ABSTRACT

This Ph.D. thesis provides a detailed investigation into the synthesis of novel Thiophene, Indole, Thiazole, and Thiazolo[3,2-a]pyrimidine derivatives. It further explores their potential anti-cancer, antimicrobial, anti-malarial, and anti-diabetic properties.

Chapter 1 details the synthesis of a novel series of Ethyl (*Z*)-5-(arylcarbamoyl)-2-((2-cyano-3-((4-fluorophenyl)amino)-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate derivatives, initiated through Gewald's reaction which involves one-pot reaction of a ketone with an activated nitrile and elemental sulfur in the presence of morpholine as base according to method describe in literature. Next compound 4 was reacted with 2-cyano-3,3-bis(methylthio)-N-arylacrylamide 5 and potassium carbonate in DMF to produce thiophene derivatives that are novel and highly functionalized. The National Cancer Institute (NCI) chose synthesized molecules for in vitro anticancer testing. The primary in vitro anticancer study consisted of giving a single dosage to all NCI 60 cell lines that correspond to nine subpanels of tumors: breast, CNS, ovarian, prostate, renal, colon, lung, melanoma, and leukemia. After displaying strong anti-cancer activity in initial screening against all the cell lines, 12 substance was chosen for five- dose assay.

Chapter 2 of this thesis present the synthesis and characterization of novel indole derivatives. A novel series of (*Z*)-*N*-aryl-3-(3-((3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)methyl)-1*H*-indol-1-yl)propanamide has been synthesized starting from Vilsmeier-Haack reaction. The Vilsmeier-Haack reaction was used to initiate the process by formylation of indole. Following this, several N-phenyl propanamide derivatives were reacted with the formylated indole to form molecules 4a-j, which were formed with good yields. The final step involves the interaction of the formylated indole derivatives 4a-j having the methylene group that is active in the pyrazole 5, aided by a small quantity of piperidine in methanol, providing the desired product 6a-j as indicated in Scheme 1. A variety of human cancer cell lines were used in the screening process for new synthetic indole derivatives to determine their anticancer potential., comprising ovarian cancer, CNS cancer, non-small cell lung cancer, colon cancer, renal cancer, melanoma, These cell lines underwent further, Breast Cancer and Prostate Cancer. These cell lines underwent further split to increase screening efficiency. The NCI used a total of 60 distinct sub-cell lines to assess a single drug for enhanced antitumor potential. We

submitted 10 compounds, all the synthesized compound (6a, 6b, 6c, 6d, 6e, 6f, 6g, 6h, 6i and 6j) were chosen for their single-dose response study in the screening for anticancer properties. Chapter 3 describe a novel series of ethyl (Z)-2-cyano-3-{[4-methyl-5-(2-((Z)-1-arylethylidene)hydrazine-1-carbonyl)thiazol-2-yl]amino}-3-(methylthio)acrylate. The process generates novel thiazole derivatives in good yield, using low-cost, readily available chemicals with simple reaction conditions. The novel synthesized molecules were confirmed by using 1H NMR, Mass and IR spectroscopic analysis. Desired synthetic compounds were subjected to antimicrobial screening against a range of bacterial and fungus species. It was discovered that among all tested molecules, methoxy derivative and nitro derivatives exhibited a good activity against *E. coli*, *P. Aeruginosa* and chloro, hydroxy, and nitro derivatives exhibited an outstanding action taken against *A. niger*, *A. clavatus*. Molecular docking studies of synthesized molecules was performed on E. coli dihydropteroate synthase using the Auto Dock technique. An analysis of their physicochemical and pharmacokinetic properties related to ADMET has been also carried out.

Chapter 4 of this thesis present a novel series of (*Z*)-*N*'-(1-(aryl)ethylidene)-6-cyano-5-imino-3-methyl-7-(methylthio)-5*H*-thiazolo[3,2-*a*]pyrimidine-2-carbohydrazide. The procedure generates new thiazolo[3,2-a]pyrimidine derivative using affordable reagent, good yield, low cost and having mild reaction condition. The novel synthesized molecules were characterized through ^{1}H NMR, ^{13}C NMR, FTIR and Mass spectroscopic analysis. The antimalarial effectiveness of all synthesized molecules against the parasite Plasmodium falciparum was examined. It was discovered that, of all tested molecule, 4-Cl substitution and 2,4-Cl substitution in aromatic ring exhibited an excellent activity. Molecular docking analysis of the significantly active molecules was performed on the PfDHFR enzyme. Molecule with 4-Cl substitution demonstrates a binding energy of –9.0 kcal/mol, while that with 2,4-Cl substitution exhibits a binding energy of –9.3 kcal/mol. An analysis of their physicochemical and pharmacokinetics properties related to ADMET study has also been completed for every molecule that has been created.

Chapter 5 specially focuses on the series of novel (*Z*)-2-((2-cyano-3-(arylamino)-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-*N*-aryl-4-methylthiazole-5-carboxamide derivative. Thiazoles derivative that contain amide, thiomethyl, ethyl ester, and ketene N, S-acetal linkages. Initially, easily accessible substances such as NBS, thiourea and acetoacetanilide were used to synthesize 3a-o. Subsequently, compounds 3a–o were reacted with 4a-o in DMF with potassium carbonate as catalyst. This produced new and highly functionalized derivatives of thiazole 5a–o, which are shown in Scheme 5. The Thiazole molecules 5a-o were synthesized

and analyzed for their in vitro activity against the human pancreatic α-amylase enzyme, with acarbose used as a reference compound following Mor's technique. The findings of the α-amylase inhibitory investigation are shown in Table 3, which shows that the investigated compounds 5a–o showed moderate to high levels of inhibition.