Synthesis and cytotoxic evaluation of novel poly aromatic acenaphtho[1,2-e]-1,2,4-triazine derivatives containing substituted thiomethylene (aryl- 1-2-3- triazole) on C3 of triazine

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Cancer is one of the most common causes of death in the world. Cancer can be treated in different ways including radiation, surgery and chemotherapy. Unfortunately, the number of effective drugs in cancer therapy is declined due to the development of resistance. Therefore, studies on developingnovel classes ofanti-cancer drugs with new performance are among the most important goalsofmedicinal Chemistry. This study is a molecular hybridization and synthesis of novel poly aromatic acenaphtho[1,2-e]-1,2,4-triazine derivativescontaining substituted thiomethylene (aryl- 1-2-3- triazole) on C3 of triazine with the purpose of DNA intercalation via polyaromatic structure of *acenaphthoquinone, as well as*Bcl-2 inhibitors which are investigated biologically.

The synthesis was performed in three steps. First step included reactionbetween thiosemicarbazide and *acenaphthoqunone*in acetic acid medium resulted in acenaphtho[1,2-e]-1,2,4-triazine-9-thiol production.(product 1) In second step, (prop-2-ynylthio)acenaphtho[1,2-e][1,2,4]triazine is formed following the reaction of product 1 and propargyl bromide in the presence of sodium hydroxide and ethanol at room temperature in. In the last step, different aromatic acenaphtho[1,2-e]-1,2,4-triazines products derivativescontaining substituted thiomethylene (aryl- 1-2-3- triazole) were obtained using click reactions in presence of corresponding azide reactant, sodiumascorbateandCuSO4 in two stages. Resulted compounds were further purified using chromatography and crystallography methods.

The structure of compounds were identified via different spectroscopic methods (FT-IR, ^{1}HNMR, MS). Cytotoxic activity of resulted products were investigated using MTT colorimetric method in MOLT-4 cancer cell lines. Molecular docking study was performed via AutoDock4.2 software in order to reconfirm the speculated mode of action and tendency of the bond between acenaphtho derivatives and active status of Bcl-2.

Finally, 8 different derivatives of were synthesized in good yields (60-70%). Evaluation of the biological activity of compounds showed moderate to high cytotoxic effect on cancer cell lines. The most effective compound of this scaffold containing para-fluoro-substituted benzyl 1,2,3-triazole with significant cytotoxic effects in MOLT-4 cells (IC_{50} = 12.8 μ M). The binding interaction study of these compounds with potential molecular

target Bcl-2 showed that this compound has a significant inhibitory effect via key interactions, especially π - π stacking with Phe105 of Bcl-2 binding site.

Key words: Acenaphthoquinone, triazole, click reactions, cytotoxic, Bcl-2 inhibitors