

Área: ORG

New 3,4-dihydropyrimidin-2(1H)-one Analogous to the Antitumor SAHA

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Highlights

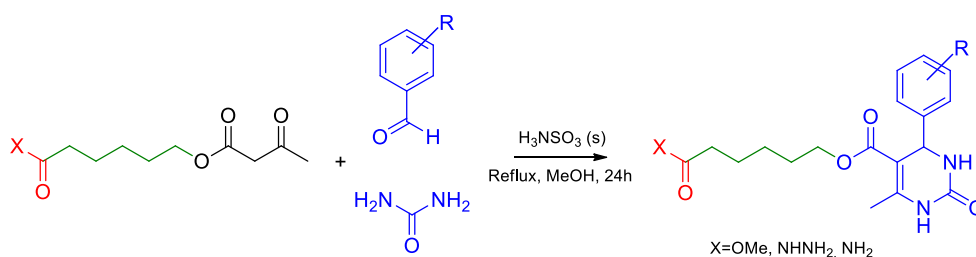
- Novel SAHA analogs from DHPMs.
- Biginelli Multicomponent Reaction.
- New candidates for HDAC inhibition and anticancer agents.

Abstract

The development of cancer and the activity of HDACs (Histone Deacetylases) are associated in several ways (apoptosis, DNA damage, metastasis, etc.), and one of the strategies to counteract this deregulation of enzymatic activity is through the use of HDAC inhibitor drugs. Suberoylanilide hydroxamic acid (SAHA) or Vorinostat® was the first HDAC inhibitor (HDACi) approved by the U.S. Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma (CTCL).

In this work, we carried out the synthesis and characterization of new 3,4-dihydropyrimidin-2(1H)-one (DHPM) analogs and hybrids of Vorinostat® (SAHA) using multicomponent reactions, with the aim of evaluating their antitumor activity. In the first stage, for the synthesis of amides, δ -valerolactone ($n = 1$) and ϵ -caprolactone ($n = 2$) were opened using a solution saturated with gaseous ammonia introduced into the reaction medium by bubbling (yields of 88% and 90%). For the synthesis of hydrazide derivatives, the respective lactones reacted with hydrazine hydrate under stirring and reflux at 65 °C for 24 hours (yields of 90% and 92%). For the synthesis of methyl ester derivatives, the reaction was carried out in methanol in the presence of catalytic amounts of sulfamic acid, followed by the addition of δ -valerolactone and ϵ -caprolactone (yields of 92% and 99%).

Subsequently, the synthesis of acetoacetates containing methyl ester, amide, and hydrazide groups derived from δ -valerolactone and ϵ -caprolactone was performed in the presence of anhydrous sodium acetate (NaOAc) and diketene (or TMD). The reaction was conducted under stirring and reflux at 85 °C for 24 hours. Finally, a Biginelli multicomponent reaction was carried out using the acetoacetates obtained in the previous step, with different aldehydes, urea, catalytic amounts of sulfamic acid, and isopropanol as the solvent, at 85 °C for 24 hours.



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