Quantum chemical study of binding affinity of the purine inhibitor and its bioisosteres to cyclin-dependent kinases

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The aim of this work is to explain the difference in binding affinity of the purine inhibitor Roscovitine and its pyrazolopyrimidine bioisosteres to cyclin-dependent kinases (CDK) 2 and 9. The increased activity of CDK significantly contributes to the loss of control over cell proliferation, which is one of the basic properties of cancer cell formation. They thus represent an interesting target of cancer chemotherapy. The accurate description of binding mechanism enables us to design specific inhibitors. The binding affinity between the inhibitor and the protein is estimated by using the scoring function, which is based on the semi-empirical quantum mechanical (SQM) PM6-D3H4 method with corrections for dispersion energy (D) and hydrogen bonding (H) [1,2,3]. The calculated scores correlate well with experimental binding data (R^2=0.92). The interaction 'free' energy between fragments of the inhibitor and the whole protein is computed in the same way, and it correlates well with experimental data too (R^2=0.81). The ligand fragmentation, NBO analysis and electrostatic potential of the studied inhibitors rationalize changes in binding affinity. Gas phase interaction energy (IE) between the fragments of the protein and the whole inhibitor is described by the PM6-D3H4, DFT-D3 and MP2 methods. IE calculated by PM6-D3H4 agree well with DFT-D3/def2-QZVP (R^2=0.99). On the other side, the sum of interaction 'free' energies between the inhibitor and the protein fragments does not correspond to the experimental data. This result shows that it is important to consider whole protein.

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