Abstract

Introduction and Goal:

Stomach cancer is one of the most common cancers and kills many people every year. Cell migration plays an important role in the spread of cancer cells, tissue invasion and metastasis, which is the main cause of death in cancer patients. For this reason, the development of compounds that can inhibit cell migration can help reduce cancer mortality. In this project, a number of new aryl/alkyl-carbonyl *N*-hetero aryl/alkyl thiourea derivatives with various substitutions on aromatic rings were synthesized. After purification and structural analysis of the compounds by various spectroscopic techniques, the intended derivatives were subjected to the cytotoxicity assessment and subsequently their effects were evaluated on the migration behavior of AGS human cancer cells (gastric cancer cells).

Materials and Methods:

In this project, new compounds with the structural base of aryl/alkyl-carbonyl *N*-hetero aryl/alkyl thiourea were synthesized using one-pot two-step method and TLC test was used to ensure the purity of the synthesized materials. If the sediments were impure, recrystallization was done. The identification and validation of the structures were done by melting point measurement, ^{1}H-NMR, ^{13}C-NMR, FT-IR and Mass methods. To find out the cytotoxic properties of the synthesized compounds on AGS cell line, toxicity assay was performed by MTT method. In the next step, the inhibiting effect of the synthesized compounds were assessed with the wound-healing method.

Results:

Compounds **3** and **5** had higher toxicities than cis-platin. Substitution of a halogen group at the *para* position in compound **3** and especially compound **4** with a methoxy group to give compound **5** significantly improved the cytotoxicity of compound **5**. It is also important to note that the replacement of 4-methoxyphenyl in compound **5** by a cyclopropyl ring of compound **10** reduced the cytotoxicity of AGS (> 85%). Compound **6**, which has furan, was less toxic than compounds **7** and **8** (with thiophene group). The toxicity of compounds **3**-**5** was higher than other compounds. In vitro wound healing assay showed more inhibitory effects on AGS cell migration at IC_{50} doses of compounds **3**-**6** compared to untreated cells (control group) after 24 hours. It was also revealed that cell migration effect could not be prohibited in the presence of compounds **1**, **2** and **9**.

Discussion and conclusion:

No significant correlation was established between the cytotoxic and lipophilic activities of the evaluated compounds. Although a comprehensive structure-activity relationship (SAR) could not be provided due to the low structural diversity of the compounds, some useful structural hints may be derived based on similar derivatives. In compound **4**, compared to

compound **3**, the steric hindrance of the chlorine group with the target binding site has probably reduced its toxicity. Considering compounds **3**, **4** and **5** and comparing them with other compounds indicated that the presence of methoxy substituent on the *para* position on the phenyl ring of the benzoyl part increased the cytotoxic effect. And finally, by comparing compounds **6**, **7**, and **8**, it was found that the presence of *N*-furan-2-yl group in compound **6** (IC_{50}: 35.198±0.904 µg/ml) reduces toxicity compared to other compounds: **7** (IC_{50}: 20.65±1.882 µg/ml) and **8** (IC_{50}: 21.86±0.147 µg/ml). In the meantime, the remarkable point was the sensitivity of the cell migration inhibitory effect to the position of substitutions of the phenyl ring, which could be used as an important structural and traceable determining factor in the design of more desirable molecules. The obtained results showed that compounds **3-6** could be further evaluated and developed as potential anti-metastatic agents in the case of invasive AGS cancer cells.

Keywords:
Cancer, AGS, Metastasis, Cell migration, Aryl/alkyl thiourea, Wound-healing