
Abstract:
Latent HIV reservoirs have been a bottleneck for finding a cure for HIV-AIDS. In the “shock and kill” approach, HIV-1 transcription is induced in latently infected cells and the immune system and/or viral cytopathic effects are used to target these cells. For the “shock and kill” strategy, the most studied targets are the Histone Deacetylases (HDAC), enzymes that remove acetyl groups from DNA-bound histone proteins. In the case of HIV-1 infected cells, HDAC deacetylates the long terminal repeat (LTR) promoter and plays a key contributory role in regulating HIV expression and maintaining proviral quiescence and latency. Ideally, HDAC inhibitors activation of latent viruses should be spatially and temporally linked to the antiviral activity. Dual-action drugs of the type targeting HIV latency and preventing new infections is a novel approach that has not been explored previously. We have identified HDAC as the target for latency and HIV-1 protease (HIV-1 PR) as the target for preventing new infections. To the best of our knowledge, no study has been published which has successfully targeted both HDAC and HIV-1 PR with a single molecule.

Macrocyclic inhibitors of HIV-1 PR and HDAC were identified from the literature as potential lead compounds towards the development of dual inhibitors. These compounds were synthesized, and their macrocyclic core was studied to understand the solution phase structure, employing 2-D NMR. The data from the NMR studies was used to identify the energy minimized structure of the macrocyclic core using Schrödinger Maestro®. The study revealed good overlap of the macrocyclic cores and gave credence to the theory that a dual inhibitor could be designed based on these controls. The two macrocyclic HDAC inhibitors synthesized were tested against HDAC 1 and 3 to check their efficacy as control HDAC inhibitors and assays did not show any noticeable inhibition. HDAC 3 inhibition is paramount for HIV-1 latency activation. This prompted a rethink of our strategy and based on literature we posed that changing the zinc binding group of the macrocycles could help improve the HDAC 3 inhibition. A molecular dynamics (MD) study using DESMOND was undertaken to see if these macrocycles with different zinc binding groups could be good HDAC 3 inhibitors. The compounds showing good binding based on the MD studies were identified and synthesized and tested for HDAC 3 and 1. These compounds again showed no noticeable inhibition based on the assay results. These results forced us to develop a new approach towards the development of dual inhibitors and we began looking at FDA approved and/or compounds that are in advanced clinical trials as the control compounds. Dual inhibitors were designed, synthesized, and tested; these compounds show micromolar inhibition. We are glad to report the first dual inhibitor of HDAC and HIV PR. These novel compounds could be good lead compounds to develop newer, better dual inhibitors.