Área: MED

SULFONAMIDE-BASED BENZYL-HYDROXAMATE DERIVATIVES AS HDAC6i WITH POTENTIAL ANTITUMOR ACTIVITY IN HEMATOLOGICAL LINEAGES

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Highlights

Design and synthesis of sulfonamides as potential HDAC6i with antitumor activity. Five novel final compounds were obtained with a simple three-step synthetic route.

Abstract

Histone deacetylase inhibitors (HDACi) modulate the aberrant overexpression of this enzyme family, which is frequently upregulated in tumor cell lines. Recently, the LAPESSB research group designed and synthesized selective inhibitors targeting the HDAC6 isoform, highly expressed in hematological malignancies, where remission, relapse, and resistance pose significant therapeutic challenges. The lead compound exhibited antitumor activity in the micromolar range and demonstrated remarkable selectivity for HDAC6 (Fig. 1A). However, to further enhance their potency and selectivity, the current project aims to optimize these inhibitors through a strategic bioisosteric replacement, refining their structural features to improve HDAC6 inhibition.

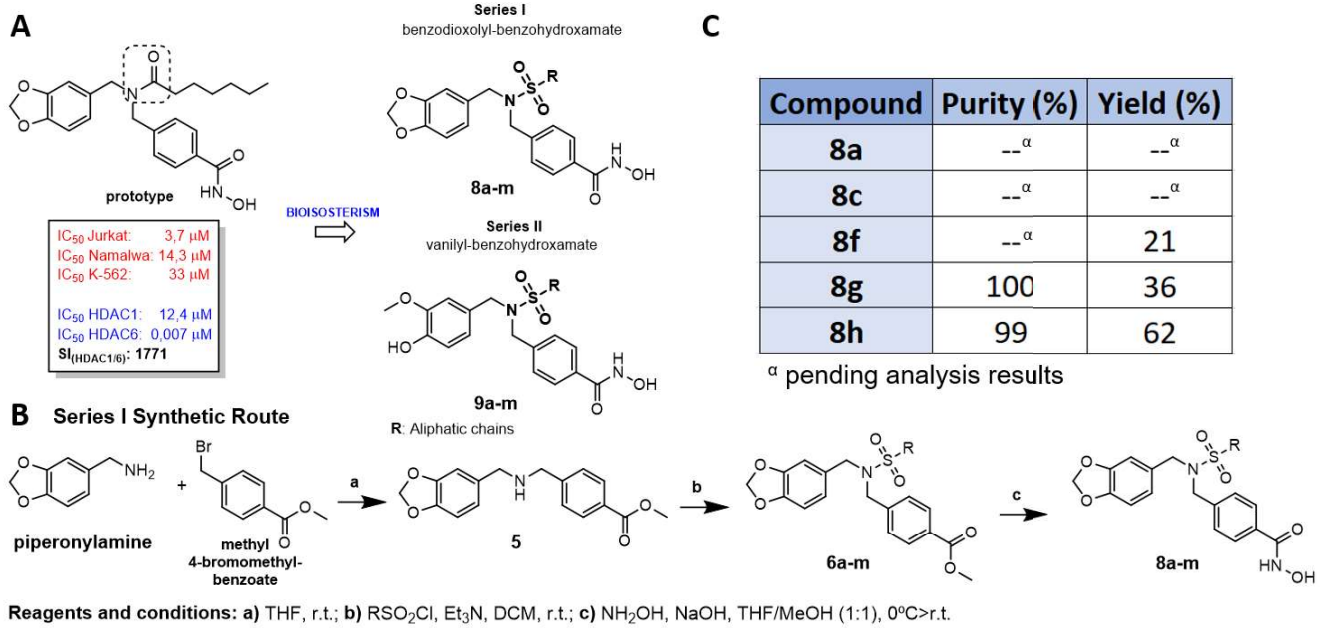

Figure 1: A) Design of compounds; **B)** Synthetic route of compounds obtained; **C)** Purity and yield data.

Using a straightforward three-step synthetic route (Fig. 1B), the final compounds **8a**, **8c**, **8f**, **8g**, and **8h** were successfully obtained, with overall yields ranging from 21% to 62% and high purity (>95%) as confirmed by HPLC analysis (Fig. 1C). These compounds will next undergo cytotoxicity assays against hematological tumor cell lines, including Namalwa (lymphoma), Jurkat, and K-562 (leukemia). Finally, the most promising candidates will be evaluated in enzymatic inhibition assays against HDAC isoforms to determine their selectivity for HDAC6.

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