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Comparison of binding affinities and ADMET properties of lysine sulfonamide and cyclic urea derivatives with commercial HIV protease inhibitors for the MDR mutants

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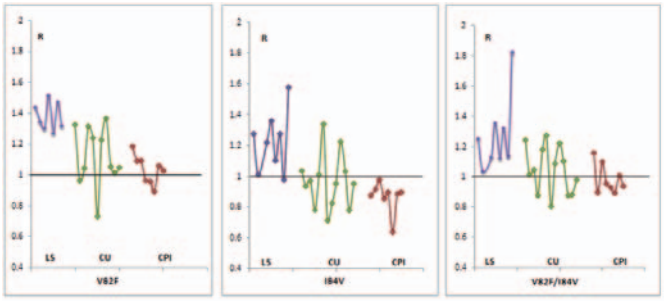
The rapid emergence of resistance of the HIV-1 protease to the commercial protease inhibitors (CPI) has created a need for novel drugs potent against the Multi-Drug-Resistant (MDR) mutants. In this regard, the binding affinities of a series of lysine sulfonamides (LS) and cyclic urea (CU) derivatives along with eight CPI towards HIV protease enzymes and their ADMET properties are compared. The binding free energies are calculated using ligand-protein docking with flexible ligand approach as implemented in Arguslab 4.0.1 software. We define an empirical parameter, R, equal to the ratio of the relative binding free energies of an inhibitor with a mutant (V82F, I84V or V82F /I84V) to that of the non-mutant (WT) protease. We found that most of the inhibitors from LS and CU series either maintain or show an increased affinity ($R > 1$) towards the mutants, while those of CPI series show a decreased affinity. The studied compounds also show acceptable bioavailability and toxicity levels. Thus LS and CU series yield promising leads against the MDR mutants of HIV protease enzyme.



Relative binding affinities of selected lysine sulfonamides (LS), cyclic urea compounds (CU) and commercial protease inhibitors (CPI) against V82F, I84V and V824/I84V double mutants of HIV protease enzyme over the WT non-mutant.

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