ABSTRACT

This Ph.D. thesis provides a detailed investigation into the synthesis of novel hybrid heterocyclic compounds like quinoline, oxadiazole, isoxazole and pyrimidine have been synthesized by using various methods. It further explores their potential anti-cancer and antimicrobial properties.

Chapter 1: A series of hybrid quinoline derivatives featuring substituted oxadiazole-5(4*H*)-one were synthesized. The newly synthesized compounds were confirmed using ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopic analysis techniques. Further, compound **6a-p** were subjected to *in vitro* anticancer cell-line investigation. Under conventional conditions for experiments, one dosage response parameter (GI_{50}) was determined for each of the **60** human tumour cell lines (NCI-60) at Developmental Therapeutics Program that falls under DCTD (Division of Cancer Treatment & Diagnosis) of National Cancer Institute, National Institute of Health (NIH), Germantown, USA. In that, some compounds **6d**, **6g**, **6j**, **6o** were showing good anti-cancer activity against many cell lines like Melanoma Cell Line: MDA-MB 435 & SK-MEL 5, Breast Cancer Cell Line: MDA-MB-468, Breast Cancer Cell Line: T- 47D, CNS (Central Nervous System) Cancer Cell Line: SNB-75.

Chapter 2: A variety of hybrid quinoline compounds containing substituted oxadiazole-5(4*H*)-thione were produced. The newly synthesized compounds were validated by 1H NMR, 13C NMR and mass spectrometric analytical techniques. The National Cancer Institute (NCI) selected synthesized compounds **6a-o** for *in vitro* anticancer evaluation. The principal in vitro anticancer investigation involved administering a single dosage to all NCI-60 cell lines representing nine tumor subpanels: breast, CNS, ovarian, prostate, renal, colon, lung, melanoma, and leukemia. In that, some compounds **6a** and **6c** were showing good anti-cancer activity.

Chapter 3: A series of novel quinoline-DHPM hybrids **6a–j** has been created by a multistep synthesis method. All synthesized compounds were confirmed using ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopic analysis techniques. Additionally, compounds **6a–j** underwent in vitro antimicrobial evaluation against multiple bacterial and fungal species, including *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella typhi, Aspergillus niger,* and

Candida albicans. Among these, compounds **6e**, **6f**, and **6l** were found most active having equally potent compared to standard drug Ampicillin and Gentamycin Molecular docking experiments of generated compounds were conducted on *E. coli* DNS gyrase utilizing the Auto Dock technology.

Chapter 4: A series of novel quinoline-isoxazole hybrids **6a–o** has been synthesized via multistep synthetic approach involving hetero Diels-alder reaction strategy. The target compounds were obtained in good yield, using low-cost readily available starting materials using simple reaction conditions. The newly synthesized compounds were confirmed using ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopic analysis techniques. Further, compounds **6a–o** were subjected to *in vitro* antimicrobial screening against various bacterial and fungal strains, such as *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella typhi, Aspergillus niger*, and *Candida albicans*. Among these, compounds **6i**, **6j**, and **6l** were found most active having equally potent compared to standard drug Ampicillin and Gentamycin. Moreover, in silico studies of **6a–o** with *E. coli* DNA gyrase through molecular docking and MD simulations showed excellent binding properties of these derivatives with protein site.

Chapter 5: Contemporary drug development efforts focus on small compounds containing hybrid nitrogen-rich heterocycles that influence biological processes. The **12** diverse molecules having quinoline-isoxazole in the core unit (**7a-l**) synthetic approach involve Wittig reaction strategy. The Wittig reaction was performed by clubbing ((3-(2-chloroquinolin-3-yl)isoxazol-5-yl)methyl)triphenylphosphonium with various substituted aldehydes. The adducts were screened for their cytotoxic study against a panel of sixty human cancer cell lines in a single concentration (10^{-4} M) and five dose concentration-response (0.01, 0.1,1, 10 and 100 μM) through the calculation of log GI_{50}, log TGI and log LC_{50} and among them, three were selected for five dose assays. The growth inhibition values (mean) were found for lead compounds **5**, **7f** and **7h** with high lethality ratio. Molecular docking study was performed against the Colchicin receptor to gain insight into the plausible mechanism of action for these compounds. The results of *in silico* studies could identify the key thermodynamic interactions that governed the binding affinity of these compounds towards Colchicin receptors. The five-dose assay of these adducts also showed promising results by comparing its MG_MID and Δ (near **1.02** for **7f**) values.