Notification No.: **COE/ Ph.D./(Notification)/546/2023**
Date of Award: **06-10-2023**

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Topic of Research: **Integration of Computational Biology Tools with Experiments for the Development of Therapeutic and Non-Toxic Small Molecules**

FINDINGS

The present Ph.D. thesis work is focused on the structure-based design of new therapeutic and non-toxic small molecules using computational biology (*in-silico*) tools followed by chemical synthesis and biological investigations. For drug design, *in-silico* tools such as Schrödinger, AutoDock Vina, Discovery Studio, PyMol, ParDock, and GROMACS were used. The designed compounds were synthesized using multi-step organic synthetic protocols. The diverse array of organic synthetic reactions such as multicomponent Petasis boron–Mannich reaction, nucleophilic substitution reaction, nucleophilic-aromatic (SNAr) substitution reaction, Vilsmeier–Haack reaction, etc. were utilized to achieve target compounds. The thesis successfully delivered more than 100 new structurally diverse small molecules based on quinoline, pyrazine, pyrimidine, quinazoline, and sulphonamide. The developed molecules demonstrated their potential therapeutic ability in antimalarials, anti-neurodegenerative agents, and antifungals. The present research work, published in peer-reviewed journals of scientific repute such as *Eur. J. Med. Chem*, *J. Biomol. Struct. Dyn*., *RSC Med. Chem*. this year. The thesis comprises seven chapters including the first chapter as an introduction and the rest are experimental works.

Chapter 1 provides an overview of drug design and computational biology advancements, focusing on quinoline, pyrazine, and quinazoline-based molecules. **Chapter 2** presents seventeen novel oxospiro chromane quinoline-carboxylates as inhibitors for *Plasmodium* N-myristoyltransferase. These compounds displayed potent activity against drug-susceptible and drug-resistant strains of *Plasmodium falciparum*, with IC_{50} values of 3.96 μM and 2.8 μM, respectively. The potent compounds able to stop the growth of the parasite at the ring stage. **Chapter 3** introduces diphenylmethylpiperazine hybrids of chloroquinoline and triazolopyrimidine as *Plasmodium falciparum* Falcipain inhibitors. These compounds exhibited an IC_{50} of 0.74 μM against both drug-sensitive and drug-resistant strains of *Plasmodium falciparum*.

Chapter 4a details the development of pyrazine-based multi-target directed anti-Alzheimer's agents using the Petasis reaction. These compounds showed strong inhibition of AChE and *tau*-oligomerization with an IC_{50} of 0.71 μM and EC50 of 2.21 μM, surpassing known drugs. **Chapter 4b** focuses on repurposing diphenylmethylpiperazine analogues of pyrazine as *Plasmodium falciparum* Falcipain inhibitors for antimalarial use. The compounds exhibited good binding affinities and IC_{50} values against different strains of *Plasmodium falciparum* parasites. **Chapter 5** utilizes a molecular hybridization approach to develop potent antimalarial compounds. Hybrid N-(2-chloro-4-((4-(4-(((tetrahydrofuran-2-yl)methyl)amino)quinazolin-2-yl)piperazin-1-yl)sulfonyl)phenyl) acetamide displayed an IC_{50} value of 3.43 μM against drug-susceptible strain of *Plasmodium falciparum*. **Chapter 6** explores the repurposing of pyrimidin-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamides as antifungals targeting *Candida albicans*. Two lead compounds with promising MIC values are identified, showing strong binding to lanosterol 14α-demethylase.

Overall, these chapters highlight the development of various novel molecules with significant potential for the treatment of malaria, Alzheimer's disease, and fungal infections.

Keywords: Medicinal chemistry, Antimalarials, Anti-neurodegenerative agents, Drug repurposing, Computational biology, Antifungals.