ABSTRACT

This Ph.D. thesis provides a detailed investigation into the synthesis of novel fused heterocyclic compounds like indole, benzoxazole, imidazole with naphthalene and indoline have been synthesized by using various methods. It further explores their potential anti-cancer and/or antimicrobial properties.

Chapter 1: Some hybrid piperidine-containing indole derivatives were synthesized. Using spectroscopic analytical methods such as ^{1}H NMR, ^{13}C NMR, IR, and LC-MS analysis, the newly produced compounds were verified. Additionally, using a panel of NCI-60 human tumor cell lines (National Cancer Institute, USA), which include leukemia, non-small cell lung cancer, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast cancer cell lines, all 27 compounds (**9a-n**, **11a-g**, and **13a-f**) were evaluated for their *in vitro* anticancer activity. Compounds **9c**, **11d**, **13b**, and **13e** showed growth of -22.98%, -49.98%, -83.76%, and -82.75%, respectively against UO-31 (renal cancer). Compound **11f** exhibits sensitivity in leukemia (RPMI-8226) and breast cancer (MDA-MB-468), with growth percentages of -7.80% and -18.24%, respectively. These indole-piperidine hybrids also bind to the receptor well and form stable protein-ligand complexes with low docking scores, according to *in silico* investigations of these drugs against the Vascular Endothelial Growth Factor (VEGFR-2) protein. Additionally, the indole hybrids *in silico* drug-likeness and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) characteristics were assessed; they demonstrated encouraging pharmacokinetic profiles free of related toxicity problem.

Chapter 2: A multi-step method that incorporates the Mitsunobu reaction has been used to synthesize several benzoxazole-piperazine hybrids (**9a-n**). With inexpensive, easily accessible starting materials and gentle reaction conditions, several compounds were produced in excellent yields. The following techniques were used for structural characterization: FTIR spectroscopy, elemental analysis, LC-MS, ^{1}H NMR, and ^{13}C NMR. The bacterial strains *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli*, as well as the fungal species *A. niger* and *C. albicans*, were used to evaluate the antibacterial properties of **9a-n**. Notably, compounds **9b**, **9c**, and **9f** had strong antifungal activity equivalent to nystatin and antibacterial activity comparable to gentamicin and chloramphenicol. **9f** inhibits *E. coli* DNA gyrase, according to molecular docking and dynamics simulations, resulting in a stable protein-ligand complex with low docking scores and strong binding contacts. Their promise as promising antibacterial drugs was further highlighted

by *in silico* ADMET analysis, which showed acceptable pharmacokinetic features with no notable toxicity issues.

Chapter 3: A series of novel imidazole-naphthalene hybrids **9a-p** has been synthesized by a multistep synthetic approach including bromination, mitsunobu reaction, and suzuki coupling. The target compounds were produced in high yield using cost-effective, readily available starting materials under simple reaction conditions. The newly synthesized compounds were characterized using elemental analysis, FTIR, ^{1}H NMR, ^{13}C NMR, and LC-MS spectrum analysis. The bacterial strains *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli*, as well as the fungal species *A. niger* and *C. albicans*, Notably, compounds **9k**, and **9p** had strong antifungal activity equivalent to nystatin and antibacterial activity comparable to gentamicin and chloramphenicol. Additionally, *in silico* analyses of **9k** and **9p** with *E. coli* DNA gyrase by molecular docking and molecular dynamics simulations revealed enhanced binding properties of these derivatives to the protein site.

Chapter 4: A series of indoline hybrids with amide and sulphonamide connections, including furan (**6a-k**) and pyrrole (**13a-k**), were synthesized by a multistep procedure with favorable yields. The resulting compounds underwent purification using reverse-phase flash chromatography and were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, LC-MS, and elemental analysis. The compounds were assessed for their *in vitro* antibacterial efficacy against many bacterial strains, including *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli*. Among the studied compounds, **6k** and **13e** showed the greatest activity, exhibiting superior potency compared to typical antibiotic agents. The antifungal efficacy of these newly synthesized compounds was evaluated *in vitro* against *A. niger* and *C. albicans*, revealing that compounds **6k** and **13e** had the greatest activity relative to the traditional antifungal agent nystatin. Moreover, *in silico* analyses of compounds **6a-k** and **13a-k** with *E. coli* DNA gyrase, employing molecular docking and molecular dynamics simulations, demonstrated remarkable binding affinity of these derivatives to the protein's active region. Furthermore, *in silico* ADMET study demonstrated advantageous pharmacokinetic characteristics with no significant toxicity issues, underscoring their potential as efficacious antibacterial medicines.