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In-silico designing of acyclic nucleoside phosphonates and their anti-HIV potential

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Background

Reverse transcriptase, the viral enzyme, is a key target in the search for effective drugs useful for AIDS therapy and has critical roles in the life cycle of the human immunodeficiency virus type 1 (HIV-1), the causative agent of AIDS. HIV replication can be blocked by inhibition of the enzyme HIV RT.

Method

The object of our study is to develop newer nucleoside phosphonate analogs bearing unsaturation and modifications in heterogenous bases and prediction of their anti-HIV potential. Designing is done keeping the Lipinski's Rule of Five in focus. The diphosphates of compounds have been docked into the active site of wild type HIV-RT (PDB: ID 2B6A). The forcefield of the Chemistry at Harvard Macromolecular mechanics (CHARMm) was applied to 3D models of PD HIV RT-nevirapine complex and synthesized ligands. The energy function is based on separable internal coordinate terms and pair wise non-bond interaction terms.

Result

Docking studies revealed that the diphosphates of acyclic phosphonates had good interactions with various amino acid residues present in the active site of HIV RT. The Ludi 3 score was found to be 718 and the corresponding K_d value was 0.06μM. This is in good agreement with the observed value of 0.05μM.

Conclusion

On the basis of SAR studies, uridine phosphonate analogs are expected to be probable lead molecules against HIV-RT.

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