Section I

Chapter 3: Research Envisaged

3. Research Envisaged

Presence of key functional groups in the chemical structure (scaffold) of a molecule increases the possibility of it exhibiting some sort of biological activity. Some of these scaffolds are endowed with particular types of biological activities. These are known as the 'privileged structures/moieties'. One such 'privileged structure' is the seven-membered heterocyclic ring benzazepine which shows NMDA receptor modulating properties.

Benzazepine scaffold contains sterically constrained α-phenethylamine pharmacophore. It is an important class of heterocyclic ring, as a number of benzazepine derivatives have been claimed for acting in CNS diseases as anti-psychotic, neurological disorders like AD (Alzheimer's disease), PD (Parkinson's disease), schizophrenia, anxiety, and depression. The NMDA receptor is an ionotropic receptor that allows transfer of electrical signals between neurons in the brain and in the spinal column. Antagonism at NR2 subunit of NMDA receptor is of current interest to researchers for the development of newer chemical entities for the management of AD. There is a need for the development of compounds acting through NMDA receptors as there are only five drugs approved for the treatment of Alzheimer's disease among which only one drug, mamantine, acts through NMDA receptor. Therefore it is of worth to synthesize the benzazepine derivatives with maximum selectivity for the desired NMDA receptors for the treatment of Alzheimer's disease.

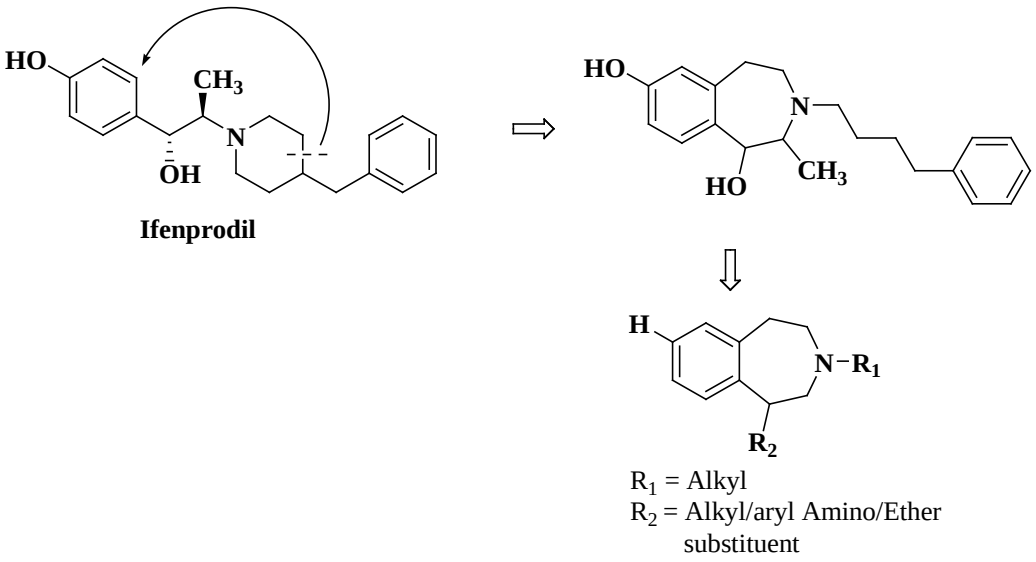

Fig. 3.1: Development of 3-benzazepins as NMDA receptor antagonists.

In 1971 ifenprodil was developed as an α1 adrenoceptor antagonist. Unfortunately, the compound turned out to have low selectivity, since it interacted with several other receptors and ion channels like 5-HT_{1A}, $5HT_2$, σ and NMDA receptors as well. To increase the selectivity of ifenprodil without losing GluN2B affinity, a number of 3-benzazepines with reduced conformational freedom was successfully developed as novel type of GluN2B antagonists (Fig. 3.1). But exhaustive research on 3-benzazepine derivatives carried out by Bernhard Wünsch revealed that the phenolic OH moiety on benzazepine is not essential but favorable for high GluN2B affinity and hence major focus was given to N-3 and C-1 position (Fig. 3.1).

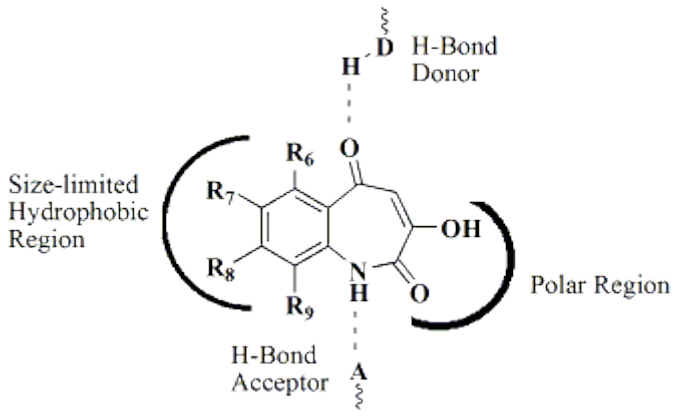

Fig. 3.2: SAR of benzazepines for NMDA receptor glycine site antagonistic activity

In another important report by Guzikowski and co-workers on detailed SAR based on the number of synthesized compounds suggested putative pharmacophore in 1-benzazepine derivatives as NMDA receptor glycine site antagonists (Fig. 3.2). This report suggests favourable substituents required for the NMDA receptor antagonistic activity like the polar region requires a carbonyl group at C-2 position and a hydrogen bond donor group is required at C-1 position.

Based on the literature survey along with these two important findings, it was envisaged to prepare a conceptually new library of 3-alkylbenzazepine-2-one derivatives for the fulfilment of the need for the development of new N-containing seven membered cyclic compounds.

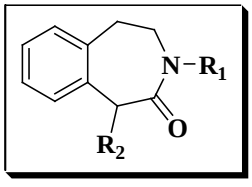

Fig. 3.3: Designed benzazepine-2-ones with substituents at 1 and 3 position

With a thorough study of various benzazepine analogs exhibiting different CNS activities as discussed in chapter 2 we decided to go for the synthesis of newer benzazepine analogs with improved activity profile. From the literature study it became clear that substitution at various positions of the benzazepine ring can produce a variety of receptor interactions in the CNS. Modification at positions 1 and 3 may lead to changes in the selectivity for different receptors thus offering compounds with different activities. Hence, our main target was to make suitable substitutions on positions 1 and 3 of tetrahydro-3-benzazepin-2-one ring system (Fig. 3.3).

So, our aim was to synthesize a series of 3-benzazepine derivatives and screening them for NMDA receptor antagonistic activity. Objectives of the research are:

- To develop and explore substitution methods at the desired position 1 of the azepine ring of the benzazepine scaffold.
- To screen the synthesized compounds for potential NMDA receptor antagonism by *in vitro* and *in vivo* methods.

MK-801, having the benzazepine core is a marketed drug as NMDA antagonist. Some hydroxybenzazepine derivatives (HBAD) are also reported for the NMDA receptor activity. Based on these findings, it was planned to substitute C-1 position in 3-bezazepin-2-one scaffold with amino, ether and imino alkyl substituents with alterations of substituents on the nitrogen at position 3, as these substituents could offer more potent compounds as far as NMDA receptor antagonistic activity is concerned.