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Docking, Pharmacophore Modeling and 3d QSAR Studies on Some Novel HDAC Inhibitors with Heterocyclic Linker

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Abstract : The application of histone deacetylase inhibitors is a well-known strategy in prevention of cancer which shows acceptable preclinical antitumor activity due to its ability of growth inhibition and apoptosis induction of cancer cell. Molecular docking were performed using Histone Deacetylase protein (PDB ID:1t69) and prepared series of hydroxamic acid based HDACIs. On the basis of docking study, it was predicted that compound 1 has significant binding interaction with HDAC protein and three hydrogen bond interactions takes place, which are essential for antitumor activity. On docking, most of the compounds exhibited better glide score values between -8 to -10 which is close to the glide score value of suberoylanilide hydroxamic acid. The pharmacophore hypotheses were developed using e-pharmacophore script and phase module. The 3D-QSAR models provided a good correlation between predicted and actual anticancer activity. Best QSAR model showed Q2 (0.7974), R2 (0.9200) and standard deviation (0.2308). QSAR visualization maps suggest that hydrogen bond acceptor groups at carbonyl group of cap region and hydrophobic groups at ortho, meta, para position of R9 were favorable for HDAC inhibitory activity. We established structure activity correlation using docking, pharmacophore modeling and atom based 3D QSAR model for hydroxamic acid based HDACIs.

Keywords : HDACIs, QSAR, e-pharmacophore, docking, suberoylanilide hydroxamic acid
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