

Design, synthesis and docking studies of novel anti-HIV agents

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Abstract

Introduction: AIDS therapeutic targets principally consists of three enzymes: reverse transcriptase (RT), protease (PR) and integrase (IN). Integrase strand transfer inhibitors among the HIV inhibitors has the advantage of suitable safety profile and high potency. The chelating motif and coplanar hydrophobic aryl group are the common pharmacophores of an integrase strand transfer inhibitor (INSTI). According to the cyclic chelating group of dolutegravir, we incorporated the chelating group into a cyclic motif and novel 2-mercaptooxazoloxocoumarin tricyclic scaffold was designed. Hydrophobic part of the ligand was attached through s-arylation to occupy the same position as the halobenzyl pharmacophoric group of INSTIs.

Methods and Results: 4-Hydroxy-3-nitro coumarin was prepared in a nitration procedure of 4-hydroxy coumarin with the aid of concentrated nitric acid and sulfuric acid. Reduction of the 4-hydroxy-3-nitro coumarin in the presence of sodium dithionite and sodium acetate in water gave the 3-amino-4-hydroxy coumarin. 2-Mercaptooxazolocoumarin was prepared by the reaction of carbon disulfide with 3-amino-4-hydroxy coumarin in methanolic potassium hydroxide. Then, this intermediate was treated with substituted benzyl halides in the presence of potassium carbonate and acetone. Final derivatives were recrystallized from ethanol and confirmed by IR, LC-MS (ESI), ¹HNMR & ¹³CNMR. According to the docking results, the tricyclic scaffold could π -stack the 3'-end reactive adenosine in the IN active site just same as the co-crystallized ligand dolutegravir and the ligand heteroatoms complexes the magnesium cofactors in the IN.

Conclusions: Here, we introduced a novel scaffold for anti-HIV activity. The superimposed structure with co-crystallized ligand dolutegravir confirmed the potential for integrase inhibitory activity just same as the second generation integrase inhibitor dolutegravir.

Keywords: 2-Mercaptobenzoxazolocoumarin, Anti-HIV-1 activity, Design; Synthesis, Molecular modeling.

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