

# Synthesis and biological evaluation of hybrid inhibitors for the treatment of hematologic malignancies

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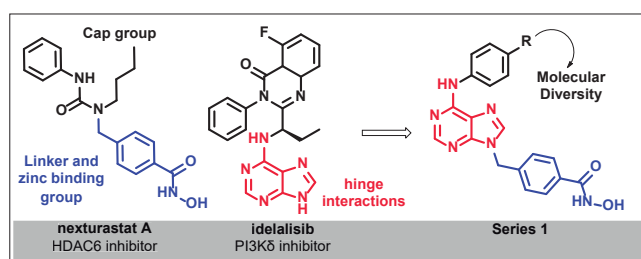
Palavras Chave: molecular hybridization, histone deacetylase, phosphoinositide 3-kinase, dual inhibitors, hybrids, cancer.

## Highlights

A hybrid PI3K/HDAC6 inhibitor has been designed from two selective molecules for treating hematologic cancer. One final molecule was synthesized.

## Abstract

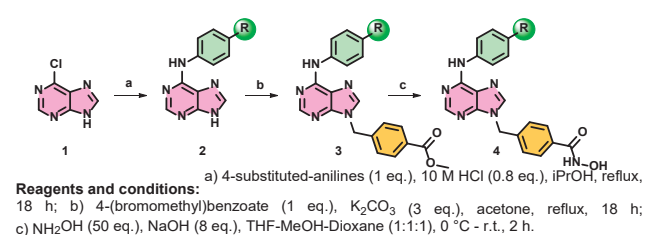
Cancer is a disease characterized by the disordered and accelerated replication of abnormal and dedifferentiated cells within which a vast number of genes are mutated. PI3K $\delta$  (phosphoinositide 3-kinase delta) mutations are widespread in leukocytic lineages and so its inhibition is being increasingly explored although the apparent resistance to monotherapy.<sup>1</sup> To overcome this situation, hybrid molecules, especially between PI3K and HDAC6 (histone deacetylase 6) inhibitors, have been shown to be an effective alternative.<sup>1</sup> Therefore, this work aims to synthesize hybrid PI3K/HDAC6 molecules based on the pharmacophores of selective inhibitors of each chosen target, idelalisib (PI3K $\delta$  inhibitor) and nexturastat A (HDAC6 inhibitor), as shown in figure 1.



**Figure 1:** Design of the hybrid inhibitor.

As shown in **Scheme 1**, the hybrid compounds of series 1 were prepared from the reaction of 6-chloropurine (**1**) with 4-substituted-anilines, through nucleophilic aromatic substitution (S<sub>N</sub>Ar), thus forming the aniline-purine intermediates (**2**). Compounds **2** were reacted with methyl 4-(bromomethyl)benzoate via bimolecular nucleophilic substitution reaction (S<sub>N</sub>2), to form benzoate methyl ester intermediates (**3**).

Finally, intermediates (**3**) were reacted with hydroxylamine (NH<sub>2</sub>OH) to yield the corresponding hydroxamates (**4**).



**Scheme 1.** Synthetic route for hybrid compounds.

Final compound **4d**, prepared by the reaction with a 4-bromoaniline, was obtained as a white solid with 51% global yield, as well as its intermediates **2d** (greenish white solid, 81% yield) and **3d** (slightly green solid, 81% yield) with the route showing good viability. All the compounds were further characterized by <sup>1</sup>H and <sup>13</sup>C NMR and their high purity will be verified by HPLC soon. In the end, we expect to have ten different final products. After their complete characterization and purity evaluation, the compounds will have their biological activity assessed by cytotoxicity and mechanistic assays in hematological cancer cell lineages and solid tumors, such as Jurkat cell line (T-cell acute lymphoblastic leukemia), Namalwa cell line (B-cell acute lymphoblastic leukemia), MCF-7 (breast cancer cell line) and HCT 116 (colon cancer cell line).

1. Waitman, K.; Parise-Filho, R. *Future Medicinal Chemistry*, **2022**, 14(10), 745–766.

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