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Multiple Receptor Docking and Dock Pose Clustering as a Tool for CoMFA and CoMSIA Studies

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This study was performed on 13 high resolution receptor conformations of HIV-1 protease extracted from protein data bank (1PRO, 1BVG, 1BV9, 1AJX, 1AJV, 1T7K, 1QBR, 1QBS, 1QBU, 1HVR, 1HVH, 1DMP, 1G35). A set of 150 cyclic urea protease inhibitors with diverse substructures and varied range of inhibition constants, were docked into the active site of the receptors. After analysis their binding affinities and interactions with the receptor, the docked poses were clustered to obtain the best receptor binding conformation. These dock poses from clustering were used for 3D QSAR analysis, statistically significant CoMFA and CoMSIA models were generated using 85 molecules in the training set by applying leave one out cross validation study r^2_{cv} values of 0.663 and 0.623 for CoMFA and CoMSIA respectively and non-cross validated values of 0.985 and 0.959 were obtained for CoMFA and CoMSIA respectively. The predictive ability of these models was determined using a test set of 65 cyclic urease molecules that gave predictive correlation (r^2_{pred}) of 0.54 and 0.67 respectively for CoMFA and CoMSIA indicating good internal predictive ability. Based on this information 25 non-cyclic urease molecules were taken as a test set to check the external predictive ability of these models. This gave remarkable out come with r^2_{pred} of 0.68 and 0.51 for CoMFA and CoMSIA respectively. This approach is applicable for receptor based alignment for molecules having varied structural motifs, recommending the increase in accuracy of 3D QSAR predications for considering diverse scaffolds.