Novel 9- (2-arylidenehydrazinyl) acenaphtho[1,2-e][1,2,4]triazineDerivatives: Synthesis, Cytotoxic Activity and Molecular Docking Studies on B-cell lymphoma 2 (Bcl-2)

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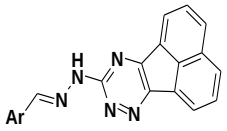
Introduction and background: Cancer is a complex pathological condition which is characterized by a high proliferative index and spread of aberrant cells from their site of origin. The B-cell lymphoma 2 (Bcl2) family of proteins play a critical role in apoptosis mediated through mitochondria, are divided into two classes: antiapoptotic members (including Bcl-2) and proapoptotic members. The antiapoptotic Bcl-2 protein is over expressed in many cancerous cell lines results in resistance to current chemoteraputics. Inhibition of Bcl-2 is a promising anticancer strategy to overcome chemoresistance of a broad spectrum of human cancers.

Methods: Acenaphtho derivatives have been reported as antitumor agents.We report herein a new and facile route for the synthesis of 9- (2-arylidenehydrazinyl) -acenaphtho[1,2-e]-1,2,4-triazines as potentially bioactive heterocyclic small-molecule inhibitors of antiapoptotic Bcl-2 proteins via efficient reactions. The antiproliferative activities of prepared compounds were assessed using a standard (MTT) -based colorimetric assay on three different human tumor cell lines (K-562, MCF-7, and MOLT-4). AutoDock4.2 software was employed for computational modeling studies acenaphtho derivatives with the Bcl-2 as the potential target.

Results: In a cellular assay, the evaluated compounds exhibited moderate to good cytotoxic activities (IC50 ~ 2.5- 24.2µM). Molecular docking studies of target compounds in Bcl-2 groove

revealed that Tyr67, Asp70, Asn102 contributed to H-bond formation. The data supported the biological data and agreed well with previous in silico data for commonly used anti-cancer drugs.



General structure of synthesized compounds

Discussion and conclusion: The outcomes of the present study may be helpful in future targeting of Bcl-2 with the aim of developing apoptosis-inducing agents.

Keywords: Synthesis, Acenaphtho-9,10-quinone, Cytotoxic activity, Docking