3. PLAN OF WORK

In recent years, heterocyclic and bi-heterocyclic compounds have emerged as structurally novel anticonvulsants. These are present ubiquitously in the structures of a large number of therapeutic agents such as antimicrobial, antifungal, anticancer, anti-HIV, antidepressant, antinociceptive, antiepileptic etc. Antiepileptic drugs belong to many different a chemical class of compounds.

Drug discovery for numerous central nervous system (CNS) disorders such as epilepsy, depression, neuropathic pain, psychoses, etc. have attracted the medicinal chemists worldwide due to several reasons that include the safety of the medication apart from their efficacy.

Epilepsy is a chronic neurological disorder characterized by the periodic and unpredictable occurrence of seizures that affects the people of all ages. Being one of the world’s oldest recognized disorders, it is surrounded by fear, discrimination, social and frightening manifestation. A global campaign against epilepsy conducted by World Health Organization (WHO) in partnership with International Bureau for Epilepsy (IBE) and International League Against Epilepsy (ILAE) suggests that around 1% of world population at any time (about 50 million people worldwide) is afflicted with this neurological disorder. Every year about 2.4 million new cases are added to these figures. Currently available antiepileptic drugs (AEDs) provide adequate seizure control in many patients, still about 28–30% of patients are estimated to be poorly treated.

Much efforts devoted in the recent years for the development of novel therapeutics resulted in the availability of several newer drugs (such as pregabalin, stiripentol, zonisamide, tiagabine, lamotrigine, levetiracetam, topiramate) as promising anticonvulsants. These drugs have proven to be effective in reducing seizure, whilst their therapeutic efficacy is overcome by some undesirable side effects such as headache, nausea, hepatotoxicity, anorexia, ataxia, drowsiness, gastrointestinal disturbances and hirsutism. Search for newer candidates that can treat these disorders better and have no or minimal toxicity is the major area of concern these days.
Drugs clinically active against epilepsy include derivatives with common structural characteristics such as nitrogen heterocyclic system with a carbonyl group and an aromatic or heteroaromatic nucleus linked to the heterocyclic system. The suggested pharmacophore model for derivatives that could act via voltage-dependent sodium channel blockade should have at least one aryl ring (R), one electron donor atom (D), and a second donor atom in close proximity to the NH group forming a hydrogen bond acceptor/donor unit (HAD).

These valuable findings prompted us to design, synthesize and investigate various derivatives of benzimidazole, benzothiazole and isatin possessing optimum lipophilicity in order to fulfil the requirements of drug candidates for CNS activity.

In the present study various benz fused five membered heterocyclic moieties (benzimidazole, benzothiazole and isatin) were aimed to be synthesized using different schemes and their anticonvulsant screening was considered to be performed by two most adopted seizure models maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) tests. The most active compounds were planned to be screened for other CNS activities viz. antidepressant and antinociceptive activities. Since, all the synthesized compounds are new; their toxicity on central nervous system and other body parts will be assessed by established methods.

The pharmacological testing for some of the compounds of two different series were planned to be performed by National Institute of Neurological Disorders and Stroke (NINDS), USA under Anticonvulsant screening program (ASP), following the protocol adopted by the Antiepileptic Drug Development (ADD) program.