CHAPTER 1

INTRODUCTION
The task of the scientific community to develop potent, selective therapeutic agents is dependent upon methods for rapidly assembling compounds of high molecular diversity in rational and efficient ways. Furthermore, the ability of chemists to optimize newly discovered lead compounds as well as to produce analogues or mimics of biologically active natural products relies upon the advancement of synthetic technology.

Medicinal chemistry is the discipline concerned with the determination of the influence of chemical structure on biological activity. As such, it is therefore necessary for the medicinal chemist to understand not only the mechanism by which a drug exerts its effects, but also the physicochemical properties of the molecule. The term physicochemical properties refers to the influence of the organic functional groups present within a molecule on its acid/base properties, water solubility, partition coefficient, crystal structure, stereochemistry etc. All of these properties influence the absorption, distribution, metabolism and excretion (ADME) of the molecule. In order to design better medicinal agents, the medicinal chemist needs to understand the relative contributions that each functional group makes to the overall physical chemical properties of the molecule. Studies of this type involve modification of the molecule in a systematic fashion and determination of how these changes effects biological activities. Such studies are referred to as studies of structure activity relationships i.e. what structural feature of the molecule contribute to, or take away from, the desired biological activity of the molecule of the interest.

Epilepsy is not a disease, but a syndrome of different cerebral disorders of central nervous system (CNS), which is characterized by paroxysmal, excessive and hyper synchronous discharges of large numbers of neurons. In India, studies have reported the prevalence rate of epilepsy varying from 1710 to 9780 cases per million population. Despite the optimal use of available antiepileptic drugs (AEDs), many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic effects. The limitations with the conventional AEDs highlighted the need for developing newer agents for epilepsies and the AED search has come a long way, particularly over the last two decades.
Constraints in antiepileptic drug development (AEDD)

1. Primary pathology of epilepsy remains ill defined.
2. EEG is the single most useful diagnostic test.
4. Lack of definitive models, which mimic the human condition.
5. Governmental regulatory

Methods for epilepsy control

1. Surgery
2. Pharmacological

Advances in AED development

The conventional AEDs

- 1857-Potassium bromide
- 1912-Barbiturates
- 1938-Phenytoin
- 1944-Oxazolidinediones
- 1953-Carbamazepine
- 1960-Succinimides
- Benzodiazepines
- Sodium Valproate

Potassium bromide was the first antiepileptic drug, introduced by Charles Locock in 1857. On repeated administration bromide accumulates in the body and produces a condition known as bromism and bromide rash. Later on in 1912, barbiturates such as phenobarbital and mephobarbital were used for grandmal epilepsy. Recently it has been found that pancreatitis was associated with potassium bromide and phenobarbitone combined therapy in epileptic drugs. Diphenyl hydantoin, a significant advance in the medical therapy of epilepsy, was the first anticonvulsant to be introduced in 1938 as a result of a planned search for new organic chemicals capable of suppressing experimentally induced convulsions in laboratory animals.

In 1944, Richard and Everett reported that trimethadione, a potent analgesic compound prevented pentylenetetrazole induced threshold seizure in rodents. Since then a large number of similar compounds with slight difference in structure like succinimides derivatives were synthesized and ethosuximide was approved for absence seizures in 1960.
Carbamazepine, which was introduced in 1953, was also a very effective drug in the treatment of epilepsy. Thus this has given an impetus to medicinal chemists throughout the world to developed new drugs on different molecular structures resulting in the marketing of valproate and benzodiazepines similar to diazepam and clobazam.

These presently available AEDs are associated with a number of shortcomings. They are unable to control seizures effectively in as many as 25% of the patients. Their dose related neurotoxicity and other side effects at times become a major limitation in their clinical use.

**Strategies for development of newer AEDs**

The limitations with the conventional AEDs, highlighted the need for developing newer agent for epilepsies and the AED search has come a long way, particularly over the last two decades, with increased understanding of pathophysiology underlying epilepsies, the conventional approaches have, to a great extent, been replaced by "mechanism based approaches." The mechanism based approaches rely on the basic premise that epilepsies are due to an imbalance between excitatory and inhibitory transmission in the brain.

Key inhibitory and excitatory players in the brain are gamma amino butyric acid (GABA) and excitatory amino acids (EAAs) respectively. Thus, for developing newer AEDs, the basic approaches are:

1. Augmentation of GABAergic transmission.
2. Inhibition of excitatory amino acid transmission.
3. Modulation of membrane cation (\(Na^+\), \(Ca^{++}\) or \(K^+\)) conductance.

Current front line drugs like benzodiazepines, barbiturates, and valproate act through GABA mediation while drugs like phenytoin, carbamazepine, block sodium channel-induced excitation. Eight new AEDs have been licensed in the past ten years all over the world these include felbamate, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide. Many others in various stages of development e.g. remacemide, losigamone, stiripentol, flunarizine, loreclezole, levetiracetam.
Lamotrigine has received regulatory approval for conversion to monotherapy among patients who have failed on monotherapy with a traditional first line anticonvulsant agent. Further more with advent of neurobiological techniques, there has been a tremendous increase in our knowledge on possible molecular targets for AED development and screening has been identified. These include ion channels, neurotransmitter receptors, neurotransmitter transporters, ion exchangers and range of enzymes involved in transmission metabolism or in protein phosphorylation.

**Mechanism of action:**

The mechanism of action of currently marketed anticonvulsant drugs are not understood fully. Although numerous molecular targets exists wherein anticonvulsants may exert an effect, the final common pathway appears to be through modulation of voltage-gated and/or neurotransmitter-gated ion channels. Most of the prototype anticonvulsant presently are thought their primary action by:

- Reducing sustained, high frequency, repetitive firing of action potentials by modulating voltage dependent sodium channels (phenytoin, carbamazapine and valporate).
- Enhancing GABA-mediated inhibitory neurotransmission via a receptor gated chloride channels (benzodiazepines).
- Modulating neurotransmitter release and neuronal bursting thorough an effect on voltage-gated and receptor gated calcium channels (ethosuximide, dimethadione and valporate)

In addition, newer anticonvulsant substances still under preclinical development have been found to open potassium channels. Another promising area currently being pursued involves identifying novel therapies which are aimed at either reducing excitation by blocking specific excitatory amino acid receptors and those aimed at enhancing inhibition by blocking high affinity uptake of neuronally released GABA.

As is customary, these two terms anticonvulsant and antiepileptic will be used interchangeably in this discussion. Strictly speaking, however the term anticonvulsant designates an agent that blocks experimentally produced seizures in laboratory animals, and an antiepileptic drug used medically to control the epilepsy, not all of
which are convulsive, in humans. Tests used for screening the drugs effective in epilepsy are:

1. Maximal Electroshock Seizure (MES) Test
2. Subcutaneous Pentylene Tetrozol (scPTZ) (Metrazol) Seizure Threshold Test
3. Increasing Current Electroshock (ICES) Test
4. Rotarod Toxicity Test

The structural requirements for activity in the maximal electroshock (MEZ) anticonvulsant screen, which is claimed to identify compounds with efficacy against generalized tonic-clonic ("grandmal") seizure have been stated to be two electron donor close to a bulky hydrophobic group. Similarly, in the subcutaneous pentylenetetrazol (scPTZ) test, which is thought to detect compounds with usefulness in treating generalized absence ("petitmal") seizures, two electron donor atoms are also considered to be necessary for bioactivity, but close to a smaller, less hydrophobic group than in compounds active in MES screen.

Algesia (pain) is an ill-defined, unpleasant sensation, usually evoked by an external or internal noxious stimulus. An analgesic may be defined as a drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness. Pain is a warning signal and primarily protective in nature, but cause of discomfort. It is the most important symptom that brings the patient to the physician.

Excessive pain may be unbearable and cause other effects like sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in blood pressure, tachypnoea. Analgesics relieve pain as a symptom, without affecting its cause. They are used when the noxious stimulus (evoking the pain) cannot be removed or as adjuvant to more etiological approach to pain. Pain relieving agents are also called antinociceptives. There are three major groups of analgesic drugs:

❖ Opioids
❖ Non-steroidal antiinflammatory drugs (NSAIDs)
❖ Local anesthetics
There are also several useful drugs that do not fit into these groups:

- Alpha-2-adrenergic receptor agonists
- N-Methyl-D-aspartate (NMDA) receptor antagonists.

Mechanism of action:

While cellular and molecular studies of opioid receptors are invaluable in understanding their anatomical and physiological context to fully understand the opioid system. Pain control by opioids needs to be considered in the context of brain circuits modulating analgesia and functions of the various receptor types in these circuits.\cite{13, 14}

It has been well established that the analgesic effects of opioids arise from their ability to inhibit directly the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, via the rostral ventromedial medulla, to the spinal cord dorsal horn. Opioid peptides and their receptors are found throughout these descending pain control circuits.\cite{15, 16}

Depression is a serious psychiatric illness with a lifetime prevalence\cite{17} of 5%. An even higher number, up to 20%, of individuals suffer from a depressive episode once in their lifetime. Typical symptoms of depression include depressed mood, diminished interest of pleasure (anhedonia), feelings of worthlessness or inappropriate guilt, decrease in appetite and libido, insomnia, and recurrent thoughts of death or suicide. Depression is potentially fatal since most patients think about suicide, about 50% try to commit suicide and up to 15% of patients with severe depression die from suicide.\cite{18, 19} In addition, in the last few years, depression has been found to be a risk factor in diseases such as diabetes and cardiovascular disease.\cite{20, 21} Depression most often occurs in defined episodes, which can last from weeks to months, in severe cases for years. Many patients suffer from several relapses and/or chronification, which then often leads to severe cognitive and functional impairment as well as psychosocial disability.\cite{22, 23} Treatment of depression includes various forms of psychotherapy as well as pharmacotherapy with antidepressants.
Mechanism of action:

In severe cases or in treatment-resistant depression, electro convulsive therapy (ECT) is also applied. Depression is also a remitting disease in which normal clinical studies show a placebo response rate of about 40%. It is of interest that the rate of improvement under placebo treatment is identical to that seen in drug studies suggesting that the underlying mechanisms are very similar. In view of the efficacy of drugs (about 60%) and ECT (80-90%), it is clear that we still have a need to better understand the pathophysiology in order to develop effective medications.

Neurobiological basic research as well as clinical studies have revealed that two monoaminergic systems are involved in the etiology and therapy of affective disorders, namely serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine.

Thus, the common basis of pharmacotherapy is based on the enhancement of serotonergic and/or adrenergic neurotransmission by either inhibiting the intracellular degradation of the monoamines with monoamine oxidase inhibitors or blocking their reuptake back into the synaptic cleft by selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), or tricyclic antidepressants (TCA). SSRI and SNRI bind with high selectivity and affinity to the monoamine transporter proteins and thereby block the neurotransmitter translocation process that, in turn, leads to an increase of synaptic monoamines (MAO).

The thesis contains the synthesis and biological screening of six series of compounds and it is designed in the form of seven chapters.

- Chapter 1: The first chapter includes the introductory part of the thesis.
- Chapter 2: In the second chapter literature survey is presented.
- Chapter 3: The third chapter is attributed to the rationale of the present study based on the literature survey.
- Chapter 4: The chapter four treat systematically with the experimental section which is further divided into subsections:
  - Chemistry
  - Biological screening
- Chapter 5: The fifth chapter establishes the computational parameters.
- Chapter 6: The sixth chapter covers the result and discussions.
- Chapter 7: The last, seventh chapter concludes the work presented in the thesis.
References


