ABSTRACT

Heterocycles are important class of compounds, building up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, many natural products, most vitamins, biomolecules and biologically active compounds, including antimicrobial, antitumor, anti-inflammatory, antiviral, anti-HIV, antidiabetic, antimalarial, herbicidal, fungicidal and insecticidal agents. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs.

Benzothiazole and its derivatives are the most important among the heterocyclic compounds, which are common and essential features of a variety of natural products and pharmaceutical agents. Benzothiazole displays a variety of pharmacological properties, and its various derivatives offer a high degree of structural diversity that has demonstrated useful of the search of new therapeutic agents. The associated research and developments in benzothiazole based medicinal chemistry have become a rapidly developing and progressively more active topic. Particularly, several benzothiazole based compounds as clinical drugs have been widely used in practice to treat various types of diseases with high therapeutic potency. It must be emphasized that combination of benzothiazole with other substituent at 2,6-position is a well-known approach to design new drug-like molecules, which allows achieving new pharmacological profile, action, toxicity lowering.

The work presented in this thesis consists of synthesis, characterization and various biological screening of 2,6-substituted benzo
thiazole derivatives. There were three series of 2,6-substituted benzo thiazole derivatives namely BZ-AX (BZ-A1 to BZ-A14), BZ-BX (BZ-B1 to BZ-B13), and BZ-CX (BZ-C1 to BZ-C10) synthesized using standard procedures found in the literature. All the synthesized compounds were characterized by FT-IR, $^1$H-NMR, $^{13}$C-NMR and mass spectroscopy. In the $^1$H-NMR spectra of the synthesized compounds, all the protons have been identified by multiplicity patterns and the total number of protons which are agreement with the expected molecular structure. In $^{13}$C-NMR spectra, the number of signals found corresponds with the presence of magnetically non-equivalent carbon atoms, which was assigned by comparison with the experimental chemical shift with those calculated from the incremental method. The FT-IR and mass spectral data are in agreement with expected and proposed molecular structure of all the synthesized compounds. All the compounds from three series were screened for their in vitro anticancer, antidiabetic and anti-inflammatory activities. The selected compounds from BZ-BX series were subjected to antiplasmodial activity (antimalarial).

In vitro cytotoxicity of all the synthesized benzothiazole derivatives were evaluated by standard 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay on MCF-7 (breast cancer), HeLa (cervical cancer), and MG63 (bone cancer) cell lines. From the results, it is observed that the compound 1-[(2,5-dichloro-3-thienyl)sulfonyl]-N-(6-nitro-1,3-benzo thiazol-2-yl)piperidine-4-carboxamide (BZ-B7) displayed the most potent inhibitory activity with IC$_{50}$ values ranging from 15-30 µM. The compounds N-(6-[(4-cyclohexylphenyl)sulfonyl]amino}-1,3-benzothiazol-2-yl) acetamide (BZ-A9), 1-[(2E)-3-(2-furyl)prop-2-enoyl]-N-(6-nitro-1,3-benzo thiazol-2-yl)piperidine-4-carboxamide (BZ-B6) and 1-(4-fluorophenyl thio carbamoyl)-N-(6-nitrobenzo[d]thiazol-2-yl)piperidine-4-carboxamide (BZ-B13) exhibited good cytotoxicity on three tested cell lines. The IC$_{50}$
values of these three compounds were observed between 20 and 50 µM for all the tested cell lines.

The antidiabetic activities of all the benzothiazole derivatives were examined by standard $\alpha$-amylase inhibition assay. Among the all compounds synthesized from three series, the compounds N-(2-acetamidobenz[d]thiazol-6-yl)-1-(2-(3-fluorophenyl)acetyl)piperidine-4-carboxamide (BZ-C2) and N-(2-acetamido-1,3-benzothiazol-6-yl)-1-[(2,5-dichloro-3-thienyl)sulfonyl]piperidine-4-carboxamide (BZ-C10) showed excellent $\alpha$-amylase enzyme inhibition when compared with standard drug acarbose (IC$_{50}$ = 48.9 µg/ml). The compounds BZ-C2 and BZ-C10 showed IC$_{50}$ values 53.4 µg/ml and 54.8 µg/ml, respectively.

As a part of the investigation on the anti-inflammatory activity, the ability of all series benzothiazole derivatives inhibit protein denaturation was studied. The compounds 1-(p-tolylthiocarbamoyl)-N-(6-nitrobenzo[d]thiazol-2-yl) piperidine-4-carboxamide (BZ-B12), N$_{4}$-(6-nitrobenzo[d]thiazol-2-yl)-N$_{1}$-p-tolylpiperidine-1,4-dicarboxamide (BZ-B8) and N-(2-acetamido-1,3-benzothiazol-6-yl)-1-(4-pyridoyl) piperidine-4-carboxamide (BZ-C6) showed potent anti-inflammatory activity. Compounds BZ-B12, BZ-B8 and BZ-C6 showed IC$_{50}$ values 60.2 µM, 65.4 µM and 63.7 µM, respectively.

Selected five compounds from BZ-BX (BZ-B1 to BZ-B13) series were subjected to anti-plasmodial studies against \textit{Plasmodium falciparum}. The compound 1-(2-furoyl)-N-(6-nitro-1,3-benzothiazol-2-yl) piperidine-4-carboxamide (BZ-B5) showed equal activity to positive control chloroquine (IC$_{50}$ = 12.6 µM) at 48 h. The calculated IC$_{50}$ value of BZ-B5 against \textit{p.falciparum} strains at 48 h of parasitemia suppression is 12.3 µM. The compound 1-[(2,5-dichloro-3-thienyl)sulfonyl]-N-(6-nitro-1,3-benzothiazol-2-yl)piperidine-4-carboxamide (BZ-B7) also showed good antiplasmodial activity where the IC$_{50}$ value is 19.4 µM.