Design and Synthesis of New CDK2 Inhibitors Containing Thiazolone and Thiazolthione Scafold with Apoptotic Activity

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Abstract

Cyclin dependent kinase 2 (CDK2) inhibition is a well-established strategy for treating cancer. Different series of novel thiazolone (1, 7-9) together with fused thiazolthione (2-6, and 10) derivatives were designed, then synthesized and evaluated for their biological inhibitory activity against CDK2. Additionally, the cytotoxicity of the new compounds was explored against breast and colon cancer cell lines. The novel thiazolone and the fused thiazolthione derivatives exhibited potent CDK2/cyclin A2 inhibitory effect of an IC50 values ranging 105.39-742.78 nM. Amongst them compounds 4 and 6 revealed highest IC50 of 105.39 and 139.27 nM, respectively. Most compounds showed significant inhibition on both breast cancer and colon cancer cell lines with IC50 range 0.54-5.26 and 0.83-278 ÕM, respectively. Further investigations involved flow cytometry analysis on MCF-7 cancer cell line for compounds 5 and 7 which resulted in arrest cell-cycle at two phases Pre G1/G2-M and re-enforced apoptosis via activation of caspase-7. Molecular modeling simulation of the designed compounds revealed that they were well fitted into CDK2 active site and their complexes were stabilized through the essential hydrogen bonding. Three dimensional quantitative structure activity relationship (3D QSAR) pharmacophore, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies were also carried out showing proper pharmacokinetic and drug-likeness which aided in the prediction of the structure requirements responsible for the observed antitumor activity.

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