MOLECULAR DOCKING AND 3D QSAR RESEARCH OF INDOLOCARBAZOLE SERIES AS CYCLIN-DEPENDENT KINASE INHIBITORS

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Fifty indolocarbazole series as cyclin-dependent kinase inhibitors (CDKs) are used to establish a three-dimensional quantitative structure-activity relationship (3D QSAR) model based on docking conformations resulting from the Topomer comparative molecular field analysis (Topomer CoMFA). The statistic parameters show that the cross-validation (q^2), the multiple correlation coefficient of fitting (r^2), and external validation statistic (Q^2_{ext}) are 0.953, 0.968, and 0.954, respectively. It is demonstrated that this Topomer CoMFA model has good stability and prediction ability. The methodology of the fragment-based drug design (FBDD) was also used to virtually screen new CDKs by the Topomer Search technology. Four similar substitutional groups selected from the ZINC database were added to the basic scaffold. As a result, 18 new CDKs with high activities were obtained. The template molecule and new designed compounds are used to study the binding relationship between the ligands and the receptor protein with Surflex-Dock. The docking results suggest good binding interactions of the designed compounds with protein. There are several hydrogen bondings between CDKs with amino acid residues of LYS33, LYS89, ASP86, LEU83, GLU81.

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