Área: MED
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Design and synthesis of new potential PI3K and HDAC6 hybrid inhibitors for cancer treatment

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Highlights

Pharmacophores of PI3K and HDAC6 inhibitors have been hybridized into a single entity. They were synthesized and its anticancer and enzymatic activities were evaluated.

Resumo/Abstract

Hybrid inhibitors have the potential to overcome cancer resistance, by blocking multiple signaling pathways at once. Both PI3K (phosphoinositide 3-kinase) and HDAC6 (histone deacetylase 6) are commonly mutated on tumors and their inhibition has been shown beneficial for treatment. To construct hybrid PI3K/HDAC6 inhibitors, pharmacophores of known selective inhibitors bearing anilino-purines, benzyl-hydroxamates, and benzyl-benzamides (idelalisib, nexturastat A, and chidamide) have been connected through a linker and hybridized into a single entity (Figure 1).

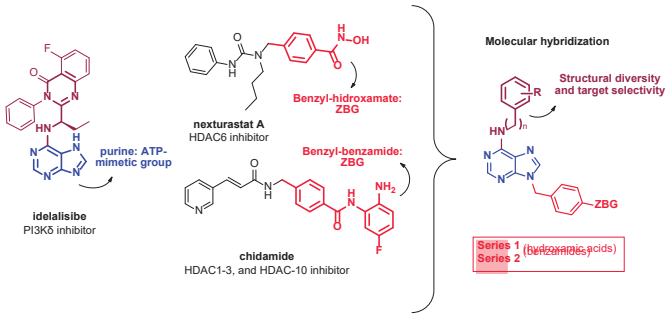

Figure 1: Design of PI3K/HDAC6 hybrid inhibitors.

Eight final compounds and five intermediates have been synthesized with yields from 6-48% and characterized by ^{1}H, ^{13}C NMR, and cancer cell cytotoxicity. The most promising ones were subjected to DMPK tests and personalized enzymatic assays to evaluate their activity on target and selectivity. The results obtained for the most successful compounds are summarized in Table 1.

Table 1: Synthesis, yields and biological evaluation of most promising hybrid compounds.

Compound	Yield (%)	Purity (%)	IC_{50} HCT116 (μM)	IC_{50} MCF-7 (μM)	IC_{50} Jurkat (μM)	IC_{50} Namalwa (μM)	IC_{50} HDAC1 (μM)	IC_{50} HDAC6 (μM)	$T_{1/2}$ human/ mouse (min)	Cl_{int} human / mouse (μL/min/mg)	Inhibition CYP450 (%)
6a	31	99.9	9.3	9.3	0.02	0.04	118.4	232.4	>120 / 50	< 6/ 14	50 / 34 / -23 / -16 (1A2 / 2C9 / 2D6 / 3A4)
6c	22	98.7	8.3	19.5	0.05	0.01	83.5	184.3	>120 / 35	< 6/ 20	47 / 42 / -55 / -14 (1A2 / 2C9 / 2D6 / 3A4)
6d	48	97.8	21.7	31.7	0.03	0.04	188.5	341.0	>120 / 35	< 6/ 20	46 / 52 / -39 / -62 (1A2 / 2C9 / 2D6 / 3A4)

1. Waitman, K. & Parise-Filho, R. New kinase and HDAC hybrid inhibitors: recent advances and perspectives. *Future Med. Chem.* **14**, 745–766 (2022).

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