Abstract

Introduction and Goal: Cancer is a condition in which abnormal cells proliferate uncontrollably and can affect nearby tissues. There are more than 200 different types of cancer, each of which develops in its own way. Gastric cancer is the fifth most common cancer in the world and ranks third in terms of mortality. In Iran, the highest prevalence of gastric cancer has been reported in the north and northwest of Iran. Metastasis of cancers of epithelial tissue origin, including gastric cancer, is the most common cause of death in cancer patients. Preventing cell migration, which can prevent metastasis, can be very effective in accelerating and improving the treatment of these cancers.

Materials and Methods: In this project, a number of new derivatives of 2-aminothiazole 3,4-dihydropyrimidinone were synthesized and after purification, identification and structural confirmation using H-NMR, IR and MS methods, cytotoxic properties were studied on AGS cell line. In the next step, the inhibitory properties of cell migration of the synthesized compounds were investigated by the wound-healing method. Molecular docking simulations on Eg5 was conducted by means of AutoDock4.2 package and qualitative/quantitative analysis of ligand-protein interactions was done with PLIP computational server.

Results: Compound M2 exhibited the lowest IC_{50} value against AGS cells when compared to other compounds and caused cytotoxicity at lower doses. Evaluation of the effect of compounds M1-M3 on cell migration indicated that aforementioned derivatives and particularly M2 induced cell migration with regard to the normal untreated cells. Molecular docking simulations showed that *S*-enantiomer of DHPMs exhibited higher binding affinity toward Eg5 which is compatible to the binding pattern of monastrol. It was revealed that H-bond and hydrophobic contacts were determinant in binding to the Eg5 and Glu116 participated in hydrogen bond interaction with amide NH in *R*-1 and *S*-3. Glu166 is a key residue of Eg5 binding site in attachment to avariety of Eg5 targeting agents. Structure binding studies proved the importance of dihydropyrimidinone ring within the structure of assessed compounds mainly due to the involvment of carbonyl oxygen of *S*-3 and N3H hydrogen atom of *R*-1 in H-bond with Trp127 and Glu117 residues, respectively.

Discussion and conclusion: Analysis of ligand-protein interaction patterns revealed that thiazole ring of the M1-M3 derivatives might not participate in any interaction with the binding site residues of Eg5 and this result along with the data obtained from the effect on cell migration direct us toward a new design strategy. Extension of thiazole ring to a bulkier and more hydrophobic benzothiazole moiety with some substituents may lead to the possible effective interactions with amino acids of adjacent hydrophobic pocket. Such approach may unravel the way toward developing DHPM derivatives that are able to inhibit cell migration.

Key words: Cancer, Dihydropyrimidinone, metastasis, Wound-healing, AGS