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3D-QSAR Study of Some 5, 6-Dihydropyran-2-ones as Protease Inhibitors

S. KUMAR, REENA R. JACOB AND MEENA TIWARI*
Department of Pharmacy, Shri Govindram Seksaria Institute of Technology and Science, 23, Park Road, Indore-452 003.

In the present study three dimensional quantitative structure activity relationship studies were performed on a series of 5,6-dihydropyran-2-ones as HIV protease inhibitors using CS Chem Office Version 6.0. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally as well as externally for the prediction of activity. The best quantitative structure activity relationship model was selected having a correlation coefficient (r) of 0.8285 and cross-validated correlation coefficient (Q^2) of 0.5169. The study indicates that thermodynamic descriptors (torsion energy, total energy, molar refractivity and Vander Waals energy) and electronic descriptor (lowest unoccupied molecular orbital) play an important role for the HIV Protease binding affinities. The information generated from the present study may be useful in the design of more potent protease inhibitors as antiHIV agents.

Acquired immunodeficiency syndrome (AIDS) leads to opportunistic infections or malignancies associated with the immune system characterized by the progressive loss of CD4 helper T cells. The HIV genome encodes enzymes such as protease, transcriptase and integrase for the viral replication[1,2]. The enzymes protease (PR) performs the proteolytic cleavage during viral assembly and maturation[1-3]. Therefore, Protease is an essential enzyme for HIV life cycle, the inhibition of the HIV-1 protease *in vivo* leads to immature and noninfectious viral particles and represents very attractive target for the synthesis of new antiviral drugs. The effect of binding various inhibitors on the protease structure is currently the focus of intensive research. HIV-1 PR is an aspartyl protease that is functional as a dimer of two identical subunits with 99 amino acid residues. The dimer has an active site, situated at the interface between the two monomers, with one catalytic triad (Asp-Thr-Gly) from each monomer[1-4].

Many crystallographic[1-4] and energetic studies[5-9] about the HIV-PR, wild type and mutants, have made the enzyme an attractive target for the computer-aided drug design[10-12]. The series selected for the present study have shown *in vitro* HIV PR binding affinities with better bioavailability. X-ray crystal structures of the dihydropyrones reveal that it occupies the inner four pockets of the enzyme and enolic hydroxyl group forms H-bonds with the aspartate residues at the cleavage site while the lactone moiety interacts with the Ileu residues[13,14]. No QSAR studies have been carried out on 6-Substituted-5,6-dihydropyran-2-one derivatives. It appears to be interesting to perform 3D QSAR analysis employing CS Chem. Office 2001 version 6.0[15] to correlate various physicochemical parameters to the biological activity for the design of novel protease inhibitor.

*For correspondence
E-mail: surendramph@indiatimes.com

MATERIALS AND METHODS

A data set of 26 molecules has been taken from published article (*Prasad et al)*[16]. The structure and HIV PR binding affinities tested *in vitro* are shown in Table-1 and fig.1. All the values of biological data were shown in IC_{50} (nM), which were converted into $-LogIC_{50}$ (nM) for convenience of computational work. All structure of 6-Substituted-5,6-dihydropyran-2-one derivatives were constructed using Chem Draw and transferred to CS Chem 3D to convert