Abstract

Introduction

Cancer is a complex disease in which a series of genomic and molecular changes is cause the uncontrolled growth and proliferation of cells. In recently decades, among the types of cancer, gastric cancer is one of the main reasons of death. Therefore, discovering new anti-cancer compounds is the biggest goal of researchers. According to the good results of previous studies on tetrahydropyrimidine derivatives against different cancer cell lines and especially AGS, in this project a series of novel these derivatives were designed and synthesized and then their biological effects were evaluated.

Material and method

In this project, a number of tetrahydropyrimidine derivatives were synthesized using the Biginelli method. After that, their chemical structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR and MS spectroscopy methods. Then, the cytotoxicity activity of the compounds was evaluated on the gastric cancer cell line (AGS). Finally, the effect of the synthesized compounds was analyzed on apoptosis and cell cycle profiling.

Results

According to the results, the compounds 5-bromo-6-(3,4-dimethoxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid (**M3**) and 5-bromo-6-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2,3,6- tetrahydropyrimidine-4-carboxylic acid (**M4**) showed the highest cytotoxicity activity compared to other compounds in AGS cell line (**M3**: IC_{50}= 69.60±5.08 µM), (**M4**: IC_{50} = 73.80±5.20 µM). These compounds had the bromine atom at the C5 position of tetrahydropyrimidine ring. Also, the results showed that **M3** was the best compound in inducing apoptosis and **M4** was the best compound in CDKN2A gene expression.

Discussion and conclusion

Structure-activity relationship of compounds showed that the presence of bromine substitution at C5 position of the tetrahydropyrimidine ring increased the effect due to its electron-withdrawing property and high lipophilicity. According to the substitutions on the phenyl ring, presence of electron-withdrawing and lipophilic groups in the *para* position of the phenyl ring increased the cytotoxicity effect of the compound, but presence of two substitutions in the *para* and *meta* positions of the phenyl ring decreased cytotoxicity effect probably due to conformation change and the formation of intramolecular hydrogen bond.

Key words: cancer, tetrahydropyrimidine, cytotoxicity, apoptosis, cell cycle