Chemistry & Biology Interface, 2018, 8, 3, 135-137

REVIEW PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Benzothiazole: A Versatile Synthetic Auxillary for Antiepileptic Drugs

Dinesh Kumar Agarwal[a] , Shikha Agarwal[b]*, Divyani Gandhi[b]

[a]*Department of Pharmacology, Pacific College of Pharmacy, Udaipur-313001, India*
[b]*Synthetic Org. Chem. Laboratory, Department of Chemistry, M. L. S. University, Udaipur*
E-mail: shikha_urj@yahoo.com
Received 5 April 2018; Accepted 15 May 2018

Abstract: Heterocycles containing nitrogen, sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compounds. Benzothiazole and their heterocyclic derivatives represent an important class of compounds possessing a wide spectrum of biological activities. A large number of anticonvulsant drugs are available for the treatment of different types of seizures and many are in clinical trials. But not a single molecule is available for treatment of all type of seizures having no side effects, toxic effects, adverse reactions etc. Therefore, the development of newer molecules which serve for most of the seizures with high tolerance, having good pharmacokinetic properties and clinical efficacy with less side effects or toxicity is needed.

Keywords: Benzothiazole, Epilepsy, Hydrophobic domain, AED

Introduction

Epilepsy is the recurrent and fourth most common neuro-pathological syndrome affecting about 1-2% of the world's population covering over various types of human seizures and is characterized by paroxysmal and hyper synchronous discharge of large number of neurons. It is the commonest neurological condition affecting people of all ages, race and social class. Over the years, the field of epilepsy has received a great deal of attention from research investigators in the hope of discovering new drugs that are more effective and have minimal adverse effects. Though several new anticonvulsants have been introduced, some types of epilepsies are still not adequately controlled with the current therapy. Adverse reactions and lack of efficacy for certain types of epilepsies are some of the limitations of existing medications [1]. Taking into consideration the above limitations, many authors conducted attempts to identify the structural features crucial for anticonvulsant activity. On the basis of these researches, several pharmacophoric models, enabling a more rational design of new anticonvulsants, have been described (Fig. 1). Thus, one of the

important core fragments of anticonvulsants is defined by nitrogen heterocyclic system, usually imide or lactam and phenyl or alkyl groups attached to the heterocyclic system [2, 3, 4]. This common template is present in the structures of old, however well established Anti Epileptic Drugs (AEDs), such as ethosuximide and phenytoin as well as among the newest drugs, e.g., levetiracetam, brivaracetam or seletracetam [5, 6].

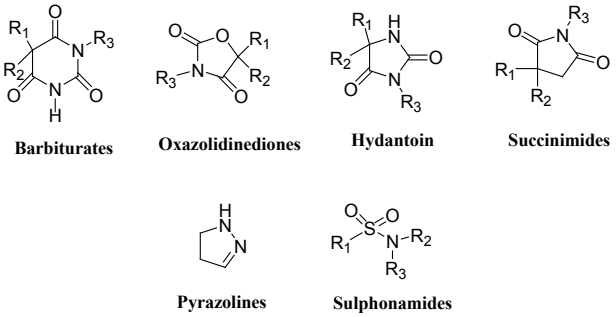

Fig. 1: Different Pharmacophores for potent antiepileptic activity

Role of Benzothiazole nucleus:

Benzothiazoles (BT) are promising candidates for the design of novel antiepileptic drugs [7-17]. They constitute a family of heterocyclic compounds where the skeleton is constituted from a benzene ring fused with a thiazole ring. The endocyclic sulfur and nitrogen present in the nucleus has been found to be critical for the anticonvulsant activity. During the last years, thousands of benzothiazole derivatives have been synthesized and screened for their anticonvulsant potential. The benzothiazole nucleus might serve as a hydrophobic domain which increases the lipophilicity of compounds. Coupling of hydrophobic benzothiazole moiety with hydrogen bonding domains (like hydrazide, amide, urea, thiourea, semicarbazone, thiosemicarbazone etc.) having an electron donor system have led to the discovery of a number of potent anticonvulsant agents. For the designing of benzothiazole derivatives as anticonvulsant agents, the essential pharmocophore elements involve hydrophobic domain (A), hydrogen bonding domain (HBD), electron donor atom (D) and distant aryl ring (R). (**Fig. 2 and 3**).

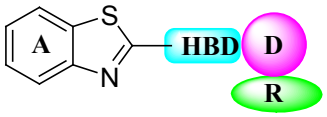

Fig. 2: Designing of benzothiazole derivatives as anticonvulsant agents.

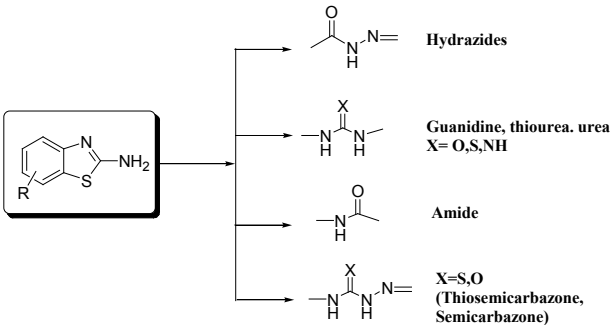

Fig. 3 Benzothiazole with different HBDs

The presence of an amide linkage as hydrogen bonding domain (HBD) is an optimal pharmocophoric feature in various AEDs as like riluzole, lacosamide, phenacemide, valrocemide, retigabine etc. The amide linkage –NHCO- with delocalized electrons is a key determinant of anticonvulsant activity due to strong hydrogen bonding with putative receptor, which would be greatly influenced by the nature of adjoining substituents. Various amide derivatives have been synthesized by numerous researchers to explore the effects of adding substituents to amide linkage at benzothiazole ring. Some of the known antiepileptic drugs have been shown here with pharmocophoric characteristics necessary for antiepileptic activity (Fig. 4).

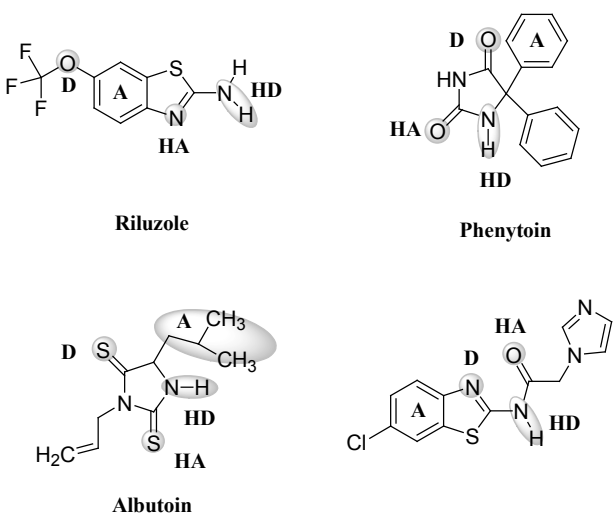

Fig. 4 Some established Antiepileptic Drugs showing essential pharmocophoric elements

Conclusion

Each year witness the growing inclusion of many thousands of heterocyclic compounds in literature, both on account of their intrinsic chemical interest and on the basis of their therapeutic, biological and industrial potential. In today's scenario, drug synthesis with effective pharmacological action is an urgent issue. Thus in the current context, there is an urgent need for the development of more effective AEDs with lesser side effects.

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