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Computational Approach to Cyclin-Dependent Kinase 2 Inhibitors Design and Analysis: Merging Quantitative Structure-Activity Relationship, Absorption, Distribution, Metabolism, Excretion, and Toxicity, Molecular Docking, and Molecular Dynamics Simulations

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Abstract : The present study aims to investigate the quantitative structure-activity relationship (QSAR) of a series of Thiazole derivatives reported as anticancer agents (hepatocellular carcinoma), using principally the electronic descriptors calculated by the density functional theory (DFT) method and by applying the multiple linear regression method. The developed model showed good statistical parameters (R^2= 0.725, R^2_{adj}= 0.653, MSE = 0.060, R^2_{test}= 0.827, Q^2_{cv} = 0.536). The energy of the highest occupied molecular orbital (EHOMO) orbital, electronic energy (TE), shape coefficient (I), number of rotatable bonds (NROT), and index of refraction (n) were revealed to be the main descriptors influencing the anti-cancer activity. Additional Thiazole derivatives were then designed and their activities and pharmacokinetic properties were predicted using the validated QSAR model. These designed molecules underwent evaluation through molecular docking (MD) and molecular dynamic (MD) simulations, with binding affinity calculated using the MMPBSA script according to a 100 ns simulation trajectory. This process aimed to study both their affinity and stability towards Cyclin-Dependent Kinase 2 (CDK2), a target protein for cancer disease treatment. The research concluded by identifying four CDK2 inhibitors - A1, A3, A5, and A6 - displaying satisfactory pharmacokinetic properties. MDs results indicated that the designed compound A5 remained stable in the active center of the CDK2 protein, suggesting its potential as an effective inhibitor for the treatment of hepatocellular carcinoma. The findings of this study could contribute significantly to the development of effective CDK2 inhibitors.

Keywords : QSAR, ADMET, Thiazole, anticancer, molecular docking, molecular dynamic simulations, MMPBSA calculation
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