ABSTRACT

The thesis entitled "**Synthetic Studies on Pharmaceutically Privileged Bioactive Heterocycles: Synthesis, Chemistry and Biological Evaluation"**, focused mainly towards the development of novel pharmaceutically privileged bioactive heterocycles having promising biological activities against various infectious diseases.

The present doctoral thesis has the following specific objectives:

- Development of novel functionalized halogenated 1,2,4-trioxanes as a potent antimalarial as well as anticancer agents.
- Development of novel functionalized arylated 1,2,4-trioxanes as an antimalarial and anticancer agent.
- Development of a new amino based organocatalyst, which will be utilized in the intermolecular cross-coupling reactions of two unactivated arenes.
- Development of a new transition metal-free methodology, which will be utilized in the direct coupling of aldehydes with terminal alkynes.
- Utilization of different spectroscopy technique such as ESI-MS, ^{1}H NMR, ^{13}C NMR, IR and HRMS for the structural confirmation of all the novel synthesized compounds.
- Assessment of all the novel synthesized 1,2,4-trioxane analogues against different drug-resistant strains to determine their antiplasmodial and cytotoxic potential.
- Assessment of all the novel synthesized 1,2,4-trioxane analogues under *in silico* molecular docking studies to determine their probable protein target.

The present doctoral thesis will be comprised of the five chapters. The highlights and the important results of all the five chapters are summarized below:

Chapter 1: In this chapter, we have collected and represented a direct statistics on some of the most significant chronological advancements observed in recent years in the synthetic approaches for the synthesis of selected pharmaceutically privileged bioactive heterocycles and their analogues such as artemisinin, 1,2,4-trioxolanes (ozonides), 1,2,4-trioxanes, biaryl based molecules, *α,β*-unsaturated ketones/chalcones and propargyl alcohols.

Chapter 2: In this chapter, we have developed a series of mono, di and tri halo substituted synthetic endoperoxides (**8a**-**g**) in 40-72% yield range. Out of all the twenty-eight synthesized halogenated 1,2,4-trioxanes, ten analogues were found *in vitro* potent antiplasmodial agents with IC_{50} less than 27 nM range (IC_{50} = 4.47-26.58

nM) against the chloroquine-resistant *Pf INDO* strain. The most potent analogue from the series, **8a$_4$** was also found promising in animal study model as compared to reference drug chloroquine and produce *in vivo* 100% suppression of parasitaemia against *P. berghei* ANKA infected Balb C mice *via* intraperitoneal route at 50 mg/kg × 4 days dose after 30 days of post-infection. Further, **8e$_1$** (IC_{50} = 0.81 μM; SI = 20.66) and **8f$_2$** (IC_{50} = 0.69 μM; SI = 16.66) the the two most active compounds of the series were also found to be ~ 123-folds and ~145-folds more potent with higher selectivity in comparison to reference drugs chloroquine (IC_{50} = 100 μM; SI = 0.03) and artemisinin (IC_{50} = 100 μM), respectively against the (A549) lung cancer cell line.

Chapter 3: The present chapter deals with the synthesis of a novel series of synthetic aryl-vinyl-1,2,4-trioxanes (**8a-p**), which were prepared in 29-78% yields range. Compound **8g** (IC_{50} = 0.051 ± 0.035 μM, SI = > 588) and **8m** (IC_{50} = 0.059 ± 0.023 μM, SI = > 56) were found to be the most potent antiplasmodial analogues from the series showed *in vitro* ~**11-fold** and >**9-fold** more antimalarial activity in comparison to chloroquine (IC_{50} = 0.546 μM, SI = 36.6), respectively against chloroquine-resistant *Pf INDO* strain of *Plasmodium falciparum*. *In-vitro* anticancer studies against lung (**A549**) and liver (**HepG2**) cancer cell lines revealed that five derivatives (**8a**, **8h**, **8l**, **8m** and **8o**) (IC_{50} = 1.65-31.7μM and SI = 1.08-10.96) from the aryl-vinyl-1,2,4-trioxanes (**8a-p**) series possessing high order of cytotoxicity and selectivity against lung (**A549**) cancer cell lines in comparison to different reference molecules such as artemisinin (IC_{50} = 100 μM), artesunic acid (IC_{50} = 9.85 μM) and chloroquine (IC_{50} = 100 μM). The two most active analogues from the series, **8l** (IC_{50} = 1.65 μM, SI = 10.96) and **8m** (IC_{50} = 3.36 μM, SI = 0.23) showed >**60-fold** and ~**30-fold** *in vitro* more potency in comparison to reference drug artemisinin (IC_{50} = 100 μM), respectively against lung (**A549**) cancer cell lines.

Chapter 4: In this chapter, we have successfully developed 2,3-bis-(2-pyridyl)pyrazine as a new organocatalyst, which will be utilised for the inter-/intra-molecular cross-coupling reactions of two unactivated arenes *via* $C_{(sp^2)}$-H bond activation. We have also prepared a library of arylated arenes/hetero-arenes (**3a-u**) in up to 98% excellent yield *via* utilizing 2,3-bis-(2-pyridyl)pyrazine as an organocatalyst under transition metal-free environment and mild reaction conditions. The susceptibility towards functional group variation, kinetic isotopic effect, trapping of the K^+ cation, radical scavenger experiments, quantitative elemental analysis,

gram-scale synthesis and its practical applications to the synthesis of pharmaceutically privileged scaffolds further highlights the utility of the present methodology.

Chapter 5: In this chapter, our study uncovered an unprecedented, highly efficient, transition-metal-free, Cs_2CO_3-Et_3N-mediated direct alkynylation and (*E*)-alkenylation protocol for the synthesis of propargyl alcohols **4a-c**, **7a-k** and **9a-j** and *α*,*β*-unsaturated ketones **5a-u**, respectively under mild basic conditions. With the rapid operational simplicity, functional group compatibility and substrate selectivity; the present protocol demonstrates a fast method for the facile synthesis of bioactive scaffolds in good to excellent yields. The gram-scale synthesis and its practical applications to the synthesis of bioactive heterocyclic scaffolds (**10**-**13**) further highlight the practicality of this methodology.

Conclusion: Overall, we have coordinated our consideration towards the development of such an approach that would allow direct access to pharmaceutically privileged bioactive heterocycles utilizing low cost and widely available starting materials without using any poisonous or harmful substrates. The versatility of our work is further described here by synthesizing an exemplary set of 1,2,4-halogenated/arylated trioxanes, biaryl-based analogues, *α*,*β*-unsaturated ketones/chalcones and propargyl alcohols in detail.