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SP HSP-Exploration of structural and physicochemical requirements and search of virtual hits of HSP90 inhibitors as potential anticancer agents

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HSP90 is a protein having potential for design of anticancer agents. Molecular modeling and virtual screening of some HSP90 inhibitors were performed. 144 HSP90 inhibitors were used for developing regression models. Classification models were developed with another dataset containing active and inactive molecules (decoy set). The best 2D-QSAR model (Q^2=0.777, R^2_{Pred}=0.748) showed significance of donor feature, solvent accessible surface area (SASA), lipophilicity and molecular fragments for higher activity. The recursive partitioning (RP) classification model (ROC_{CV}=0.926, ROC_{Pred}=0.843) depicted SASA and donor feature as the major classifiers. The best ligand-based Hypogen pharmacophore model (R^2=0.880, R^2_{Pred}=0.668) had two hydrophobic (H), one each of acceptor (A), donor (D), positive ionisable (P) features and four exclusion volumes. This model also showed considerably higher GH score of 0.81 against decoy set. The best structure-based (SB) pharmacophore model contained three D, one each of A and H features. Inclusion of shape constraints produced higher GH score (0.780) for SB model. Two docking tools (GLIDE and LibDock) were validated against the decoy set compounds.GLIDE-based molecular alignment of 144 compounds were used for developing CoMFA (Q^2=0.731, R^2_{Pred}=0.862) and CoMSIA (Q^2=0.673, R^2_{Pred}=0.854) models. Pharmacophore models and GLIDE docking were used for primary screening of databases (NCI, Specs and Asinex). Finally, seven most potential drug-like (Lipinski and Veber rules) virtual hits were selected on the basis of higher docking scores, shape similarities, predictive activities against 2D QSAR, RP and Hypogen models.

Biography

Amit Kumar Halder completed his MPharm from Department of Pharmaceutical Technology, Jadavpur University, India in 2008. He is now a Senior Research Fellow under Council of Scientific and Industrial Research (CSIR), India. He has published 18 research articles and one book chapter so far.

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