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Abstract

Molecular Modeling and Synthesis of New HIV Latency-Reversing Agents Targeting the Lymphatic System †

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Abstract: During the HIV infection, a small amount of the virus remains in a latent state, forming a viral reservoir in places with limited access to drugs such as lymph nodes. HIV latency reversing agents, as HDAC inhibitors, have been used in the "kick and kill" strategy aiming to reactivate the latent virus and its subsequent elimination. Combining these compounds with a lipophilic group may promote an increase in lipophilicity and improve the bioavailability. In order to target these compounds to lymphatic system, we described the design, synthesis and evaluation of pro-drugs of HDAC-3 inhibitors. In silico studies were performed using the molecular modelling Maestro by Schrödinger environment using HDAC-3 (PDB: 4A69). All compounds were prepared through divergent synthesis. The reactions consisted of NH_2 protection in 5-fluoro 2-nitroaniline reagent using di-tert-butyl dicarbonate, reduction of the NO_2 group with Fe and NH_4Cl/MeOH and coupling reactions using HATU/DIPEA or oxalyl chloride with palmitic and α-linolenic acid. LogP values were determined by HPLC-UV (C18, MeOH:H2O). Docking simulation suggests that all compounds are able to interact with HDAC-3, with docking score values of −6.078 to −8.369. Four compounds were synthesized at global yields ranging from 21–68%. All structures were characterized by analytical methods. LogP values were determined ranging from 4.89–6.5. Pro-drug compounds were designed and synthesized. The results of in silico studies and experimental LogP justify that these compounds can be targeted to the lymphatic system, to act as HDAC-3 inhibitors.

Keywords: HDAC inhibitors; kick-and-kill; HIV

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