OBJECTIVES AND PLAN OF WORK

3.1 Objectives

Literature survey reveals that, fungal infections pose a continuous and serious threat to human health and life, in recent years there has been an increased use of antifungal agents and has resulted in the development of resistance and toxicity, low efficacy rates. The antifungal drugs works by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effects on the host.

Unlike the development of antibacterial agents, to date relatively few drug targets in fungi have been exploited in the development of currently available antifungal agents. Antibacterial agents have taken advantage of multiple targets available in bacteria that are not present in mammalian cells. Fungi have similarities to mammalian cells that have made the search for antifungal drug targets difficult. To date, three targets – plasma membrane sterols, nucleic acid synthesis and cell wall constituents (chitin, β 1,3-glucan, and mannoproteins) – have been exploited with varying degrees of success.

Most of the current antifungal agents available for systemic use rely on the direct (the polyenes) or indirect (the azoles) interaction with the plasma membrane sterol ergosterol. The cell wall-acting echinocandin class of antifungal agents was the first major class of systemically acting antifungals to exploit a unique target, β 1,3 glucan synthase.

The vast majority of the current antifungal agents target the fungal cell wall or its biosynthesis, leaving many of the essential metabolic functions unexplored as therapeutic targets. Such essential enzyme, are sterol 14- demethylase (P45014DM) and dihydrofolate reductase (DHFR).

3.1.1. Sterol 14-α-Demethylase (P45014dm)-Sterol 14 α-demethylase (14DM, the CYP51 family of cytochrome P450) is an essential enzyme in sterol biosynthesis in eukaryotes. It serves as a major drug target for fungal diseases and can potentially become a target for treatment of human fungal infections. Sterol 14 α demethylase is a highly promising potential drug target because inhibitors of its fungal ortholog (imidazole and triazole derivatives) have been successfully used for many years for treatment of human infections with fungi.

3.1.2. Dihydrofolate Reductase (DHFR)-DHFR is an enzyme that plays important role in the folate biosynthesis pathway and is crucial for cell viability, which makes it
a potential target for antifungal drugs. Since DHFR is essential to all cells, inhibitors targeting pathogenic organisms must be selective. The objective is to find potent and selective inhibitors against pathogen DHFRs through high resolution structural characterization.

To overcome the drawbacks of the current antifungal drugs and to obtain more efficacious drugs, an antifungal drug having a novel target or mode of action that are highly selective for the fungus should be developed. This rapidly growing area of research will continue to be important as the need for potent, less toxic antifungal agents continues to increase. This has given rise to search for a new heterocycle with distinct action or multitargeted combination therapy.

Considering the above aspects the present work entitled “Design, Synthesis and Biological Evaluation of Novel Anti-Fungal Agents” was undertaken with the objectives to design and synthesize Sterol 14-α-Demethylase and Dihydrofolate Reductase (DHFR) inhibitors by structure based approach and there in vitro antifungal evaluation.

### 3.2. Plan of work

The work was plan as follows

- Literature survey of Antifungal agents.
- Designing of Antifungal Agents (Molecular Docking Studies and Lipinski’s parameter)
- Synthesis and characterization-
  1. Scheme I-
     - Synthesis of aryldeneoxazolones from benzoylglycine.
     - Synthesis of benzamides from aryldeneoxazolones.
  2. Scheme II-
     - Synthesis of 2-amino-3-carbethoxythiophenes.
     - Synthesis of thieno [2,3-d]pyrimidin-4(3H)-thiones.
     - Characterization of synthesized compounds by physical and spectral methods
- Biological evaluation
  - *In-vitro* antifungal screening