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A Case Study:

New antiepileptic agents: structure activity relationships

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ABSTRACT

Epilepsy is a common neurological condition, affecting 0.5% to 1% of the population worldwide. 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 chemical diversity and various mechanisms of action of anticonvulsants make it difficult to find a common way of identifying new drugs. Novel anticonvulsant agents are discovered through conventional screening and/or structure modification. The new AEDs and anticonvulsant agents representing various structures have been reviewed in the present review. The newer agents include sulfonamides, amino acids, amides (analogs of g-vinyl GABA, *N*-benzylamides, 2,6-dimethylanilides, carboxyamides, hydroxyamides, alkanoamides); heterocyclic agents ((arylalkyl) imidazoles, tricyclic indoles, indazoles, arylpiperazine and piperazines, pyrrolidin-2,5-diones, pyridazinone, lactams, semi- thiosemicarbazones, thiadiazoles, quinazolin-4 (3H)-ones, 2,5-disubstituted 1,2,4-thiadiazoles, xanthones, derivatives of isatin), enaminones, imidooxy compounds and valproic acid derivatives. These new structural classes of compounds can prove useful for the design of future targets and development of new drugs.

Key words : Anticonvulsant agents, Structure – Activity – Relationships, AED's.

Epilepsy, a common neurological disorder characterized by recurrent spontaneous seizures, is considered to be a major health problem that affects approximately one to two per cent of the population worldwide (45-100 million people) [1, 2].

Despite the considerable progress in our understanding of the pathophysiology and pharmacotherapy of seizures and epilepsy[3] the cellular basis of human epilepsy remains an enigma. In the absence of etiological understanding, approaches to pharmacotherapy must be directed to the control of symptoms, that is the suppression of seizures.

Over the years, there has been considerable success in the development of novel antiepileptic drugs (AED) along with new improved formulations. Conventional antiepileptic 'first generation' drugs such as primidone, phenytoin, carbamazepine, phenobarbitol, valproic acid, ethosuximide and benzodiazepine, are widely used but exhibit an unfavorable side effect profile and failure to adequately control seizures. In the recent years several new 'second generation' drugs such as lamotrigine, vigabatrin, tiagabine, topiramate, gabapentin, levetiracetam, oxcarbazepine, zonisamide, fosphenytoin, vigabatrin and felbamate have been added to the list of therapeutic agents against epilepsy[4,5].

However, there is a significant group of patients (up to 30%) who are resistant to the available antiepileptic drugs. The long-established AEDs control seizures in 50% of patients developing partial seizures and in 60-70% of those developing generalized seizures[6-10]. Hence, there is an urgent need to develop new AEDs[11].The selection of an antiepileptic drug for treatment is predicted on its efficacy for the specific type of seizures, tolerability and safety[12,13]. The search for antiepileptic compounds with a more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. A rational drug design process of a new anticonvulsant could be achieved in several ways[14,15].

Epileptic seizures can be generalized, originating in both hemispheres of the brain simultaneously, or partial (focal seizures) originating in one or more parts of one or both hemispheres, most commonly the temporal lobe. Epilepsy or epileptic syndromes can be either idiopathic (etiology or cause is unknown) with a presumed genetic basis or symptomatic (acquired). The known potential causes of epilepsy include brain tumors, infections, traumatic head injuries, perinatal insults, developmental malformations, cerebrovascular diseases, febrile seizures and status epilepticus[16].

Traditionally, pharmacological strategies for treatment of epilepsy are aimed at suppressing the initiation or propagation of seizures rather than the underlying processes that lead to epilepsy[17]. The first strategy is the identification of new targets through better