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In silico designing and development of novel anti-HIV molecules

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HIV/AIDS continues to be one of the major challenges before the scientific community. HIV is a retrovirus, having ssRNA as the genetic material, which gets converted into dsDNA (provirus) in the presence of an enzyme called reverse transcriptase (RT). Various drugs used for treatment of AIDS are mainly the inhibitors of this RT enzyme. NRTIs and NNRTIs represent this class of inhibitors. NRTIs or nucleoside reverse transcriptase inhibitors, the analogs of natural nucleosides involved in inhibition of viral DNA synthesis, interact at substrate binding or active sites on HIV-RT. NNRTIs or non-nucleoside reverse transcriptase inhibitors interact at the allosteric site, approx 10Å away from the active site, on HIV-RT. Non-competitive inhibition of the enzyme occurs because of this interaction. We have successfully carried out the designing, synthesis and screening of novel NNRTIs derived from N-(4-amino-2-methylphenyl)-4-chlorophthalimide having imine, amide, sulfonamide and thioamide linkages containing different moieties. Molecules were designed first with an idea of hydrophobic and hydrophilic sites on HIV-RT. The energy minimized structures of these molecules were docked into HIV-RT. Docking experiments were done using DS 2.5 software and very good interactions were observed between these molecules and RT enzyme. Docking experiments revealed good interactions with HIV-RT showing 1 to 7 H-bonds with various amino acid residues, like K101, K103, V106, Y181, Y188, P236 and Y318 constituting the allosteric site. The non-covalent interactions involved H-bonding and some other electrostatic forces. The molecules were then synthesized and screened against HIV-1 using TZM-bl cell lines. The results of *in vitro* screening showed that some of these molecules were effective inhibitors of HIV-1 replication at nanomolar concentration. SAR studies revealed that the linkages in these molecules did affect their anti-HIV activity and the molecules having sulfonamide linkages were the most potent HIV RT inhibitors with selectivity indices ranging from 33.75 to 73.33 under *in vitro* conditions.

Biography

Ramendra K Singh is an Associate Professor of Chemistry at the University of Allahabad, India, is Director of the Nucleic Acids Chemistry and Antiviral Research laboratory and is member of several national committees. He has several awards/fellowships, like ISCA Young Scientists Award, INSA Visiting Fellowship, UNESCO Fellowship, XVI IUBMB Fellowship, Jawaharlal Nehru Visiting Fellowship, Post-Doc Fellowship, Govt of Japan, INSA International Exchange Fellowship and Fulbright-Nehru Senior Research Fellowship to his credit. His research interest lies in computer-aided designing and development of antiviral molecules against HIV, HPV and JEV and developing fluorescent oligonucleotides for use in the field of molecular biology and diagnostics. He has about a dozen anti-HIV and half-a-dozen anti-JEV compounds under patent processing. He is on editorial board of several international journals and referee to more than a dozen journals.

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