involvement in non-oncologic diseases, histone deacetylase 10 (HDAC10) has received relatively little attention by drug discovery campaigns[1].

Among the 11 metal-dependent histone deacetylases (HDACs), the class IIb isozyme HDAC10 is the most intriguing in terms of its catalytic function and structure. In fact, unlike the other HDACs, which regulate gene expression by removing acetyl groups on lysine residues in histone and non-histone proteins, HDAC10's substrate is the small molecule N^8-acetylspermidine, revealing that this enzyme actually is a polyamine deacetylase [2].

Besides the Zn^{2+} ion, key features for substrate recognition, are the negative gatekeeper Glu274 and the steric hindrance of the site cleft by the 3_{10}-helix containing the "PEACE" motif: both can be exploited for the development of selective HDAC10 inhibitors (HDAC10i)[3].

In the last years, several HDAC10i were achieved, starting from optimisation and chemical modifications of the structure of HDAC inhibitors already approved as therapeutics[3-5] but there is still lack of safe, potent inhibitors with improved selectivity over the close IIb group relative HDAC6.

Hence, the aim of this project is the rational, computer assisted design and chemical synthesis of safe, selective inhibitors of HDAC10. In detail, the pharmacophore model inspired by N^8-acetylspermidine and HDAC10i reported in literature[1,3-5] will be followed. Extensive investigation will encompass alternative Zinc binding groups, linkers of appropriate length and capping groups bearing a basic amine, to strongly engage with the gatekeeper residue Glu274 and the PEACE motif. Lastly, to support and accelerate the achievement of new target molecules, the design of a procedure to assess the inhibitors and recognize the binding will be developed.

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