TARGETING THE BIOACTIVE DIHYDROPYRIMIDINES BY ECOFRIENDLY PROCEDURE OF BIGINELLI REACTION: STUDY CASE OF MONASTROL

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Biologically active compounds decorated with dihydropyridine moiety are counted amongst the numerous broad-spectrum therapeutic agents that explain the increasing role of this scaffold in rational drug design [1]. The Biginelli reaction is a multicomponent reaction of aldehyde, (thio)urea, and β-ketoester, involving Mannich reaction in the first step, which produces multifunctionalized 3,4-dihydropyrimidin-2-(1H)-ones and related heterocyclic compounds [2]. The attractiveness of this acid-catalyzed one-pot condensation reaction lies in the simplicity of grafting the substituent into the structure of the products, which can later be transformed into different functional groups that are required for subsequent syntheses. Monastrol, the most representative Biginelli adduct in anticancer drug development, proved to be a cell permeable molecule whose mechanism of action on cancer cells involves the selective inhibition of the motility of the mitotic motor enzyme kinesin Eg5 [3]. Thus the remarkable therapeutic and pharmacological potential of it maintains expressive interest of chemists, some green synthesis approaches being recently reported, as well [4,5].

In continuation of our research line [6], we herein report on a facile ecofriendly synthesis of (±)-M, based on the use of oxalic acid (20mol/%) as green catalyst instead of toxic Lewis acids. The proposed procedure also offers the advantage of shortening the reaction time twice, in comparison with the classic reaction, producing the racemic target compound in 60% yield, m.p. 182-184⁰C (crystallized from ethyl acetate), rep. 182-184⁰C [4,5].

The prepared (±)-monastrol has shown antifungal activity against Candida albicans and Saccharomyces cerevisiae at concentrations 8 times lower than reference antifungal agent Nystatin.

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References: