Área: MED

Design and synthesis of benzodioxol-hydroxamate hybrids as potential anticancer agents

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Highlights

Capsaicin and nexturastat A hybrids were designed to be potential antitumoral compounds. Molecular docking studies were performed in HDAC6. Six benzodioxol-hydroxamate hybrids were synthesized and characterized.

Resumo/Abstract

Nexturastat A (HDAC6-selective inhibitor) have shown potential activity in hematological cancer therapy. At the same time, previous studies related to pepper-derived capsaicin and synthetic analogues have contributed to obtaining compounds with high antitumor activity, including hematological malignances [*Molecules, 26 (2021), 1521-1542*]. Thus, this project aims to obtain compounds, designed by the molecular hybridization of nexturastat A and capsaicin (**Figure 1A**), which could generate potential antitumoral candidates, and also new and selective HDAC6 inhibitors. The general scaffold of the hybrid compound started from using capsaicin as the *cap* group of the HDAC inhibitor (variation in this region can modulate selectivity, since the surface of the catalytic cavity of HDACs tolerates a wide molecular diversity) and the benzyl-hydroxamate moiety from nexturastat A as a linker and *Zinc Binding Group* (ZBG). Furthermore, the acyl-amidic carbon chain of capsaicin was replaced by different R groups in order to modulate affinity/selectivity of the *cap* group. Benzodioxyl-benzyl-hydroxamate analogues **26a- k** were designed by replacing the vanilloid group with a benzodioxol ring. Our previous studies have demonstrated the strong influence of this bioisosteric substitution into capsaicin-derived compounds, improving selective cytotoxicity [*Bioorg. Med. Chem., 28 (2020), 115600-115610; RSC Med. Chem.,11 (2020), 1032-1040; Bioorg. Med. Chem., 27 (2019), 1-21*].

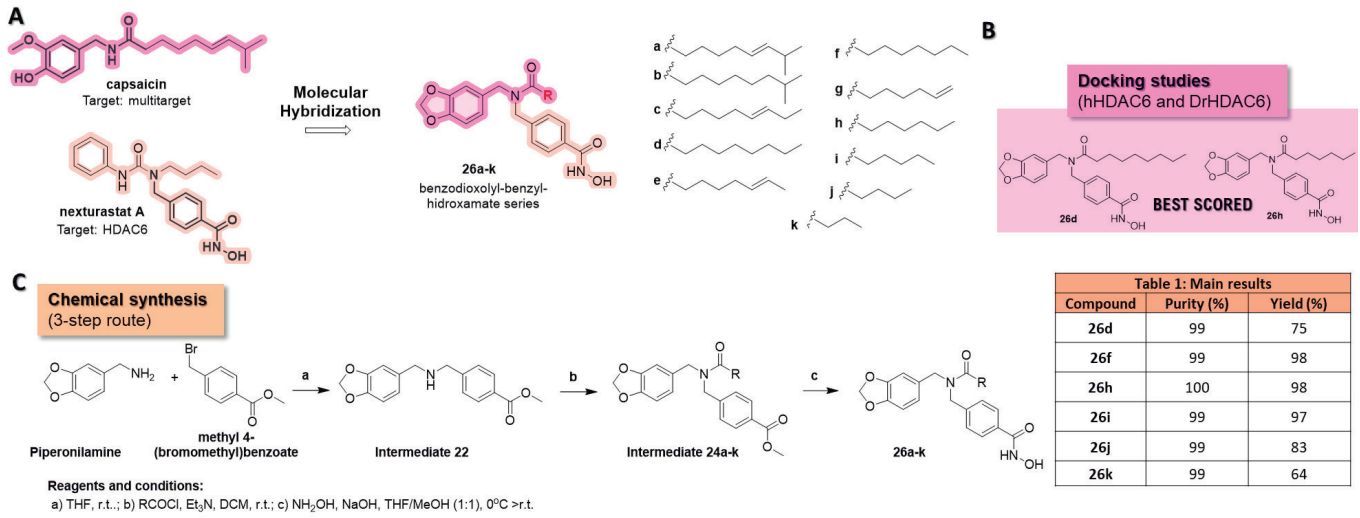

Table 1: Main results		
Compound	Purity (%)	Yield (%)
26d	99	75
26f	99	98
26h	100	98
26i	99	97
26j	99	83
26k	99	64

Figure 1: A) Design of compounds; B) Best scored compounds in docking studies; C) Synthetic strategy and main results.

The designed hybrids were submitted to molecular docking studies over human and zebrafish HDAC6 isozymes, and compounds **26d** and **26h** demonstrated the best scores in both enzymes (**Figure 1B**). The best scored compounds (**26d** and **26h**) and further four analogues (**26f**, **26i**, **26j** and **26k**) were synthesized in a facile 3-step synthetic route and they were obtained in good-to-high yields (64%-98%) and, moreover, HPLC purity greater than 99% (**Figure 1C**, **table 1**). All the compounds were characterized by $^{1}H/^{13}C$ NMR and HRMS. Phenotypic screening against different cancer cell cultures, such as Jurkat, Namalwa and K562, and enzymatic inhibition assay against HDACs are underway.

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