Notification No: **COE/ Ph. D./(Notification)/590/2025**
Date of Award: **05-12-2025**

Name of the scholar: **Abdur Rahman**

Name of the Supervisor: **Prof. Nasimul Hoda**

Department: **Department of Chemistry**

Topic of Research: **Study towards the development of new heterocyclic and carbocyclic based therapeutic agents**

FINDINGS

The present Ph.D. thesis work is focused on developing new disease-modifying agents based on heterocyclic and carbocyclic bioactive scaffolds such as pyrimidine, spirocyclic chromane, quinazoline, deoxyvasicinone, and colchicine. This thesis comprises the following six chapters.

Chapter 1 provides a detailed description of malaria disease including its current state, the life cycle of the malaria parasite, its symptoms, causes, diagnosis, treatments, and the different drug targets of the disease, as well as the FDA-approved antimalarial medications that are currently on the market. We also tried to explore various disease-modifying agents for malaria especially based on pyrimidine, sulfonamide, quinazoline, and spirocyclic scaffolds. Additionally, a current literature review about developing several antimalarials was provided.

Chapter 2 includes the design and synthesis of a novel series of pyrimidine-tethered spirochromane-based sulfonamide derivatives (SZ1-SZ14) aimed at combating drug resistance in malaria. The antimalarial effectiveness of these compounds was assessed in vitro. Notably, compounds SZ14 and SZ9 demonstrated particularly potent effects, with compound SZ14 showing IC_{50} values of 2.84 μM and SZ9 3.22 μM, indicating single-digit micromolar activity. Further, the enzymatic assays indicated that SZ14 and SZ9 inhibited *Pf*FP-2 (IC_{50} values: 4.1 and 5.4 μM, respectively), and *Pf*FP-3 (IC_{50} values: 4.9 and 6.3 μM, respectively). The *in vitro* cytotoxicity against Vero cell lines revealed strong selectivity indices and no significant cytotoxic effects. Additionally, *in vitro* hemolysis testing showed these compounds to be non-toxic to normal human blood cells. Moreover, predicted in silico ADME parameters and physiochemical characteristics demonstrated the drug-likeness of the synthetic compounds. These collective findings suggest that sulfonamide derivatives based on pyrimidine-tethered

oxospirochromane could serve as templates for the future development of potential antimalarial drugs.

Chapter 3 details synthesizing thiourea-based compounds (QS1-QS16) by blending quinazoline and oxospirochromane. These compounds underwent testing to assess their *in-vitro* efficacy against both drug-sensitive and drug-resistant strains of the *Plasmodium* parasite as antimalarial agents. Among all the synthesized compounds, QS5 showed good inhibitory efficacy against *Pf*3D7 and *Pf*W2 with IC_{50} 3.18 and 3.98 μM respectively, and QS13 with IC_{50} 3.56 and 4.43 μM respectively. The promising compounds were screened against the *Plasmodium* parasite's falcipain-2 and falcipain-3 enzymes. The ligands QS5 and QS13 displayed inhibition against *Pf*FP-2 (IC_{50} 3.9 and 4.9 μM) and *Pf*FP-3 (IC_{50} 4.6 and 5.9 μM) respectively.

Chapter 4 introduces another new series of quinazoline-based Micheal acceptors (QM1-QM15) containing electrophilic warheads as antimalarial agents. The compounds QM10 and QM13 showed the highest inhibitory activity among others with IC_{50} values of 6.22 μM and 6.47 μM against *Pf*3D7, respectively.

Chapter 5 includes a new set of eighteen triazole-based hybrids (Tz1–Tz18), which were designed, synthesized, and characterized using ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS). The compound Tz5 and Tz18 exhibited good percent inhibition with 54% against esBChE and hAChE respectively.

Chapter 6 provides the design and synthesis of a novel set of thiourea-based colchicine derivatives (CTU1-CTU12) and evaluated for proteasome inhibition against the chymotrypsin-like activity of the β5 subunit in proteasome-enriched Jurkat Cell Lysates. The thiourea-based derivative CTU5 bearing methoxy group at para position exhibits the highest activity with 65.29% inhibition at 50 μM when compared to the well-known covalent inhibitors MG132. The molecular docking investigation was carried out to find out the possible binding interactions. Moreover, the *in silico* ADME parameters predicted CTU5 could possess drug-like properties and may be developed in orally active pharmaceuticals. Therefore, these collective findings suggested that CTU5 could act as new scaffolds as a starting substrate for the development of new potent proteasome inhibitors in the future.

Therefore, the current thesis effectively described the synthesis of five different sets of potentially therapeutic compounds that may be used as a template for developing new types of antimalarial, anti-neurodegenerative drugs, and proteasome inhibitors in cancer therapy.