Application of Pharmacophore Models for the Design and Synthesis of New Anticonvulsant Drugs

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Abstract: The chemical diversity and various mechanisms of action of anticonvulsants make it difficult to identify a common pharmacophore. The present review outlines different pharmacophore models for anticonvulsant activity with emphasis on the development of new drugs. Some of them represent models for structurally different classes of compounds with similar mechanisms of action. Others represent pharmacophore models for similar chemical classes of compounds for which the mechanism of anticonvulsant action is not clear. A pharmacophore model for sodium channel blocking compounds, anticonvulsants with the phthalimide pharmacophore, a model for anticonvulsant semicarbazones, and a model for GABA uptake inhibitors are presented.

Keywords: Pharmacophore models; anticonvulsants; Na-channel blockers; 4-aminobenzamide, *N*-phenylphthalimide, semicarbazones; GABA uptake inhibitors.

INTRODUCTION

Epilepsy is a relatively common neurological condition affecting 0.4-1% of the world's population (45-100 million people). The conventional antiepileptic drugs (AEDs) phenobarbital, primidone, phenytoin, carbamazepine, valproate, ethosuximide, and benzodiazepine, are widely prescribed but suffer from a range of side effects. Furthermore, there is a significant group of patients (20-30%) that is resistant to the currently available therapeutic agents. During the past decade, several new drugs have been approved, e.g., felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide, or are in the process of being approved, e.g. losigamone, pregabaline, remacemide, rufinamide, licarbazepine, retigabine, ganaxolon, and talampanel [1, 2]. In general, the efficacy of AEDs is due to the main activities which include potentiation of inhibitory mechanism (i.e., GABA-ergic transmission), inhibition of excitatory mechanisms (i.e. glutamatergic transmission), inhibition of excessive firing of neurons (modulator of membrane cation conductance *via* sodium, calcium or potassium channels). Most available agents have multiple actions which may account for their efficacy. However, none of the currently available AEDs is ideal and most of them are used as add-on therapy to existing standard therapy and can be associated with chronic and acute adverse effects [3,4]. Thus the search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry.

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STRUCTURE-ACTIVITY RELATIONSHIPS OF ANTICONVULSANT DRUGS

AEDs belong to many different chemical classes of compounds [5,6]. The most common structural elements of the older generation clinically active drugs anticonvulsants derived from hydantoins, oxazolidinediones, succinimides and glutarimides can be defined as a nitrogen heteroatomic system bearing one or two phenyl rings and at least one carbonyl group [7, 8]. Many investigations indicated that the presence of at least one aryl unit, one or two electron donor atoms, and/or an NH group in a special spatial arrangement seems to be necessary in the structure of anticonvulsants [9]. The conformational analysis of the older generation clinically active anticonvulsant drugs such as hydantoins, succinimides, glutarimides, oxazolidine-2,4-diones, pyrimidine-2,6-diones, barbituric acids led to the proposal of a general model for anticonvulsant activity comprising two aromatic rings or their equivalent in a favoured orientation, and a third region, usually a cyclic ureide, containing a number of hydrogen-bond-forming functional groups. The specific placement of hydrogen-bonding groups in this region appeared to be of less importance than the correct conformational arrangement of the hydrophobic elements [8].

Some of the clinically used drugs have not been linked with a specific binding site within the brain; therefore, drug identification is usually conducted via *in vivo* screening tests. Two major pharmacological screening tests used to evaluate compounds for anticonvulsant activities are the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens [10]. These test are claimed to detect compounds possessing activity against generalized tonic-clonic (grand-mal) and generalized absence (petit mal) seizures, respectively. The structural requirements for activity in the MES screen have been stated to be the presence of a large hydrophobic group which is in close proximity to at least two electron-donor atoms. For activity

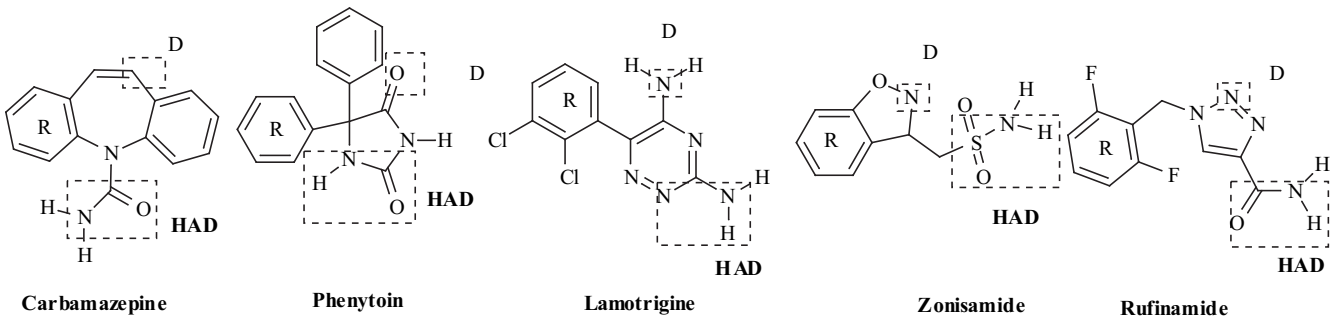

Fig. (1). Selected anticonvulsants used for the development of a pharmacophore model. The essential structure elements are indicated by dotted rectangles (R, hydrophobic unit; D, electron donor group; HAD, hydrogen donor/acceptor unit).

in the scPTZ screen, a smaller, less hydrophobic group than is required for activity in the MES screen should be present near to a minimum of two electron-donor atoms [11].

The chemical diversity and various mechanisms of action of anticonvulsants make it difficult to identify a common pharmacophore. The present review outlines different pharmacophore models for anticonvulsants with emphasis on the development of new drugs. Some of them represent models for structurally different classes of compounds with similar mechanisms of action. Others represent pharmacophore models for similar chemical classes of compounds for which the mechanism anticonvulsant action is not clear.

PHARMACOPHORE MODEL FOR SODIUM CHANNEL BLOCKING COMPOUNDS

Voltage-dependent sodium channels have been recognized as targets for developing anticonvulsant drugs (e.g. phenytoin, carbamazepine, lamotrigine). In the past some attempts were made to postulate a pharmacophore for anticonvulsants acting by blockade of the voltage-dependent sodium channel. Brouillette *et al.* [12-14] investigated several mono- and bicyclic phenytoin analogues which blocked sodium channels and were effective in the MES test. It was concluded for monocyclic hydantoins that a specific aromatic ring orientation, and a free imide group were optimal for high binding affinity to the sodium channel. However, the conclusions of these studies were not related to other compounds acting at the same receptor site.

Unverferth *et al.* (1998) compared the five well-known and structurally different compounds with anticonvulsant activity, carbamazepine (CBZ), phenytoin (DPH), lamotrigine (LAM), zonisamide (ZON), and rufinamide (CGP)) [15] Fig.(**1**). These compounds act according to the same mechanism by blockade of voltage-dependent sodium channels. In the structure of these five molecules it was possible to indicate their common chemical elements. The investigated compounds have at least one aryl ring (R), one electron donor atom (D), and a second donor atom in close proximity to the NH group forming a hydrogen bond acceptor/donor unit (HAD). In most cases this is an amide bond. On the basis of the molecular dynamics distance estimations, the pharmacophore model for compounds acting as antagonists of the voltage-dependent sodium channel was suggested Fig.(**2**). This model comprises an electron donor D in relatively limited distance ranges of 3.2-5.1 Å to an aryl ring or other hydrophobic units R and of 3.9 – 5.5 Å to a hydrogen bond acceptor/donor unit. The distance between R and HAD spans a wider range of 4.2-8.5 Å. The hydrophobic unit R was not oriented in the same plane like the other essential elements and an indication for a specific orientation of the aromatic ring was not found. The latest conclusion was not in agreement to earlier works (Brouillette *et al.*,). The aromatic rings were rotated in relation to the R-D-HAD plane by 10-40^{o}. In some cases even free rotation of the phenyl ring was possible. To support the suggested pharmacophore model, authors considered some more structurally different anticonvulsants which act by blockade of the voltage-dependent sodium channels Fig. (**3**). All of these structurally very dissimilar compounds i.e. AWD 140-190, vinpocetine, dezinamide, and remacemide, contain aryl rings, electron donor, H-bond donor/acceptor functions, and fulfil the essential demands of the suggested pharmacophore model. It was corrected that the distance range for D-HAD could possible be larger than originally suggested. Possibly the presence of only one component of the HAD unit at the postulated position, e.g. only the H donor part in addition to the two other essential structure elements R and D may be sufficient for antagonistic activity at the voltage-dependent sodium channel. In fulfilling the requirements of the suggested pharmacophore model, 3-amino-, 4-amino- and 5-aminopyrazoles were synthesised and tested *in vivo* for anticonvulsant activity [16, 17]. Among them 3-aminopyrazoles exerted a strong anticonvulsant effect. 4-Chlorophenyl-3-(morpholin-4-yl)-1H-pyrazole distinctively blocked sodium channels and was strongly effective in the MES test Fig. (**4**).

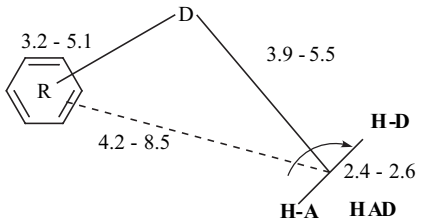

Fig. (2). Suggested pharmacophore model for anticonvulsants acting at the voltage-dependent sodium channel on the basis of molecular dynamics simulations using carbamazepine, phenytoin, lamotrigine, zonisamide, and rufinamide according to Unverferth *et al.* (1998). Distances in angstroms.

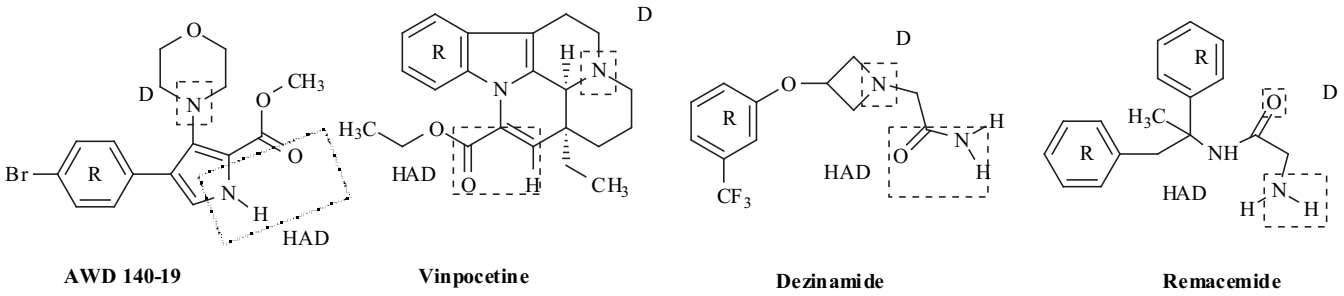

Fig. (3). Structure of four anticonvulsants from different structure classes fulfilling the demands of the general pharmacophore model of Fig. (**2**)

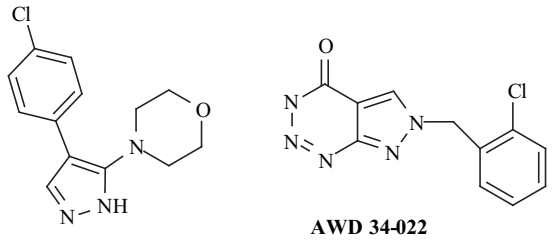

Fig. (4). Anticonvulsants acting at the voltage-dependent sodium channel.

The pyrazolotriazinones and pyrazolopyrimidinones which fit to the suggested pharmacophore are new examples for sodium channel blockers. Among them AWD 34-022 a novel drug for the treatment of epilepsy, structurally unrelated to the major drugs currently in the therapy, is now in preclinical study [18].

ANTICONVULSANTS WITH PHTHALIMIDE PHARMACOPHORE

The phthalimide pharmacophore was developed by Vameq *et al.* [19-21]. Phenytoin, carbamazepine, ameltolide and phthalimide derivatives have been taken as reference of pharmacomolecular models for rational anticonvulsant drug design [19]. Phenytoin and carbamazepine are effective against partial and generalized tonic seizures. They bind preferentially to the inactivated state of the sodium channel and exhibit both voltage- and use-dependence crucial to the clinical efficacy of these drugs, resulting in a remarkable selectivity for pathological burst firing of action potentials. Ameltolide exhibits a phenytoin-like profile in *in vivo* tests. Some investigations indicated that the antiepileptic activity of ameltolide was the result of its interaction with the neuronal voltage-dependent sodium channel [20]. *N*-Phenylphthalimide derivatives possessed a similar degree of anticonvulsant potency also associated with a phenytoin-like profile. The empiric design of the phthalimide pharmacophore were following. In a first approach, ameltolide was considered for assembling the various components of carbamazepine; the two phenyl rings, an amide bond and an NH_2 function. On a similar way the 4-amino-*N*-(2-methylphenyl)phthalimide was designed from phenytoin, see Fig. (**5**). In a second approach compounds corresponding a rigidified analogous of ameltolide were obtained. This design led to the development of a series of amino-*N*-phenylphthalimides and a series of *N*-(amino-phenyl) phthalimides i.e. retrophthalimide.

By analogy to the series of benzamides, the corresponding series of retrobenzamides were development Fig. (**6**). Some of the obtained retrobenzamides were shown

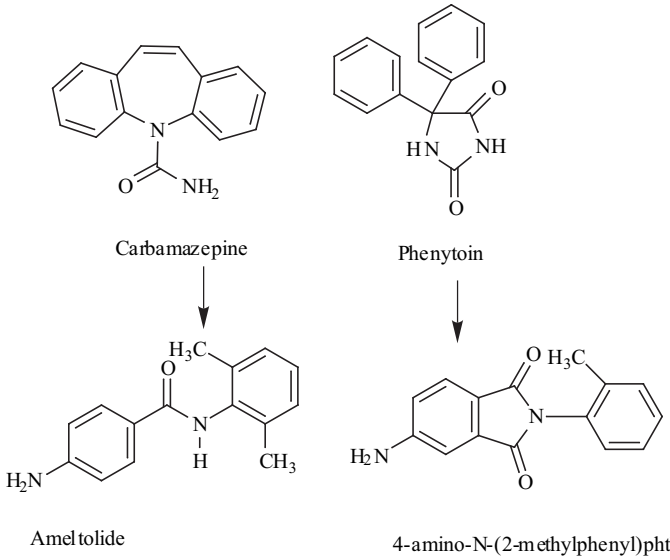

Fig. (5). Selected anticonvulsants used for the development of a pharmacophore model.

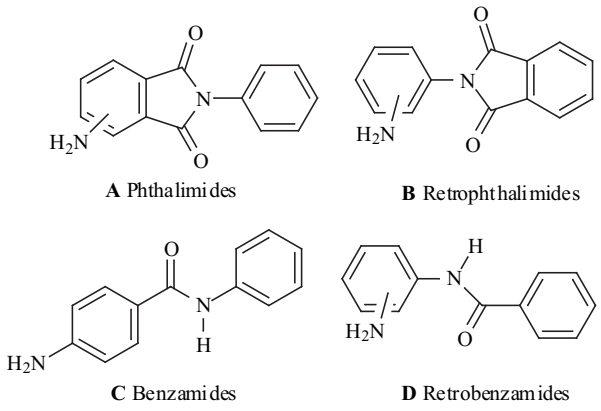

Fig. (6). Comparative formula of phthalimides [amino-*N*-phenylphthalimides] (A), retrophthalimides [*N*-(amino-phenyl)phthalimides] (B), benzamides [amino-*N*-phenyl-benzamides] (C), and retrobenzamides [N-(aminophenyl) benzamides] (D).

to possess a similar degree of anticonvulsant potency also associated with a phenytoin-like profile. Using the same procedure 4-amino-*N*-(2,6-dimethylphenyl)phthalimide was designed from ameltolide and thalidomide Fig. (**7**) [21]. In continuating substituted *N*-phenyl derivatives of the phthalimide pharmacophore without 4-amino substituent were investigated. The most active compound was 4-amino-2-chlorophenylphthalimide, Fig. (**8**), which acts on both seizure spread (inhibition of neuronal voltage-dependent sodium channels) and seizure threshold. It was stated that lowering of seizure threshold by this compound was mediated by interaction with both the GABAergic (potentiation effect) and glutamatergic (inhibition effect) pathways. Therefore, 4-amino-2-chlorophenylphthalimide is new potential antiepileptic drug, which enters adequately the current strategy devoted to treating pharmacoresistant epilepsies and reducing epilepsy-related CNS surgery indications.

PHARMACOPHORE MODEL FOR ANTICONVULSANT SEMICARBAZONES AND RELATED COMPOUNDS

Dimmock *et al.* [22-24] investigated series of aryl semicarbazones, which displayed anticonvulsant activity in

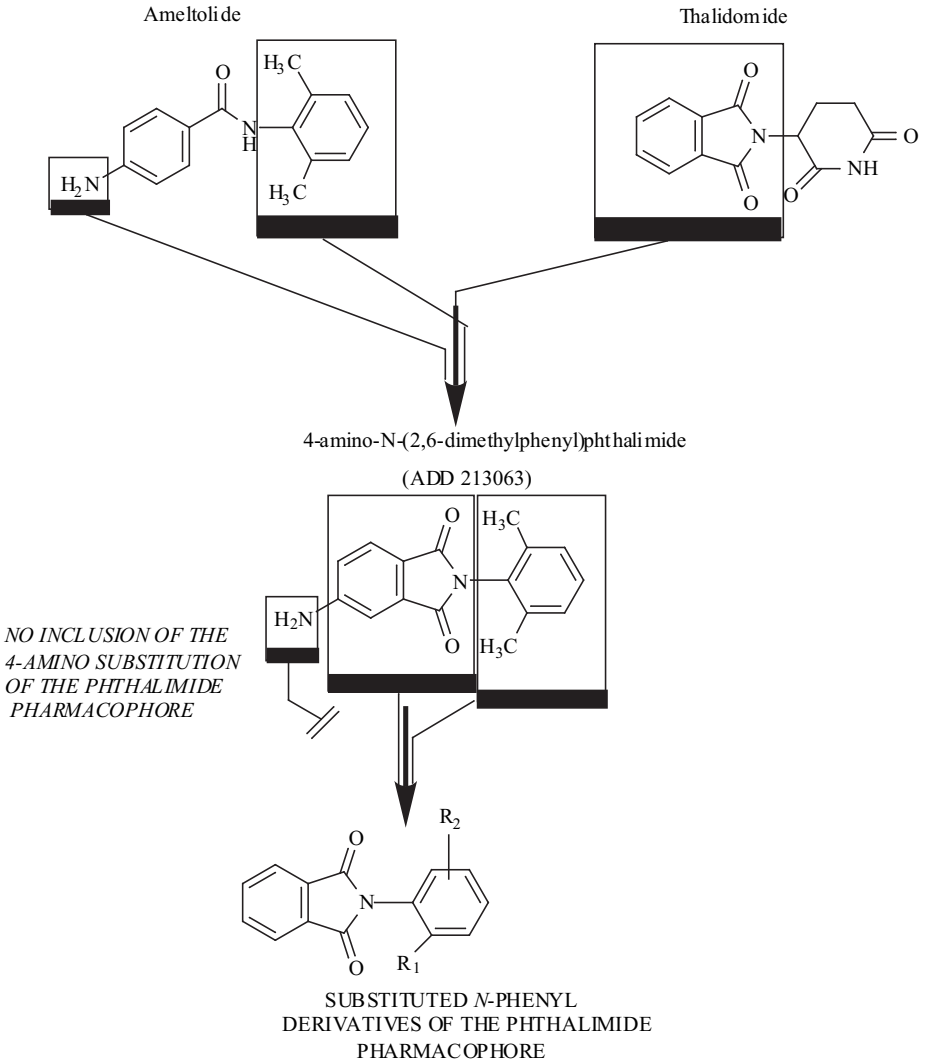

Fig. (7). Anticonvulsant compounds designed from ameltolide and thalidomide.

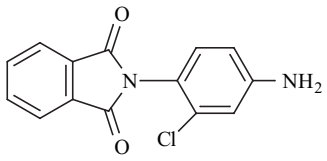

Fig. (8). Compound related to the *N*-phenyl substituent of the phthalimide pharmacophore.

the MES screen. Analysis of the structure-activity relationship led to the definition of a specific binding side; these possible interactions are presented in Fig. (**9**). It was proposed that the semicarbazone group and the aryl ring align at complementary areas on a macromolecular complex *in vivo*; these areas have been referred to as the hydrogen bonding area and the aryl binding site, respectively. Further investigations were conducted for different series of (aryloxy)aryl semicarbazones and related compounds, which displayed significant potencies in the MES screen, accompanied by a very high protection indices. For these (aryloxy)aryl semicarbazones a binding site was proposed using structure-activity relationships (from both a qualitative

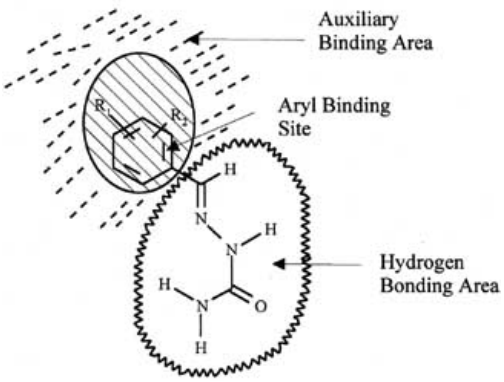

Fig. (9). Proposed binding site of aryl semicarbazones according to Dimmock *et al.* [24].

and quantitative view-point) and X-ray crystallography Fig. (**10**) [24]. Three dimensional measurements were employed for the examination of the shapes of five semicarbazones.

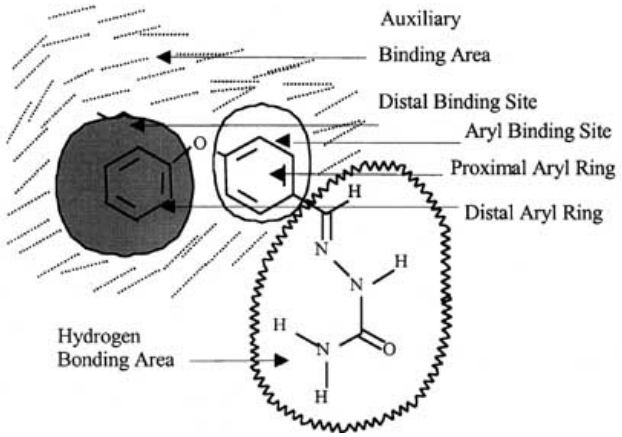

Fig. (10). Proposed binding site of (aryloxy)aryl semicarbazones [24].

Results were obtained for four compounds which displayed anticonvulsant activity in *in vivo* tests and one semicarbazone which was very weakly active or inactive in these tests. The X-ray data showed that in the crystal state the proximal ring occupies a similar position in all five compounds, however, the distal aryl rings were found in three distinct locations. The proximal rings were nearly coplanar with the ureido group. These data indicated that the distal aryl ring occupied different positions at the distal binding site and that certain interatomic distances and bond angles affected potency.

This model was validated by synthesis of a number of novel aryl, arylidene and aryloxyaryl semicarbazones [25]. The most active compounds were a series of aryloxyaryl semicarbazones which had oral activity in the MES screen substantially greater than phenytoin and with protection indices of over 100. The proposed interaction of a representative compound at the binding site is shown in Fig. (**11**). For examination of this hypothesis, and to quantify the positions of the proximal and distal rings in relation to the ureido group, the measurements by X-ray crystallography of selected molecules was obtained [25]. The obtaining results indicated that the attachment of the distal ring to the proximal aryl ring increased the van der Waals bonding at the binding site and increased anticonvulsant potency of the investigated aryloxyaryl semicarbazones.

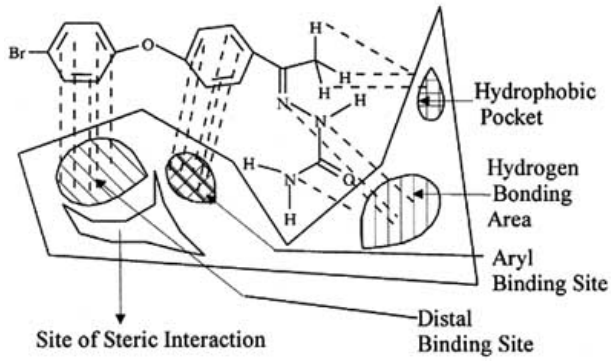

Fig. (11). The proposed interaction of a representative compound at the binding site of anticonvulsant semicarbazones [25].

For further evaluating the binding site hypothesis various acetylhydrazones, oxamoylhydrazones and semicarbazones were prepared [26]. The biological results obtained revealed that in general the acetylhydrazones and semicarbazones afforded good protection against convulsions while the oxamoylhydrazones were significantly less active. Atomic charge calculations were undertaken to determine the hydrogen bonding capacities of various molecules. The obtaining results supported the hypothesis that terminal electron-donating groups enhanced the hydrogen bonding capabilities and anticonvulsant properties of these molecules. The biodata generated suggested that the hydrophobic bonding area could accommodate groups other than aryl rings.

These results from previous studies of Dimmock's led to the postulate that a number of anticonvulsants aryl semicarbazones interacted at both a hydrophobic and a

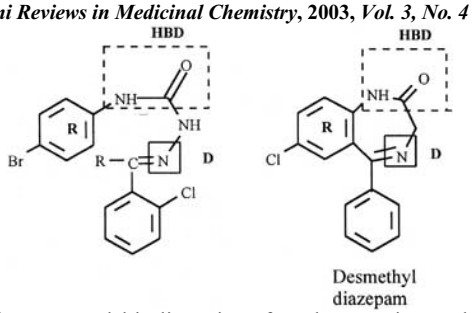

Fig. (12). Proposed binding site of urylene anticonvulsant [27].

hydrogen bonding areas on a specific binding site. These two parts of binding site might be simply referred to as areas A and B, respectively, (Fig. **12**). The presence of a carbimino group (C=N) in semicarbazones might effected toxicity and acid lability, therefore some related ureylenes analogues were investigated [27]. A new binding site hypothesis of ureylene anticonvulsants was proposed, see Fig.**12**. It was suggested that the anti-MES activity of a series of ureylene derivatives was mediated by interaction at a binding site consisting of two or possibly three contiguous areas. The locations A and C are considered to be hydrophobic binding areas and B is the hydrogen bonding site. Several compounds including $C_6H_5CH(CH_3)$-NH-CO-NH-$(CH_2)_2CH_3$ serve as prototypic molecules for subsequent molecular modification in the search for novel anticonvulsants.

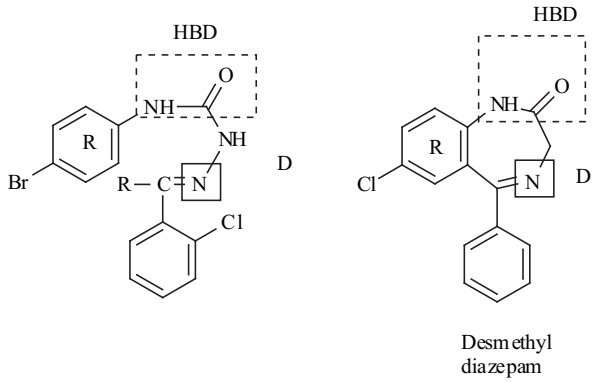

Fig. (13). Development of a pharmacophore model for aryl semicarbazones. **R**-hydrophobic unit; **HBD**-hydrogen bonding domain; **D**-electron donor.

Pandeya *et al.* [28] obtained a series of 4-bromophenyl-substituted aryl semicarbazones. The 4-bromophenyl group has been attached at the terminal amino function of the semicarbazone in contrast to compounds synthesised by Dimmock [25] with a free terminal amino function. These compounds displayed anticonvulsant activity in *in vivo* tests, such as MES, scPTZ and subcutaneous strychnine (scSTY). Their chemical features which contribute to interactions at the binding site were established as a lipophilic moiety R (4-bromophenyl ring) and a hydrogen bonding domain HBD (amide function, NHCO) and an electron donor D. The 4-bromophenyl semicarbazones largely resembled to the standard anticonvulsants such as phenytoin, carbamazepine and desmethyldiazepam. The pharmacophore model of these aryl semicarbazones is presented in Fig. (**13**). Comparing the structure of 4-bromophenyl semicarbazones and desmethyl diazepam it was stated that these semicarbazones could emerge as bioisosteres of desmethyl diazepam (CH_2 replaced with NH). It was also suggested, that the distal aryl ring at the carbimino terminal (benzylidene ring) might be essential for the pharmacokinetic properties of the compounds because the various modifications in the substituents at the distal aryl ring was found to affect the biological activity. The SAR results indicated that the terminal amino function of the semicarbazone was not essential for activity and could be substituted with a lipophilic aryl ring. These new aspects might be useful for designing prototypic molecules with potential anticonvulsant activity.

A MODEL OF THE GABA UPTAKE INHIBITOR MODE

Tiagabine is a clinically effective antiepileptic drug, which acts by potentiation of GABAergic transmission through inhibition of the GABA transporter type 1 (GAT-1) and consequent inhibition of synaptic GABA reuptake. This drug, which has a unique mechanism of action among marketed anticonvulsant agents, has been launched for add-on treatment of partial seizures with or without secondary generalization [3, 29]. Other cyclic amino acid derivatives (Cl-966, SKF 89976A) which act via inhibition of the uptake of GABA in the CNS have been investigated in human clinical trials Fig. (**14**) [29-32]. A putative model of the ligand interaction at GABA uptake site GAT-1, based on the structures of know potent inhibitors has been elaborated. This new model postulated the presence of a positively charged domain in the protein structure of the site controlling the GABA transporter type 1 (GAT-1). It was suggested that this domain interacted with an electronegative moiety which is part of the linker, Fig. (**15**), in the potent CNS-active compounds comprising cyclic amino acids *N*-substituted *via* this linker by two aromatic functions. Using this model several novel GABA uptake inhibitors were synthesised [31-33]. These compounds were derivatives of nipecotic acid, guvacine, and homo-beta-proline,

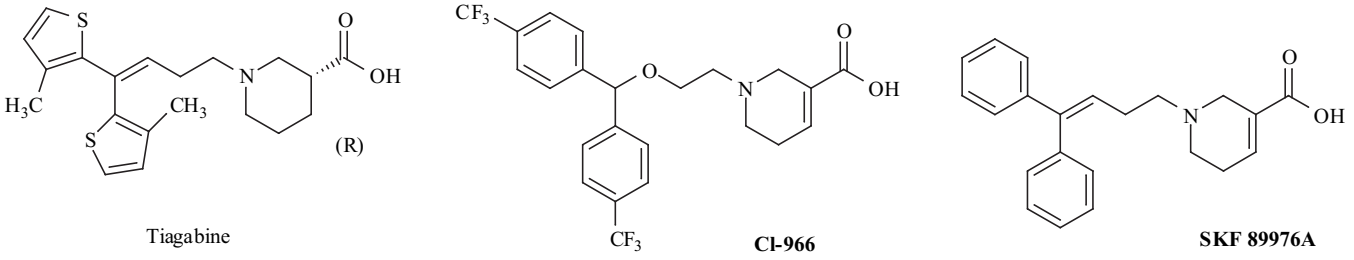

Fig. (14). Structures of the main reference GABA uptake inhibitors.

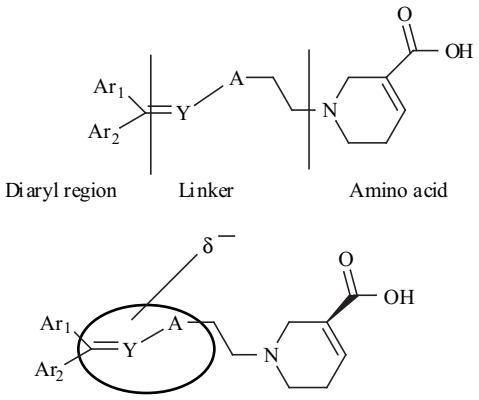

Fig. (15). A model of the GABA uptake inhibitor pharmacophore proposed by Knutsen *et al.*[31].

substituted at the nitrogen of these amino acids by various lipophilic moieties such as diarylaminoalkoxyalkyl, diarylalkoxyalkyl. The obtained compounds were potent as GABA uptake inhibitors *in vitro*. It was found that several of the novel compounds showed a high potency comparable with that of the reference compounds SKF 89976A, Cl-966 and tiagabine. Structure-activity results confirmed, that an electronegative centre in the chain connecting the amino acid and diaryl moiety was very critical in order to obtain high potency *in vitro*. It was also indicated that a five-atom linker was the optimum linker length. The novel GABA uptake inhibitors demonstrated potent anticonvulsant properties *in vivo*, and showed a protective index comparable to or slightly better than that at the recently launched anticonvulsant, tiagabine. The structure of these compounds are presented in Fig. (**16**). These highly potent GABA uptake inhibitors may have potential in the treatment of epilepsy in humans.

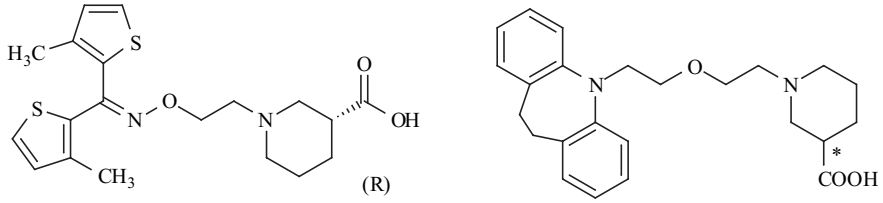

Fig. (16). Anticonvulsants obtained according to the prahmacophore model of the GABA uptake inhibitor.

SUMMARY

A number of physicochemical determinations and molecular modelling studies indicated a variety of structural features which are believed to contribute to anticonvulsant activity. From these data, ideas for future molecular modifications leading to compounds with improved pharmacological properties may be derived.

The chemical diversity and various mechanisms of action of anticonvulsants make it difficult to identify a common pharmacophore. The present review outlines different pharmacophore models for anticonvulsant activity with emphasis on the development of new drugs. Some of them represent models for structurally different classes of compounds with similar mechanisms of action i.e., pharmacophore model for sodium channel blocking compounds, and a model for GABA uptake inhibitors. Others represent pharmacophore models for similar chemical classes of compounds for which the mechanism of anticonvulsant action is not clear such as anticonvulsants with the phthalimide pharmacophore, a model for anticonvulsant semicarbazones and related compounds. Pharmacophore models are useful for design prototypic molecules, lead structure and also for explanation a possibly interactions of an identified binding site.

ABBREVIATIONS

GABA = γ-Aminobutyric acid

AEDs = Antiepileptic drugs

MES = Maximal electroshock

scPTZ = Subcutaneous pentylenetetrazole

scSTY = Subcutaneous strychnine

GAT-1 = GABA transporter type 1

CNS = Central nervous system

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