NOVEL *N*-(2-AMINOPHENYL)-BENZAMIDE INHIBITORS OF HDACs WITH ANTIPROLIFERATIVE AND ANTIFIBROTIC ACTIVITY

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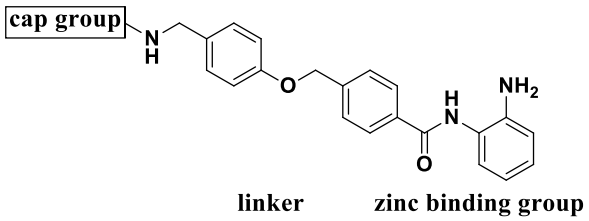
Inhibitors of histone deacetylases (HDACs) have attracted special interest through the years as potential therapeutic agents for the treatment of cancer and other diseases [1]. The most commonly studied classes of HDAC inhibitors are hydroxamic acids and benzamides [1]. In particular, *N*-(2-aminophenyl)-benzamides have been explored as isozyme-specific HDAC inhibitors and as an example, chidamide has been approved by the Chinese FDA for the treatment of peripheral T-cell lymphoma [2].
In this work, we present a series of novel HDAC inhibitors containing the *N*-(2-aminophenyl)-benzamide functionality linked to various cap groups, incorporating the amino acids pyroglutamic acid and proline. Among the synthetic compounds, new benzamides were identified, inhibiting class I HDACs at nanomolar concentrations, with antiproliferative activity at micromolar concentrations against A549, SF268 and Caco-2 cancer cell lines. Cellular analysis of selected potent inhibitors revealed downregulated expression of *EGFR* mRNA and protein. Finally, two inhibitors were investigated in a bleomycin-induced mouse model of pulmonary fibrosis and exhibited efficacy on a preventative dosing schedule. These findings suggest that such class I HDAC inhibitors may be useful for the treatment of fibrotic disorders.



References

[1] Ho, T. C. S.; Chan, A. H. Y.; Ganesan, A. Thirty years of HDAC inhibitors: 2020 insight and hindsight. *J. Med. Chem.* **2020**, *63*, 12460–12484.
[2] Lu, X.; Ning, Z.; Li, Z.; Cao, H.; Wang, X. Development of chidamide for peripheral T-cell lymphoma, the first orphan drug approved in China. *Intractable Rare Dis. Res.* **2016**, *5*, 185–191.