CoMFA and CoMSIA 3D-QSAR and Molecular Docking Studies on Biaryl Benzamides derivatives as Histone Deacetylase 1 Selective Inhibitors

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Abstract: Histone deacetylases (HDACs) are attractive therapeutic targets for the treatment of cancer and other diseases [1].It has four classes (I-IV), among them especially class I isozyme are involved in promoting tumor cells proliferation, angiogenesis, differentiation, invasion and metastasis and also viable targets for cancer therapeutics [2]. It was claimed that novel HDACIs were optimized as potential drug candidates, designed for regional or systemic release, and created as significant inhibitors [3]. In the present study, 3D-QSAR and molecular docking were used to provide a theoretical basis for finding highly potent anti-tumor drugs. QSAR was used to generate models and predict the HDAC1 inhibitory activity using the Sybyl program (x1.2 version). Biaryl benzamides (n=73) as selective HDAC1 inhibitors were selected as our data set, which was split randomly into training (n=63) and test sets (n=10). Docking was carried out using the MOE software. Partial least square was used as QSAR model-generation method. External validation and cross-validation (leave-one-out and leave-10-out) were used as validation methods. Both CoMFA (q^2, 0.663; r^2_{ncv}, 0.909) and CoMSIA models (q^2, 0.628; r^2_{ncv}, 0.877) for training set yielded significant statistical results. The predictive ability of the derived models was examined by a test set of 10 compounds and external validation results displayed r^2_{pred} and r^2_m values of 0.767 and 0.664 for CoMFA and 0.722 and 0.750 for CoMSIA, respectively. The obtained models showeda good predictive ability in both internal and external validation and could be used for designing new biaryl benzamides as potent HDAC1 inhibitors in cancer treatment. The amido and amine groups of benzamide part as scaffold and the bulk groups as a hydrophobic part were key factors to improve inhibitory activity of HDACIs.

Keywords: Histone Deacetylase; 2-Amino Benzamide; CoMFA; CoMSIA; Molecular Docking.

References

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