Medicinal Chemistry

Title: Variable Selection Based QSAR Modeling on Bisphenylbenzimidazole as Inhibitor of HIV-1 Reverse Transcriptase

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Abstract: The emergence of mutant virus in drug therapy for HIV-1 infection has steadily risen in the last decade. Inhibition of reverse transcriptase enzyme has emerged as a novel target for the treatment of HIV infection. The aim to decipher the structural features that interact with receptor, we report a quantitative structure activity relationship (QSAR) study on a dataset of thirty seven compounds belonging to bisphenylbenzimidazoles (BPBIs) as reverse transcriptase inhibitors using enhanced replacement method (ERM), stepwise multiple linear regression (Stepwise-MLR) and genetic function approximation (GFA) method for selecting a subset of relevant descriptors, developing the best multiple linear regression model and defining the QSAR model applicability domain boundaries. The enhanced replacement method was found to give better results r^2=0.8542, $Q^2_{(loo)}$ = 0.7917, r^2_{pred} = 0.7812) at five variables as compared to stepwise MLR and GFA method, evidenced by internal and external validation parameters. The modified r^2 (r^2_m) of the training set, test set and whole data set were calculated and are in agreement with the enhanced replacement method. The results of QSAR study rationalize the structural requirement for optimum binding of ligands. The developed QSAR model shows that hydrophobicity, flexibility, three dimensional surface area, volume and shape of molecule are important parameters to be considered for designing new compounds and to decipher reverse transcriptase enzyme inhibition activity of these compounds at molecular level. The applicability domain was defined to find the similar analogs with better prediction power.