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Synthesis, Inhibitory Activity, and Molecular Modelling of 2-Hydroxy-3-Oxo-3-Phenylpropionate Derivatives as HIV-1-Integrase Inhibitors

Authors : O. J. Jesumoroti, Faridoon, R. Klein, K. A. Iobb, D. Mnkadhla, H. C. Hoppe, P. T. Kaye

Abstract : The 1, 3-aryl diketo acids (DKA) based agents represent an important class of HIV integrase (IN) strand transfer inhibitors. In other to study the chelating role of the divalent metal ion in the inhibition of IN strand transfer, we designed and synthesized a series of 2-hydroxy-3-oxo-3-phenyl propionate derivatives with the notion that such compounds could interact with the divalent ion in the active site of IN. The synthetic sequence to the desired compounds involves the concept of Doebner knoevenagel condensation, Fischer esterification and ketohydroxylation using neuclophilic re-oxidant; compounds were characterized by their IR, IHNMR, 13CNMR, HRMS spectroscopic data and melting point determination. Also, molecular docking was employed in this study and it was revealed that there is interaction with the active site of the enzyme. However, there is disparity in the corresponding anti-HIV activity determined by the experimental bioassay. These compounds lack potency at low micromolar concentration when compared to the results of the docking studies. Nevertheless, the results of the study suggest modification of the aryl ring with one or two hydroxyl groups to improve the inhibitory activity.

Keywords : anti-HIV-1 integrase, ketohydroxylation, molecular docking, propionate derivatives
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