# PREFACE

*"Even in today's more rational drug discovery environment, it may be said that serendipity is one of the medicinal chemist's best friends. Of course, serendipity alone cannot provide a drug; it requires someone to recognize the opportunity and capitalize on it. As demonstrated by Sternbach and his colleagues, when chance discoveries fall into the hands of open-minded and persistent scientists, the results can be remarkable."*

***Burger's Medicinal Chemistry***

The quotation portrays the uncertainty involved in the field of drug discovery although the demand of new drugs is very high. Drug discovery process is a continuing effort of improving human life and undoubtedly a part of evolution. Diseases are an undesired but essential part of human life and as life progresses they also trail behind. Therefore, the battle against the diseases is obvious. As a result the health industry has become an important part of our economy. To overcome the situations arising due to newer diseases, a lot of finances are focused on the development of new drugs for their treatment these days.

Drug discovery involves collaborative effort to target all types of disease conditions. One of these conditions is neurological disorder, a kind of central nervous system disturbance. A central nervous system (CNS) disease can affect either the brain or the spinal cord, resulting in neurological or psychological disorders. Causes of CNS diseases are trauma, infections, degeneration, autoimmune disorders, structural defects, tumors or stroke.

'Privileged scaffolds' are those molecular frameworks which are capable of serving as ligands for a diverse array of receptors and are unique, highly potent bioactive small molecules which may dramatically accelerate the rate of critical biochemical discoveries and may ultimately enable diseases not only to be managed, but also to be eradicated. Majority of privileged structures contain nitrogen atom as an essential heterocyclic character.

The present endeavor embodies studies pertaining to the development of nitrogen containing fused ring systems as potential central nervous system active agents. The thesis has been organized into three sections, each section includes five chapters. The studies cover all the aspects of medicinal chemistry research, starting from synthetic organic chemistry to biological activity and eventually the molecular docking of active compounds. Few privileged scaffolds have been identified for the

current study. One of them is 3-benzazepine, a seven membered bicyclic benzo-annelated fused ring system. Several protocols have been reported in literature for the cyclization and substitution on 3-benzazepine scaffold. As focus of the study was to synthesize C-1 substituted 3-benzazepin-2-one scaffold, a direct arylation method was tried with the help of palladium chemistry. The details of the developed palladium protocol is discussed in **SECTION-I**. It has been further divided into five chapters. **Chapter 1** is the introduction of palladium chemistry, incorporating recent literature. **Chapter 2** is research envisaged which highlights the idea behind the synthesis of this particular scaffold. **Chapter 3** discusses the results and discussion of the study in detail and also includes the theoretical explanations of the results obtained. All the experimental procedures and chemical data of the newly synthesized compounds are represented in **Chapter 4**. **Chapter 5** comprises the reference section. Apart from the arylation of 3-benzazepine scaffold, other substitution processes have also been explored to synthesize a small library of compounds with sufficient diversity. **SECTION-II** of the thesis contains different approaches of nucleophilic substitutions for alkylation of 3-benzazepin-2-one ring. A guileless survey of literature revealed that 3-benzazepine scaffold is an important ring system which can target different receptors present in brain, especially 5-$HT_{2C}$ receptor. 5-$HT_{2C}$ receptors are involved in different metabolic and neurological activities of human life. Hence, it was planned to design and synthesize 3-benzazepine derivatives, which may modulate the activity of 5-$HT_{2C}$ receptors. The details of the studies are presented in **SECTION-II**. This part is also divided into five chapters, like the **SECTION-I**, **Chapter 1** is the introduction part, **Chapter 2** contains research envisaged, **Chapter 3** includes results and discussion section, **Chapter 4** is experimental and finally **Chapter 5** includes all references pertaining to this section.

The next part of the studies is focused on another highly potent privileged structure i.e. guanidine. Guanidine itself is present in numerous biologically active compounds either in its acyclic form or embodied in polycyclic frameworks. Our studies were focused on the use of the cyclic guanidine scaffold for the treatment of neurodegenerative disorders viz. Alzheimer's disease (AD). Several synthetic protocols are reported in literature for the generation of open chain guanidine scaffold but very few are reported for cyclic guanidines. It was planned to explore protocols for the synthesis of cyclic guanidines. In this effort, new methods which include green chemistry, using ionic liquids are successfully explored and represented in **SECTION-III**. Like earlier sections this section is also divided into five chapters. As the studies are focused for the development of new chemical entities for AD, **Chapter 1** contains the introduction of AD. **Chapter 2** discusses the research envisaged and **Chapter 3**

discusses results and discussions. **Chapter 3** is further sub-divided into two sections, section one for **Chemical studies** and section two for **Biological studies**. Chemical studies include the details of developed synthetic protocols and suitable theoretical explanations with mechanisms. During the development of synthetic methods five, six and seven membered bicyclic guanidine scaffolds were successfully synthesized. Benzamide derivatives were obtained as intermediates when six membered cyclic guanidine derivatives were synthesized. Benzamide itself is an important pharmacophore from the medicinal chemistry point of view. This results in further division of biological studies in two parts. **Part A** of biological studies discusses the planned screening of cyclic guanidine derivatives for neurodegenerative disorders and **Part B** describes the screening of novel benzamides, obtained during the synthesis of guanidines for anti-thrombotic activity. The rationale for this screening was based on betrixaban, a benzamide derivative which is in advanced clinical trials for anti-thrombotic activity. Both the parts of biological studies also include molecular docking studies of active compounds with the respective receptors. **Chapter 4** includes all the experimental details. **Chapter 5**, the last chapter is the reference section.

The thesis has been written in a comprehensive manner representing the details of all the studies done during the course of the Ph. D. tenure.