Design, synthesis, cytotoxicity evaluation and docking studies of 1,2,4-triazine derivatives bearing different arylidene-hydrazinyl moieties as potential mTOR inhibitors

Abstract
Mammalian target of rapamycin (mTOR) is a phosphoinositide 3-kinase-related protein kinase which controls cell growth and is frequently deregulated in many cancers. Therefore, mTOR inhibitors are used as antineoplastic agents for cancer treatment. In this study, 1,2,4-triazine derivatives containing different arylidene-hydrazinyl moieties were designed and synthesized. Cytotoxicity of the compounds was evaluated on HL-60 and MCF-7 cell lines by MTT assay. S1, S2 and S3 exhibited good cytotoxic activity on both cell lines with an IC50 range of 6.42 - 20.20 μM. In general, substitution of a five-membered heterocyclic ring containing NO2, such as 5-nitrofuran-2-yl, resulted in the best potency. Molecular docking analysis was performed to study the possible interactions and binding modes of all the triazine derivatives with mTOR receptor. The most promising compound, S1, was well accommodated within the active site and had the least estimated free energy of binding (even less than the inherent ligand of the protein, PDB ID: 4JT6). It is concluded from both MTT assay and docking studies that the arylidene moiety linked to the hydrazinyl part of the structure had a prominent role in cytotoxicity and mTOR inhibitory activity.