CHAPTER - 1.2

RATIONALE
A rational drug design process of a new anticonvulsant could be achieved in several ways. The first strategy is the identification of new targets through better understanding of molecular mechanisms of epilepsy. Another way is to modify already existing drugs and formulations.

The insufficient information on the cellular mechanism of epilepsy in human and the complex mechanism of action of most of the antiepileptic drugs makes it difficult to use rational methodologies in the field of drug discovery. Therefore another design of new antiepileptics is based on the existence of different pharmacophores that were established through the analysis of structural characteristics of clinically effective drugs as well as other antiepileptic compounds.

In the literature, it is well documented that various essential pharmacophoric features which could be responsible for interaction with the active site of voltage gated sodium channels are:

(i) Hydrophobic unit (A) such as aryl ring (substituted or un-substituted).
(ii) Electron donor group (D) such as CO, NH etc.
(iii) Hydrogen donor or acceptor group (HAD) such as CONH.

This common template have been found in the structures of first generation antiepileptics (Carbamazepine, Phenobarbital, Phenytoin), second generation antiepileptics (Brivaracetam, Eslicarbazepine), newer drugs (Felbamate, Retigabine) and the drugs in clinical trial. Much efforts devoted in the recent years based on the pharmacophore model for the development of novel therapeutics resulted in the availability of several newer drugs (such Astigabine, Lamotrigine, Pregabaline, Stiripentol, Zonisamide, Topiramate, Levetiracetam) as promising antiepileptics.

The efficacy of many of the marketed antiepileptic drugs is greatly compromised by severe side effects such as ataxia, drowsiness, gingival hyperplasia, gastrointestinal disturbances, and megaloblastic anaemia. Moreover about 30% of patients have uncontrolled seizures.
Therefore, continued search for novel antiepileptic drugs with less toxicity and more selectivity continued to be an area of investigation in the field of medicinal chemistry. The literature survey revealed that following classes of compounds can be useful for the design and development of new anticonvulsant drugs.

**Pyrimidine derivatives:**

One of the most frequently encountered heterocycles in medicinal chemistry is pyrimidine with wide range of biological properties including anticonvulsant. Vertex patented a molecule [1] with pyrimidine nucleus as anticonvulsant. Similarly, Glaxo Smithkline\(^7\) also synthesized pyrimidine analogue of Lamotrigine [2].

![Pyrimidine Derivative](image1.png)

**Thiazolidinonederivatives:**

One of the structurally distinct classes of antiepileptic drugs is the thiazolidinones. Aggarwal et al synthesized a series of molecules [3] having thiazolidinone nucleus and were found to possess anticonvulsant effects\(^9\). Similarly R V Shingalapur reported compound [4] with anticonvulsant activity\(^10\).

![Thiazolidinone Derivative](image2.png)
The compounds we aimed to synthesize not only contain required pharmacophoric feature but were also found to possess reported anticonvulsant activity. It can be represented by following diagram:

**SCHEME-I**

![Diagram for Scheme-I]

For Scheme-I: R = H
For Scheme-II: R= CH$_3$

**SCHEME-II**

![Diagram for Scheme-II]

These findings prompted us to design and synthesize various heterocyclic compounds having pyrimidine and thiazolidinone moieties in order to develop compounds:
1. Which are potent in various classes of model
2. Should have potency with lesser toxicity & limited side effects
3. Should have optimum lipophilic character, so that dose may be reduced
4. With all the pharmacophoric requirements and to establish some correlation between structure and the activity of these compounds