Abstract

Introduction and Goal

Gastric cancer is one of the malignant tumors of the gastrointestinal tract that, despite its decrease in recent years, is still the fourth most common cancer and the second leading cause of cancer-related death. Today, various methods are used to control and treat cancer, the most important of which is chemotherapy. In chemotherapy, chemical molecules are used to control cancer. Recent studies have shown that dihydropyrimidinone compounds are important structures in medicinal chemistry due to their diverse pharmacological effects. The aim of this study was to synthesize new 2-amino-6-methylbenzothiazolyl derivatives of 3,4-dihydropyrimidinones and evaluate their effect on AGS cell line (gastric cancer cells) behavior by measuring cell migration.

Materials and Methods

A number of new 4-aryl-6-methyl-*N*-(6-methyl benzo[d] thiazol-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides were synthesized and structurally characterized, and then their effect on the migration behavior of human AGS cell line was investigated. Molecular docking studies on kinesin 5 enzyme (Eg5) were performed using Autodock 4.2 software and qualitative and quantitative analysis of ligand-receptor interactions was performed by PLIP computing server.

Results

Compound **F3** showed lower IC_{50} than the other compounds studied in the AGS cell line, and this result showed that **F3** caused cytotoxicity at lower dose than the other two derivatives (**F1** and **F2**). Compounds **F1**, **F2** and **F3** showed a somewhat inhibitory effect on cell migration compared to the control group and this effect was greater in the case of **F2** that possessed Br substituent in *meta* position of 4-phenyl ring; However, migration in untreated AGS cells was found to be normal in a way that cell wound was largely covered. Molecular docking simulations estimated higher binding **affinity** for **F2** with a completely hydrophobic interaction pattern in the allosteric bonding site of Eg5 ($\Delta G_{b,R\ \text{isomer}}$: -9.52 kcal/mol and $\Delta G_{b,S\ \text{isomer}}$: -8.69 kcal/mol). Participated amino acids were Asp130, Ala133, Ile136, Tyr211, Ala218 and Phe239. It should be noted that enantiomer S of assessed DHPMs showed higher binding affinity toward Eg5 which is compatible with the binding pattern of standard Eg5 inhibitor Monastrol.

Discussion and conclusion

Compound **F2** with Br substituent in *meta* position 4-phenyl ring exhibited the greatest inhibitory effect on cell migration that could probably be justified based on its bulky hydrophobic nature. Molecular docking results proposed a completely hydropobic interaction profile for **F2** within Eg5 binding site and offered this compound as a suitable candidate for further development toward inhibitors of cell migration in the AGS cell lines.

Key words

Gastric cancer, Cell migration, 3,4-Dihydropyrimidinone, Molecular docking