PART I
CHAPTER - 1.1

INTRODUCTION
Heterocyclic compounds are cyclic organic substances which contain in the ring system at least one atom other than carbon. It seems likely that more than a third of the known organic compounds are heterocyclic. Many alkaloids, vitamins, antibiotics, many synthetic medicines and dye stuffs are heterocyclic, and so also are many substances (such as nucleic acid) which are most intimately connected with the processes of life\textsuperscript{1,2}.

Medicinal chemistry involves aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds. Five and six-membered heterocyclic ring containing compounds form an important part of medicinal chemistry as large number of drugs which exist as of today bear these nuclei.

Epilepsy is one of the most common disorders of the brain, a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures that are caused by abnormal discharge of cerebral neurons.

In the ayurvedic literature of Charaka Samhita, epilepsy is described as "Apasmara" which means loss of consciousness. The term epilepsy based on Greek word epilambanein (meaning "to seize") was first described by Hippocrates. Hippocrates disputed the myth that the cause of epilepsy is supernatural and the cure is magic. The perception that epilepsy was a brain disorder did not begin to take root until the 18\textsuperscript{th} and 19\textsuperscript{th} centuries AD. In the 19\textsuperscript{th} century neurology emerged as a new discipline distinct from psychiatry, the concept of epilepsy as a brain disorder became more widely accepted and this helped to reduce the stigma associated with the disorder.

Potassium bromide introduced in 1857 as the world’s effective AEDs by Locock. In 1920, Hans Berger, a psychiatrist, developed the human electroencephalograph (EEG) brainwave. The EEG revealed the presence of electrical discharges in the brain. It also showed different seizure type. The EEG also helped to locate the site of seizure discharges and expanded the possibilities of neurosurgical treatments.

During the first half of last century the main drugs for treatment were phenobarbitone (1912) by Huptman, and phenytoin (1937) by Putman and Merrit. Since the 1960s there has been an accelerating process of drug discovery, based on a much greater understanding of the electrochemical activities of the brain, especially the excitatory and inhibitory neurotransmitters.
The term “anticonvulsant” designates an agent that blocks experimentally produced seizures in laboratory animals.

The past decades witnessed considerable progress in the pharmacotherapy of epilepsy, including the introduction of several new antiepileptic drugs (AEDs) and improved formulation of older, “First Generation” drugs, such as Phenytin, Carbamazepine, Phenobarbitone, Ethosuximide, benzodiazepines and Valproate.

Today in addition to carbamazepine, ethosuximide, valproic acid and benzodiazepines several newer AEDs such as felbamate, gabapentine, lamotrigine, levetiracetam, oxcarbazepine, and most recently tiagabine, vigabatrin, topiramate and zonisamide are widely used in the treatment of various forms of epilepsy."
The currently used antiepileptic drugs can be broadly classified into four categories on the basis of the molecular mechanisms of action, as follow:

(i) Facilitation of GABA mediated Cl⁻ channel opening
(ii) Modulation of voltage-dependent ion channels (Na⁺, Ca²⁺, K⁺)
(iii) Attenuation of excitatory (glutamate-mediated) transmission

(i) Facilitation of GABA mediated Cl⁻ channel opening:

GABA is the predominant inhibitory neurotransmitter in the mammalian CNS; impairment of GABA function is widely recognized to provoke seizures, whereas facilitation has an anticonvulsant effect. When GABA binds to a GABA-A receptor, the passage of chloride, a negatively charged ion, into the cell is facilitated via chloride channels. This influx of chloride increases the negativity of the cell (i.e., a more negative resting membrane potential). This causes the cell to have greater difficulty reaching the action potential. GABA is produced by decarboxylation of glutamate mediated by the enzyme glutamic acid decarboxylase (GAD). Some drugs may act as modulators of this enzyme, enhancing the production of GABA and down-regulating glutamate. Some AEDs function as an agonist to this mode of chloride conductance by blocking the reuptake of GABA (i.e., tiagabine) or by inhibiting its metabolism mediated by GABA transaminase (i.e., vigabatrin), resulting in increased accumulation of GABA at the postsynaptic receptors as shown in figure below.
(ii) Modulation of voltage-dependent ion channels ($\text{Na}^+$, $\text{Ca}^{2+}$, $\text{K}^+$) Na$^+$ channels:

The firing of an action potential by an axon is accomplished through voltage-sensitive sodium channels. Each sodium channel dynamically exists in 3 states, which are as follows:

- A resting state during which the channel allows passage of sodium into the cell
- An active state in which the channel allows increased influx of sodium into the cell
- An inactive state in which the channel does not allow passage of sodium into the cell

Neuronal Na$^+$ channels can cycle through these functional states within a few milliseconds. This characteristic is essential for sustaining the rapid bursts of action potentials necessary for some normal brain functions, and is implicated in the production of epileptic discharges. The neuronal Na$^+$ channel represents one of the most important targets for AED action. AEDs that target these sodium channels prevent the return of these channels to the active state by stabilizing the inactive form.
of these channels. In doing so, repetitive firing of the axons is prevented. There are many AEDs like phenytoin, carbamazepine, sodium valproate, lamotrigine etc act by inactivating the Na\(^+\) channels as shown in figure below.

Enhanced Na\(^+\) Channel Inactivation

\[Ca^{2+}\] channels:
Voltage-sensitive \(Ca^{2+}\) channels can be broadly classified into low or high threshold, according to the membrane potential at which they are activated. High threshold \(Ca^{2+}\) channels are sub classified by their pharmacological properties into L-, N-, P-, Q-, and R-types and The low-threshold T-type \(Ca^{2+}\) channel is expressed predominantly in thalamocortical relay neurones, where it is believed to be instrumental in the generation of the rhythmic 3-Hz spike-and-wave discharge that is characteristic of generalized absence seizures.
The influx of calcium currents in the resting state produces a partial depolarization of the membrane, facilitating the development of an action potential after rapid depolarization of the cell. Several AEDs like Ethosuximide, trimethadione, sodium valproate etc have been reported to block voltage-sensitive Ca\(^{2+}\) channels, an effect that may contribute to their antiepileptic actions as shown in figure below.

**K\(^+\) channels:**

Neuronal K\(^+\) channels are large protein complexes that form tetrameric structures, the monomers of which are structurally and genetically related to the \(\alpha\)- and \(\alpha_1\)-subunits of the Na\(^+\) and Ca\(^{2+}\) channel, respectively. At the neuronal level, K\(^+\) channels are intimately involved in excitability. They are responsible for the action potential down stroke or, more specifically, repolarisation of the plasma membrane in the aftermath of Na\(^+\) channel activation. Direct activation of voltage dependent K\(^+\) channels hyperpolarizes the neuronal membrane and limits action potential firing. Accordingly, K\(^+\) channel activators have anticonvulsant effects, whereas K\(^+\) channel blockers precipitate seizures. Potentiation of voltage-sensitive K\(^+\) channel currents may prove to be an important target for future AED development. The novel antiepileptic agent Retigabine, currently undergoing Phase II clinical trial, is believed to exert its effects, at least in part, by activation of the KCNQ2/KCNQ3 K\(^+\) channels.
(iii) Attenuation of excitatory (glutamate-mediated) transmission

Glutamate receptors bind glutamate, a principal excitatory neurotransmitter in the mammalian brain. Upon binding glutamate, the receptors facilitate the flow of both sodium and calcium ions into the cell, while potassium ions flow out of the cell, resulting in excitation. Like GABA receptors, ionotropic glutamate receptors are comprised of various combinations of subunits forming tetrameric and pentameric arrays. The glutamate receptor has 5 potential binding sites and causes different responses depending on the stimulated or blocked site. These sites are the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) site, the kainate site, the N-methyl-D-aspartate (NMDA) site, the glycine site, and the metabotropic site that has 7 subunits (GluR 1-7), as shown in figure below. Blockade of ionotropic glutamate receptors is believed to contribute to the antiepileptic activity of several drugs. In addition, several AEDs have been reported to reduce glutamate release. Topiramate act by blockade of the AMPA/kainate subtype of glutamate receptor and Felbamate is believed to be the first effective AED with a direct action on the NMDA subtype of glutamate receptor. It inhibits NMDA/glycine-stimulated increases in intracellular Ca^{2+}.
Although 70-80% of all epileptics are adequately treated by current available drugs, seizure protection is often accompanied by numerous side effects including drowsiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsuitism and megaloblastic anaemia. Thus search of new epileptic drugs is very essential. In recent years, the field of antiepileptic drug development has become quite dynamic offering many promising research opportunities. The search for antiepileptic compounds with a more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry.

Owing to the versatility in the field of anti-epileptics here we aim to synthesize newer anticonvulsant agents with pyrimidine and/or thiazolidinone nucleus. All the synthesized compounds were structurally confirmed on the basis of IR, $^1$H-NMR, $^{13}$C NMR and mass spectral data and evaluated for their anticonvulsant effect in both MES and scPTZ seizure test. They were also tested for their side effects i.e. neurotoxicity effect by rotarod test and CNS depression effect by Porsolt's swim pool test.