New Anticonvulsant Agents

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Abstract: The search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of intensive investigation in medicinal chemistry. This review describes new anticonvulsant agents representing various structures for which the precise mechanism of action is still not known. Many of the compounds presented in this review have been tested according to the procedure established by the Antiepileptic Drug Development Program of the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke, National Institute of Health, USA. The newer agents include sulfonamides, amino acids, amides (analogs of γ-vinyl GABA, N-benzylamides, 2,6-dimethylamilides, carboxyamides, hydroxyamides, alkanoamides); heterocyclic agents (arylalkyl)imidazoles, pyrrolidin-2,5-diones, lactams, semi-thiosemicarbazones, thiadiazoles, quinazolin-4(3H)-ones, 2,5-disubstituted 1,2,4-thiadiazoles, xanthones, derivatives of isatin) and enaminones. 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,

INTRODUCTION

Epilepsy is a common neurological condition, affecting 0.5 to 1% of the population worldwide (45-100 million people) [1]. Conventional antiepileptic drugs (AEDs) phenobarbital, primidone, phenytoin, carbamazepine, 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 drugs (oxcarbazepine, lamotrigine, topiramate, gabapentin, zonisamide, tiagabine, fosphenytoin, vigabatrin and felbamate) have been added to the list of therapeutic agents against epilepsy. 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 [2-6]. Hence, there is an urgent need to develop new AEDs [7].

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 [8, 9]. 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. AEDs belong to many different chemical classes of compounds, including: hydantoines, iminostilbenes, barbiturates, benzodiazepines, valproate, imides, oxazolidine-2,3-diones, sulfonamides and miscellaneous agents [10]. The efficacy of AEDs is due to the main activities which include interaction with ion channels or neurotransmitter systems [11-17]. Currently available AEDs can be broadly classified into four categories: (1) those whose main action relates to the inhibition of sustained repetitive firing, through blockage of voltage-dependent sodium channels and consequent inhibition of the release of excitatory neurotransmitters (phenytoin, carbamazepine, oxcarbazepine); (2) those which enhance GABA-ergic transmission (benzodiazepines, barbiturates, vigabatrin, tiagabine); (3) those stabilizing thalamic neurons through inhibition of T-type calcium channels (ethosuximide) and (4) those possessing a combination of the above actions, often coupled with additional mechanisms (valproic acid, gabapentin, lamotrigine, topiramate, zonisamide, felbamate). However, this classification has limited value because the majority of AEDs possess more than one mechanism of action, which may account for their efficacy, and it is also the fact that some of the clinically used drugs have not been linked with a specific site the brain, and the exact mechanisms of many AEDs remain unknown [18,19].

The new AEDs and anticonvulsant agents have been reviewed during last few years [20-24]. 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 rather than a mechanism-driven design. Therefore, drug identification is usually conducted via in vivo screening tests, on the basis of seizure type rather than etiology.

This review presents new anticonvulsant agents representing various structures for which the precise mechanism of action is still not known. The newer agents include heterocyclic compounds, sulfonamides, amino acids, amides, enaminones and others. These new structural classes of compounds can be useful for the design of future targets and development of new drugs.
THE ANTICONVULSANT SCREENING PROJECT (ASP)

Many of the compounds presented in this review have been tested according to the procedure established by the Antiepileptic Drug Development (ADD) Program [25, 26]. Since 1975, the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke, National Institute of Health, through its Antiepileptic Drug Development (ADD) Program, has collaborated with the pharmaceutical industry in developing new therapeutic agents for the treatment of seizure disorders. In 1993 felbamate, the first new drug in nearly two decades, was approved for sale in the United States. Felbamate’s development was a collaborative effort of both a pharmaceutical sponsor and the ADD Program. Two other drugs, topiramate and remacemide have been identified in the Branch’s preclinical evaluation and are now in late clinical development. Several other drugs, losigamone, retigabine, soretolide and rufinamide (Fig. I) are now in early clinical development [27-29]. The ADD Program boasts of both preclinical and clinical trial components. The preclinical component consists of drug discovery and toxicology elements. The Anticonvulsant Screening Project uses for its initial screening procedure two major convulsant tests: maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) as well as a toxicity screen (rotorod in mice, positional sense and gait in rats). The MES is a model for generalized tonic-clonic seizures. The behavioral and electrographic seizures generated in this model are consistent with the human disorder [30]. This model identifies those compounds which prevent the spread of seizures. The scPTZ seizure test is a model which primarily identifies compounds that raise seizure threshold. The behavioral seizure produced is not typical of absence epilepsy but clonic in nature. Like other rodent models of absence seizures, PTZ-induced seizures are potentiated by γ-aminobutyric acid (GABA) agonist. With some minor exceptions, the pharmacological profile of the scPTZ seizure model is consistent with the human condition [30, 31]. All clinically active anticonvulsants have been found to be protective in at least one of these two tests.

Compounds that possess significant anticonvulsant activity in rats and in mice and do not exhibit substantial neurotoxicity or lethality are considered for the ADD Program’s multiphase evaluation to establish a compound’s pharmacodynamic/pharmacokinetic profile. During the past five years, over 4000 compounds have been evaluated by the ADD Program. Selected results of these evaluations have been published and are presented in this review.

NEW ANTICONVULSANT AGENTS: STRUCTURE – ACTIVITY – RELATIONSHIPS

Heterocyclic Analogs of Carabersat

Carabersat (SB-204269) was originally designed by modifying the structure of cromakalim (Fig. 2). This later drug represents a class of antihypertensive agents which act via the relaxation of vascular smooth muscle caused by the opening of ATP-sensitive potassium channels. The potassium channel activators which more readily penetrate the central nervous system (CNS) may have therapeutic potential in the treatment of epilepsy [11]. Replacement of the 2-pyrrolidinone group of cromakalim by the fluoro-benzoylamino group has introduced anticonvulsant activity [32]. Carabersat, the benzopyran derivative, is a chemically novel AED with a novel mechanism of action and a stereospecific CNS binding site. It has potent oral anticonvulsant properties in a range of rat seizure models, with potency and efficacy equivalent to or better than carbamazepine and lamotrigine. Carabersat is currently being proposed for the treatment of epilepsy and migraine prophylaxis [33, 34]. Subsequent exploration of structure-activity-relationships, using high-throughput screening of the novel SB-204269 binding site led to the identification of anticonvulsant active series of the isomeric tetrahydro-isoquinolinyl (THIQ) benzamides 5-, 7- and 8-substituted [35, 36]. Compound SB-270664, the 7-substituted THIQ was
reported as a promising key lead compound with high affinity at the [\(^{3}H\)]-SB-204269 binding site (pK\(_A\), 8.9), but was later found to have poor pharmacokinetic properties. The major routes of metabolism of this compound were hydroxylation of the THIQ benzo ring, N-demethylation and aromatization to the isoquinolinium species. Starting from a series of 7-linked THIQ derivatives, a new series of 8,8-dimethylthiophenidine compounds has been identified (Fig. 3). In this series a gem dimethyl group is incorporated to prevent aromatization, and replacement of the THIQ benzo ring with piretdyl represents an attempt to reduce hydroxylation. In this new series, compound I was identified as new potential agent displaying excellent anticonvulsant activity and an encouraging pharmacokinetic profile in vivo. Compound I has high affinity at the [\(^{3}H\)]-SB-204269 binding site (pK\(_A\), 8.7), suggesting a novel mechanism of action, comparable with carbarsat. In vivo, the rat maximal electroshock threshold (MEST) test at 2 mg kg\(^{-1}\) p.o. compound I showed a good level of anticonvulsant activity. In the rat supraMES model, analysis by ‘ALLFIT’-quu compound I produced an ED\(_{50}\) value of 3.9 mg kg\(^{-1}\). This figure is comparable with that obtained with carbarsat in the same model under identical conditions (ED\(_{50}\) of 6.3 mg kg\(^{-1}\)). Compound I has excellent aqueous solubility (>1 mg mL\(^{-1}\)) and has been shown to have an encouraging pharmacokinetic profile and good in vivo activity in preclinical anticonvulsant models in rats [37].

![Fig. (3). Heterocyclic analog of carbarsat.](image)

### Sulfonamides

Acetazolamide (N-(5-aminosulfonyl)-1,3,4-thiadiazol-2-yl acetamide) and methazolamide are old members of this class, which have shown anticonvulsant activity (Fig. 4). These drugs are bifunctional 5-membered heterocycles, comprised of a sulfonamide and an amide as well as a 1,3,4-thiazole nucleus, constituting potent carbonic anhydrase (CA) inhibitors. Several new sulfonamide CA inhibitors such as topiramate and zonisamide have been and are still used as antiepileptic drugs (Fig. 4). The anticonvulsant effects of these or related sulfonamides are probably due to CO\(_{2}\) retention secondary to the inhibition of red cell and brain enzymes, but other mechanisms of action, such as blockade of sodium channels and kainite/AMPA receptors, as well as enhancement of GABA-ergic transmission, have also been hypothesized/proven for some of these drugs. Acetazolamide and methazolamide are still clinically used nowadays in some forms of epilepsy, but they are considered to belong to a minor class of antiepileptic agents. The recently developed drug topiramate is a very effective antiepileptic, and it also acts as a strong CA inhibitor with a potency similar to that of acetazolamide against the physiologically important isoenzyme CA II [38-40]. Acetazolamide, topiramate and zonisamide possess a sulfamate moiety, which is essential for their anhydrase inhibition. Several new carbonic anhydrase inhibitors derivatives of sulfonamide have been developed by Scozzafava, Supuran and coworkers [41-46]. A series of aromatic/heteroaromatic sulfonamides incorporating valproyl and other lipophylic moieties has been found to possess potent CA inhibitory properties as well as anticonvulsant in vivo effects. The hybide compound, valproyl derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide, 2) was one of the best hCA I and hCA II (human cloned isoenzymes) inhibitors in the series and it exhibited very strong anticonvulsant properties in the MES test in mice [45]. Inhibition data of carbonic anhydrase 

\[ K_i (nM) \] hCA I and hCA II are as follows: for topiramate 250, 5; for compound 2 56, 6. Both drugs efficiently protected mice against seizures induced by electroshock at a dosage of 30 mg kg\(^{-1}\); the protection rate was 75-100% at 0.5 h and 25-100% at 3 h after drug administration. Investigation at a decreased dosage of 10 mg kg\(^{-1}\) of compound 2 showed a rate of protection in the range of 25-44% at 0.5 h and 87-100% at 3 h after administration. Several other 1,3,4thiadiazole-sulfonamide derivatives possessing potent CA inhibitory properties and substituted with various alkyl/arylcaboxamido/sulfonamide/ureido moieties in the 5-position have been investigated for their anticonvulsant effects in the same animal model. It was observed that some lipophilic derivatives, such as 5-benzoxylamido-, 5-toluensulfonlamido-, 5-adamantylcarboxamido-, and 5-pivaloylamido1,3,4-thiadiazole-2-sulfonamide, show promising in vivo anticonvulsant properties and that these compounds may be considered as interesting leads for...
of this moiety led to reduced activity. Furthermore, when the acetamido (CH$_3$C(O)NH) unit in 5 was replaced with methyl, methoxy, hydroxyl, acetoxy, or halogen, the obtained compounds exhibited diminished anticonvulsant activity. Structural modifications also included replacing the C(2) unit with the corresponding N(2) group giving the structurally-related semicarbazide derivatives 6 [57]. Evaluation of aza analogues 6 of functionalized amino acids in both mice (i.p.) and rats (p.o.) showed that the compounds exhibited significant anticonvulsant activities but in most cases at levels lower than their amino acid counterparts. Comparison of a selected series of semicarbazides 6 with their FAA counterparts 5 showed that replacing the tetrahedral C(2) carbon in 5 with a trivalent N led to a reduction in pharmacological activity in most cases upon administration to mice (i.p.). It was found that oral administration of the N(2)-substituted semicarbazides to rats led to improved anticonvulsant activities. Of the investigated compounds, 1-acetyl-4-benzyl-2-(thiazol-2-yl)-semicarbazide 11 displayed moderate-excellent activity in mice (MES i.p. $ED_{50} = 22$ mg kg$^{-1}$, $PI = 5.4$) and excellent activity in rats (MES p.o. $ED_{50} = 6.2$ mg kg$^{-1}$, Tox $TD_{50} > 250$) which exceeded that of phenytoin (Table 1).

Conformationally restricted analogues of anticonvulsant functionalized amino acids have also been investigated [56]. Four peptidomimetic compounds of parent FAA 9 such as 1,5-disubstituted tetrazole 12, 3-substituted 1-benzyl-pyrrolidin-2-one 13, proline 14, and (thio)hydantoins 15, 16 as well as peptidomimetic FAA derivatives have been evaluated (Fig. 7). No improvement in pharmacological activity was observed upon conformational constraint, however new important information on the SAR of FAAs was obtained. It was shown that FAAs(1)-alkylation did not reduce anticonvulsant activity while N(3)-alkylation led to appreciable activity loss. These studies also revealed that derivatives of hydantoin 15 and thiohydantoin 16, upon p.o.

Derivatives of Amino Acids

Amino acids that are functionalized at both the $N$- and C-terminal are proven potent anticonvulsant agents [47-72]. In the recent years, Kohn and coworkers have reported on the anticonvulsant activity of a series of functionalized amino acids [47-61] (FAA) 5 (Fig. 6). A structure activity relationships study of over 250 compounds has yielded 12 compounds with anticonvulsant activity in rodents that is equal to or greater than phenytoin according to the MES-seizure test. $N$-Benzy1-2-acetamidopropionamide 9 was the parent compound in this series [55]. These investigations have enabled the selection of $(R)$-$N$-benzyl-2-acetamido-3-methoxy-propionamide 10 as the lead compound (Table 1). Compound 10 has now entered phase II clinical trials for the treatment of epilepsy and neuropatic pain. Extensive SAR study of FAA 5 revealed that the $N$-terminus is an important FAA structural unit. In the initial design of FAA, the $N$-terminal amine was protected as an amide to provide compounds with increased lipophilicity. Subsequent studies demonstrated the importance of the acetamido unit ($R_1 = C(O)CH_3$) for potent anticonvulsant activity and showed that either a decrease (i.e., $R_1 = C(O)H$) or increases (i.e., $R_1 = C(O)CH_2CH_3$, $C(O)(H)CH_2$, $C(O)CCH_3$) in the size...
administration, respectively, displayed activity comparable with phenytoin in the MES-seizure test in rats. The ED\textsubscript{50} value for compound 15 in rats (p.o.) was 27 mg kg\textsuperscript{-1}, while compound 16 protected half of the rats tested at 40 mg. After i.p. administration of compound 16 in rats, the ED\textsubscript{50} value was impressive, at 12 mg kg\textsuperscript{-1} in the MES-seizure test. Both compounds possessed moderate-to-good activity in the scPTZ-seizure test in mice. The most active compound was 16 (ED\textsubscript{50} = 46 mg kg\textsuperscript{-1}, PI = 2.5). These findings contrasted with the lack of scPTZ-activity exhibited by FAA analogues 9, 10 and phenytoin. It was concluded, that FAAs and their monosubstituted hydantoin analogues exhibited different anticonvulsant profiles. The activities of compounds 9, 10 and 15 in the voltage-sensitive Na\textsuperscript{+} channel test using patch-clamp electrophysiology techniques were tested. Hydantoin 15 exhibited significant voltage-dependant blockade of Na\textsuperscript{+} channels (35% blockage at -60mV), while the two FAAs (9 and (R)-10) had no significant effect on peak current at 100 μM. Two prototypical antiepileptic Na\textsuperscript{+} channel blockers, phenytoin and lamotrigine, provided 48 and 53 % blockage at -60mV, respectively. These findings indicate that 15 expresses its anticonvulsant activity in part by acting on the Na\textsuperscript{+} channel. The divergent SAR and the different electrophysiological findings for (thio)hydantoins and FAAs provided evidence that these two classes of compounds function by different mechanisms.

Replacing the N-terminal amide group in FAA with phenylethyl, styryl, and phenylethynyl units provided a series of functionalized amido ketones (FAK) 7 [60] (Fig. 8). It was determined that FAK exhibit excellent anticonvulsant activities that approach those observed for their FAA

| Compound | Mice (i.p.)* | Rat (p.o.) |
|----------|-------------|------------|
|          | MES, ED\textsubscript{50} | PI | MES, ED\textsubscript{50} | PI |
| 9        | 77 [1]      | 5.9       | 48 [1]      | >20 |
| (R)-10   | 8.3 [0.5]   | 5.2       | 3.8 [0.5]   | 100 |
| 11       | 22 [0.25]   | 5.4       | 6.2 [0.5]   | >40 |
| phenytoin| 9.5 [2]     | 6.9       | 30 [4]      | >100|
| phenobarbital | 22 [1] | 3.2 | 9.1 [5] | 6.7 |

\textsuperscript{*}ED\textsubscript{50} and TD\textsubscript{50} values are in mg kg\textsuperscript{-1}. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the “time of peak effect” (indicated in h in the square brackets).

Fig. (7). Conformationally restricted analogs of anticonvulsant functionalized amino acids (FAAs).
counterparts in rats. The saturated FAK 17-19 displayed a comparable activity pattern when administered to rats (p.o.). The ED$_{50}$ values for 17, 18, and 19 were 47, 23, and 18 mg kg$^{-1}$ respectively. The ED$_{50}$ values for 18 and 19 compared favorably with phenytoin (ED$_{50}$ = 30 mg kg$^{-1}$) and phenobarbital (ED$_{50}$ = 9.1 mg kg$^{-1}$), and both 18 and 19 exhibited PI values that exceeded 14. The favorable activities for FAK have been attributed to the incorporation of key R structural units within the FAK backbone and conformation of the terminal ketone unit.

Conversion of the acetamido unit in 5 to an amino moiety provided amino acid amides (AAA, 8) that are likely to have increased water solubility compared with their FAA 5 counterparts [61]. It was demonstrated that AAA 8 are potent anticonvulsants, and that the terminal amino group is prone to metabolic change. Among the investigated compounds, 20 displayed in MES test (i.p. mice) a protection level of ED$_{50}$ = 36 mg kg$^{-1}$, PI = 2.0. (p.o. rats) ED$_{50}$ = 7.1 mg kg$^{-1}$, PI = 33. The AAA anticonvulsant activity was neither strongly influenced by the C(2) substituent nor by the degree of terminal amine substitution (Fig. 9). The mechanism of action of FAA remains elusive.

![Fig. (8). Funcionalized amido ketones (FAK).](image)

![Fig. (9). Structure of N-substituted amino acid N-benzylamide (AAA).](image)

Some amino acid derivatives have also been studied by Paruszewski and coworkers [62-67]. Amides of N-substituted natural and anatural amino acids containing benzylamide, 4-fluorobenzylamide, 4-methoxybenzylamide, 2-furfurylamine, phenylethylamide, 3-pirydylmethylamide, butylamide, isobuthylamide, usoamylamide moiety as well as esters have been synthesized and evaluated according to the procedure of the ASP of NINDS. Among the tested compounds, benzylamide derivatives of β-Ala (21, 22), Ac-D-Pro-BZA (23) and (R,S)-Me-Tzl-BZA (24) were the most active. They exhibited (in MES test after i.p. administration in mice), a significant protective index (PI) of 3.2 for 21 (ED$_{50}$ = 31.17 mg kg$^{-1}$) and 4.3 for 22 (ED$_{50}$ = 53.47 mg kg$^{-1}$) and, following oral administration in rats, PI>18 with ED$_{50}$ = 27.33 mg kg$^{-1}$ for 21 and >14 with ED$_{50}$ = 34.05 mg kg$^{-1}$ for 22. Benzylamide 23 protected against MES and scPTZ seizure in mice after i.p. administration with ED$_{50}$ = 64.41 mg kg$^{-1}$ (MES) and ED$_{50}$ = 183.78 mg kg$^{-1}$ with PI = 4.5 (scPTZ). The benzylamide of N-methyl-thiazolidine-4-carboxylic acid 24 was active in MES seizure after i.p. administration in mice with ED$_{50}$ = 29.05 mg kg$^{-1}$ and PI = 3.77. Recent studies have demonstrated that some picoline and nicotinic acid benzylamides substituted on the phenyl ring also possess anticonvulsant properties [65-67]. Of these, the most active was the picolinic acid fluorobenzylamide (Pic-FBZA 25). ED$_{50}$ of the most effective amide 25 was 14.7 mg kg$^{-1}$ (MES), >50 mg kg$^{-1}$ (scPTZ) and PI < 3.4 against MES (rats, i.p.) [66].

SAR studies of alanine derivatives suggested that the structure of this amino acid, especially of fragment N-$\alpha$-C$_{\alpha}$-C$_{\alpha}$, is responsible for its action [62]. It was also found that with an $\alpha$-amino acid structure, and N-acyl- or N-alkyl group, a small substituent at C-$\alpha$ or an aromatic amide substituent appear to be the most useful for anticonvulsant activity [64]. The importance of the benzylamide group of anticonvulsant active amino acids was confirmed both by Kohn’s and Paruszewski’s research groups.

Derivatives of arylidene imidazoline-4-one amino acids were investigated by Kiec-Kononowicz and Karolak-Wojciechowska [68-71]. Several series of arylidene(aryl)-imidazolidyno-4-one derivatives incorporating glycine, modified glycine or $\alpha$-alanine and modified $\alpha$-alanine were studied as a new ligand for the glycine-NMDA binding site (iGluRs) as well as anticonvulsant agents. Selected amino acid derivatives (26-29) presented in Fig. 10 displayed anticonvulsant activity in MES seizure tests at a dosage of 100 mg kg$^{-1}$ or less.

![Fig. (10). Arylidene-imidazoline-4-one aminoacids.](image)
**AMIDES**

**Analogs of γ-vinyl GABA**

Vigabatrin (γ-vinyl GABA) is being proposed as an anticonvulsant agent with a mechanism reportedly based on an inhibitor of GABA aminotransferase [17]. Lee and coworkers have developed several analogs of vigabatrin as potential dual acting prodrugs which were covalently coupled with an amide bond of vigabatrin and GABA mimetic substances such as GABA, γ-vinyl GABA, valproic acid, isonipecotic acid, nipecotic acid and 2-pyrrolidinone [73, 74]. Most of these compounds have shown moderate anticonvulsant activities. Among them, compounds 30 and 31 displayed the most potent anticonvulsive activity and a broader spectrum when compared to vigabatrin (Fig. 11). Compounds 30 and 31 were active against MES (ED50 = 0.64, 0.76), scPTZ (ED50 = 0.58, 0.40), BIC (ED50 = 0.47, 0.34) and PCR (ED50 = 0.47, 0.49 mmol kg⁻¹) seizure tests respectively.

![Fig. (11). Analogs of γ-vinyl GABA.](image)

**N-Benzylamides of γ-hydroxybutyric Acid**

Derivatives of α-substituted γ-amino-, γ-phthalimido-, γ-acetoxy- and γ-hydroxy butyric acid, such as acids, esters and amides, have been investigated as new potent anticonvulants [75-84]. It has been shown that α-substitutes N-benzylamides of γ-hydroxybutyric acid (GHB) are the most potent compounds in this group, possessing anticonvulsant activities in MES (i.p. in mice) screens. The most potent anticonvulsants were α-(benzylamino)-γ-hydroxybutyric acid N-benzylamide 32 and N-(2-chlorobenzylamide) 33 (Fig. 12); their ED50 being respectively 63.0 and 54.0 mg kg⁻¹. In the MES screen, these compounds were less active than the commonly used anticonvulsants carbamazepine and phenytoin, but possessed higher activity than the commonly used anticonvulsants carbamazepine and phenytoin, but possessed higher activity than sodium valproate [79]. Biochemical tests have indicated that the active amides act as allosteric modulators of the γ-aminobutyric acid, GABA_A complex, and have an affinity to voltage-sensitive calcium channel receptors. N-(4-methylbenzyl)amide of α-(4-phenylpiperazin-1-yl)-γ-hydroxybutyric acid 34 displayed the binding of [35S] TBPS ([35S] tert-buthylbicyclophosphorothionate) to the chloride channel of the GABA_A receptor complex (IC50 = 95 μM) [80]. This may be the possible mechanism mediating the anticonvulsant effect of these compounds. The results of pharmacological in vivo experiments with the γ-hydroxybutyric acid amide analogues 32 and 33 have shown that the compounds possess variable influence on the CNS in mice [81].

![Fig. (12). α-Substituted N-benzylamides of γ-hydroxybutyric acid.](image)

SAR studies have enabled the definition of structural elements responsible for the anticonvulsant activity of these several series of compounds [83, 84]. These features are as follows: the presence of the N-benzylamide fragment, a hydrophobic unit (aryl ring) as a distal binding site and a group which could act as an H-bond donor. It was also concluded that a hydroxyl group was necessary for MES activity, and more lipophylic compounds showed better anticonvulsant properties [82].

**2,6-dimethylanilides, Carboxamides**

The activity of several 2-piperidinecarboxamides in the MES test in mice has been reported [85, 86]. Receptor binding studies indicate that these amides demonstrated weak binding affinity at the phencyclidine (PCP) site on the N-methyl-D-aspartate (NMDA) receptor complex; however, a correlation between affinity and seizure protection in the MES test was not observed. Using N-(2,6-dimethylphenyl)-2-piperidinecarboxamide 35 and N(α-methylbenzyl)-2-piperidinecarboxamide 36 as structural leads (Fig. 13), a variety of analogues have been synthesized and evaluated for anticonvulsant activity in the MES test in mice [87]. The following modifications led to an increase in MES activity: replacement of the piperidine ring with pyridine and movement of the carboxamide group to the 4-position, then opening the piperidine ring. The 2,6-dimethylanilides were the most potent compounds in the MES test in each group of compounds (Fig. 14). The 4-pyridinecarboxamide 37 (ED50...
Fig. (14). Structures of 2,6-dimethylanilides, derivatives of carboxamides.

= 9.7 mg kg⁻¹, TD₅₀ = 53.3 mg kg⁻¹, PI = 5.5) was highly active in the MES test in mice. The norleucine derivative 38, obtained by opening the piperidine ring between the 1- and 6-positions was among the most potent compounds in the MES test in these series of compounds (ED₅₀ = 5.8 mg kg⁻¹, TD₅₀ = 36.4 mg kg⁻¹, PI = 6.3). In these derivatives, the lipophilicity of the compound and the substitution at the α-position of the amino acid derivative played key roles in quantitative anticonvulsant activity. Pyridinecarboxamide 37 and norleucinecarboxamide 38 were selected as useful leads in the development of compounds with therapeutic potential in the treatment of tonic-clonic and partial seizures in humans.

Hydroxyamides

Brown and coworkers have evaluated a series of novel hydroxyamides [88, 89]. Anticonvulsant testing of these compounds revealed the lead, 3,3,3-trifluoro-2-hydroxy-2-phenyl-propionamide 39, to have potent anticonvulsant activity. Anticonvulsant evaluation of compound 39 administered i.p. in mice demonstrated complete (3/3 mice) protection at a dosage of 100 mg kg⁻¹ up to 4 h when challenged with MES. Compound 39 also demonstrated effectiveness against scPTZ (5/5 mice protected) for 0.5 h at the same dosage. In rats p.o. test compound 39 protected: the MES ED₅₀ value was found to be 9.9 mg kg⁻¹, the scPTZ ED₅₀ was 34 mg kg⁻¹ and the TD₅₀ noted at 100 mg kg⁻¹, yielding a therapeutic index of 10 for the MES model and 2.6 for the scPTZ model. In this new series of compounds, two, 40 and 41, were the most active. Analogue 41’s MES ED₅₀ was also determined to be 62.4 mg kg⁻¹ but has notably longer-lasting effects (up to 6 h) and a TD₅₀ over 100 mg kg⁻¹. Patch clamp electrophysiology studies demonstrated significant tonic blockade of T-type calcium current by compounds 39–41 at 1 mM. Furthermore, compounds 39 and 40 induced a use-dependent blockade of T-type calcium current. These results suggest that the mechanism of anticonvulsant activity may include blockade of T-type calcium currents. Compounds 40 and 41 are methylated versions of compound 39 at the amide and alcohol, respectively (Fig. 15). Summing up, compound 39 is an active orally available anticonvulsant with similar activity to phenytoin, and its methylated alcohol and amide have shown similar activity.

Alkanolamides

In the group of alkanolamides (42), the most interesting results were yielded by 2-N-methylaminoethanol derivative (compound 43), which displayed anti-MES activity (i.p. in mice) with a PI of 2.54 (ED₅₀ of 51.8 mg kg⁻¹), higher than that for valproate (ED₅₀ = 287, PI 1.7) in the same test (Fig. 16) [90].

HETEROCYCLIC AGENTS

(Arylalkyl)imidazoles

One of the structurally distinct classes of antiepileptic drugs is the (arylalkyl)imidazoles. Denzimol (+/-)-N-[β-[4-(β-phenylethyl)phenyl]-β-hydroxyethyl]imidazole and nafimidone (1-[2-naphthoylmethyl]imidazole are examples of a class of anticonvulsants; the (arylalkyl)imidazoles (Fig. 17) [10]. SAR studies show that anticonvulsant properties of this group are associated with the presence of a small oxygen functional group (such as carbonyl, ethylene dioxy, methoxy, acyloxy and hydroxyl substituents) in the alkylene bridge in addition to an imidazole ring and a lipophilic aryl portion facilitating penetration of the blood barrier. The introduction of oxime and oxime ether groups to the alkylene bridge of (arylalkyl)imidazole as a small oxygen functional group led to new compounds, which displayed various levels of
activity [91]. Nafimidone oxime did not exhibit any anticonvulsant activity. O-Alkylation of nafimidone oxime, i.e., addition of an oxime ether functional group to the alkylene bridge of nafimidone, resulted in new compounds possessing anticonvulsant properties. The size of the alkyl moiety on the oxime group appears to be important for these properties. The O-alkyl substituted compounds (44-45) were found to be more active than the O-arylmethyl substituted compounds (Fig. 18). Anticonvulsant activity against MES-induced convulsion showed that compound 44 E (trans) isomer, was the most active with ED$_{50}$ 17.95 mg kg$^{-1}$ and TD$_{50}$ < 150 when the drug was administered i.p. in rats. Compound 44 and 45 showed ED$_{50}$ values of 46.77 and 36.99 mg kg$^{-1}$ i.p. and PI = 1.417 and 1.411 respectively in MES test in mice.

**Pyrrolidin-2,5-diones**

Ethosuximide, a derivative of pyrrolidin-2,5-dione, belong to a group of old antiepileptic drugs and is still used in the treatment of epilepsy.

A great number of 3-phenylpyrrolidine-2,5-dione derivatives with pyridyl-, aryl- and aminophenyl-moiety at the nitrogen atom, as well as 3-arylpiperidin-2,5-dione containing a 4-arylpiperazinyl-1-yl-alkyl moiety at the nitrogen atom and 2-aza-spiro[4.4]nonane-1,3-dione have been investigated by Obniska, Zejc and coworkers [92-96]. Pharmacological studies have shown anticonvulsant activity in some compounds of that group. Recently, the most potent in the series of N-[(4-arylpiperazinyl-1-yl)methyl derivatives of 3-arylpiperidin-2,5-dione were compounds 46 and 47 (Fig. 19). In the MES test in rats (after p.o. administration) the best ED$_{50}$ = 14.18 mg kg$^{-1}$ and PI = 8.8 were recorded for compound 46. Compound 47 was less active, with ED$_{50}$ = 133.64 mg kg$^{-1}$ and PI = 2.47.

![Fig. (17). Structures of (arylalkyl)imidazoles antiepileptic drugs.](image1)

![Fig. (18). Oxime ether derivatives 44-45 of anticonvulsant nafimidone.](image2)

![Fig. (19). Derivatives of 3-arylpipirrolidine-2,5-dione.](image3)

SAR studies in this group of pyrrolidin-2,5-dione derivatives have led to a conclusion that the following structural elements are required for anticonvulsant activity: an aromatic ring at the 3-position of pyrrolidine-2,5-dione moiety and a 4-arylpiperezine fragment with selected substituents at the phenyl ring. The introduction of a spirocyclopentyl ring at the 3-position of pyrrolidine-2,5-dione did not enhance the anticonvulsant activity.

**Lactams**

Derivatives of cyclic lactams were synthesized and evaluated for antiepileptic activity [97-100]. One of the compounds, α-hydroxy-α-phenylcaprolactam (48) was particularly interesting. i.p. administration of 48 in mice, resulted in potent anticonvulsant protection in both anticonvulsant models tested (MES- and scMet-induced convulsions), exhibiting an anti-MES ED$_{50}$ = 63 mg kg$^{-1}$ and anti-scMet ED$_{50}$ 74 mg kg$^{-1}$. New synthesized analogues of this compound, α-benzyl-α-hydroxycaprolactam (49), α-ethyl-α-hydroxycaprolactam (50) and α-hydroxy-α-(phenylethynyl)caprolactam (51) (Fig. 20) displayed significant anticonvulsant activity [100]. For these compounds (i.p. in mice) anti-MES activity was seen at 100 mg kg$^{-1}$ for 49, anti-scMet at 300 mg kg$^{-1}$ for 50 and anti-MES and anti-scMet at 100 mg kg$^{-1}$ for 51. Compound 49 exhibited (oral activity in rats) an anti-MES ED$_{50}$ = 86 mg kg$^{-1}$ and anti-scMet ED$_{50}$ < 83 mg kg$^{-1}$. Given that the Rotorod TD$_{50}$ was greater than 330 mg kg$^{-1}$, this particular lactam exhibited therapeutic indices exceeding 3.9 (MES) and 4.0 (scMet). These results showed that α-benzyl-α-hydroxycaprolactam (49) was effective in halting seizures, while α-ethyl-α-hydroxycaprolactam (50) was a selective inhibitor of petite mal seizures. compound 51 protected rats against MES-seizures at 30 mg kg$^{-1}$; no toxicity was noted. The difference in activity between 50 and 51 was postulated to be a result, at least partly, of the significant change in log $P$ from the unsubstituted terminal alkyne (-0.27) to the phenyl-substituted alkyne (1.52). The potent activity of 51 in all models indicated that the substituted alkynylcaprolactams represent a new anticonvulsant structural class.
Semi- and Thiosemicarbazones

Semicarbazones and related compounds have a documented and consistent role in the design of novel anticonvulsant agents, through the work of Dimmock’s and Pandeya’s research group [101-112]. A number of semicarbazones, thiosemicarbazones, bis-carboxyhydrazones, aryl, arylidene, arloxylaryl semicarbazones, acetylhydrazones and oxamoylhydrazones have been synthesized and evaluated for anticonvulsant activity. Extensive SAR studies have led to postulating a specific binding site of semicarbazone molecules. The proposed pharmacophoric requirements in the semicarbazone molecules are: 1) aryl binding site with a hydrophobic group; 2) hydrogen bonding domain exemplified by the presence of the –NHCO- grouping; 3) two electron donor systems; 4) hydrophobic binding site whose size determines the type of activity.

Derivatives of (arlyx)aryl semicarbazones displayed greater protection in the MES test than the scPTZ screen [103]. Quantification of approximately one-third of over 100 compounds tested revealed an average protection index of approximately 9. Following oral administration to rats, a number of compounds displayed significant potencies in the MES screen (ED50 value of 1-5 mg kg\(^{-1}\)) accompanied by a very high protection index. Later studies enabled the selection, in the series of aryloxaryl semicarbazones, of a lead molecule 52 (Fig. 21). ED\(_{50}\) values of compound 52 in the MES and scPTZ screens (i.p. in mice) were 48.6 and 94.1 mg kg\(^{-1}\), with PI figures of 4.20 and 2.17 respectively [104]. Recently, compound 53 [4-(6-chlorobenzothiazol-2-yl)-1-(3-isatinimino)thiosemicarbazone] has also shown strong activity in MES seizures and scPTZ screens [111]. Knowing that isatin derivatives possess anticonvulsant properties [113,114], compound 53 was designed as hybrid molecule incorporating a thiosemicarbazone fragment and an isatine molecule. Compound 53 was more potent than valproate against MES and scPTZ tests and was more effective than ethosuximide against MES-induced seizures, with an ED\(_{50}\) of 17.86 and 6.07 mg kg\(^{-1}\) i.p. in mice and rat p.o., respectively. Compound 53 exhibited a PI value of 8.77 in the rat p.o.

Identification in the MES screen. In the preliminary hippocampal-kindling screen in rats (i.p.), compound 53 showed weak ability to block the expression of fully kindled seizures. The potency and spectrum of activity of these 6-chlorobenzothiazolyl thiosemicarbazones were comparable to those of standard drugs, and represent a structurally novel class for subsequent molecular modifications.

Thiadiazoles and Quinazolin-4(3H)-ones

New thiadiazolyl and thiazolidinonyl quinazolin-4(3H)-ones have been synthesized and screened for their anticonvulsant activity comparing with the standard AEDs [115]. These hybrid molecules comprise two fragments, quinazoline and thiazolindione, whose derivatives have been found to show anticonvulsant properties [116]. Out of the 30 new hybrid compounds, the most active was 54 (Fig. 22). Compound 54 at three graded doses of 7.5, 15 and 30 mg kg\(^{-1}\) (i.p. in mice) in MES models was found to possess more potency than phenytoin and to be equipotent to lamotrigine at all the three dosage levels. In the scPTZ model, compound 54 exhibited better anticonvulsant activity than sodium valproate at all the three tested dosages (18.5, 37 and 74 mg kg\(^{-1}\)). SAR studies have indicated that compounds having a 3-amino-2-methyl-6-bromoquinazolin-4(3H)-aryl moiety showed more protection than compounds with a 3-amino-2-methyl-quinazolin-4(3H)-aryl moiety.

Another group of new hybrid molecules represent derivatives of 1,3,4-thiadiazoles has been obtained by adding two heterocyclic nuclei possessing anticonvulsant activity, namely barbituric acid and quinazolinone (Fig. 22) [117]. Of the compounds studied, the most active one (55) displayed activity against MES and scPTZ seizure test in mice (i.p.) that was more potent than the standard drug. Compound 55 at three graded dosages of 17.5, 25 and 50 mg kg\(^{-1}\) has been found to incur 20, 40 and 90% protection in the MES model and 20, 50 and 90% protection against seizure in the scPTZ model (respectively).

In the series of 2,5-disubstituted 1,3,4-thiadiazoles, two active anticonvulsant agents (56, 57) have been found [118]. Compounds 56 and 57 have shown maximum protection (90 and 70%, respectively) comparable to sodium valproate (80%) in the scPTZ screen. The ED\(_{50}\) values of the most effective compounds 56 and 57 were 33 and 66 mg kg\(^{-1}\) respectively (Fig. 23).
Xanthones

A different group of substituted derivatives of xanthone as new anticonvulsant agents has been discovered by Marona and coworkers [119-123]. A series of alkanolamides, alkanoamines and aminoalkanolic derivatives of 2-, 3-, 6-, 7-xanthone have been obtained and evaluated for anticonvulsant activity in the MES and scPTZ assays. Several compounds have been found to be active in both anticonvulsant tests. In a series of aminoisopropanoloxy derivatives of 2-, 3-, or 6-xanthone, the most promising compounds were the 3-(tert-buthyl-amino) (58) and 3-[N-methyl-(tert-buthyl)-amino] (59) substituted 2-hydroxy-1-(2-xanthonoxy)-propane and compound 60 [122], of which 59 was active in both anticonvulsant tests [119] (Fig. 24).

Results of quantitative anticonvulsant activity in the MES screen (i.p. in mice) for the tested compounds were as follows: for 58 $ED_{50} = 42.2$ mg kg$^{-1}$ PI = 1.9, for 59 $ED_{50} = 110.0$ mg kg$^{-1}$ PI > 4.5, for 60 $ED_{50} = 173.45$ mg kg$^{-1}$ PI = 0.80.

In a series of alkanolamides and alkanoamines [120, 121] 2-amino- or 2-N-methylamino-1-butanol and derivatives of 7-chloroxanthone (61, 62) have been found active in both anticonvulsant tests, displaying anti-MES activity (i.p. in mice) with a PI in the range of 2.84-3.64 corresponding with that for phenytoin, carbamazepine and valproate. In the MES test, both racemate 62 (R,S) and 62 (R) isomer displayed activity in the similar range [ED$_{50}$ = 27 mg kg$^{-1}$ PI = 3.28 for 62 (R,S) and ED$_{50}$ = 33.4 mg kg$^{-1}$ PI = 2.848 for 62 (R)].

Among derivatives of 6-methoxy- or 6-chloroxanthone, the most active were 2-amino-1-propanol-, 1-amino-2-propanol- and 1-amino-2-butanol derivatives, which displayed anti-MES activity with a PI in the range of 2.21-5.88. In the MES test (i.p. in mice), ED$_{50}$ values were 33.89, 37.4, 41.2 and 56.2 mg kg$^{-1}$ for compounds 63 (R,S), 65 (R,S) and 65 (R,S) respectively [121]. Recent studies of some central effects of chiral xanthone derivatives demonstrated differing potencies of enantiomers and a racemic mixture of compound 65 [123].

Derivatives of Isatin

Derivatives of 1,3-dihydro-indol-2-one (isatin) have been reported to possess anticonvulsant activity [113, 114]. Recent studies of hydrazones, Schiff and Mannich, bases of isatin, have led to the discovery of a new anticonvulsant agent (66) effective in both MES and scPTZ tests [124-126] (Fig. 25). Compound 66 [3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one] yielded 87% protection at 100 mg kg$^{-1}$ with an $ED_{50}$ value of 53.61 mg kg$^{-1}$ in the scPTZ screen after i.p. administration in mice. This new agent was less neurotoxic than phenytoin, and showed greater protection than sodium valproate [124].

**MISCELLANEOUS STRUCTURES**

Enaminones

Scott and coworkers have synthesized a series of enaminones bearing the aniline, benzylamine moieties and various aromatic heterocycles such as the pyridine, phenothiazines, and currently the isoxazole nucleus [127-134]. The prototype compound in the aniline series of enaminone was methyl 4-[4-chlorophenyl]amino]-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (67). Their ethyl analogue (68) was found to be the most promising enamino in the aniline series in both rat and mouse models during preliminary pharmacological evaluation (Fig. 26). In MES model seizures, in mice, i.p. administration of 68 resulted in an $ED_{50}$ value of 16.7 mg kg$^{-1}$ and TD$_{50}$ of 110.7 mg kg$^{-1}$, PI = 6.6 and an $ED_{50}$ value of 3.0 mg kg$^{-1}$ and TD$_{50}$ > 250 mg kg$^{-1}$, PI = 83.3 p.o. administration in rats.
Compound 68 was more potent than phenytoin, however it was proposed that the enaminones possessed an anticonvulsant profile similar to phenytoin. Compound 68 was then evaluated for sodium channel binding activity. It provided a statistically significant block (P < 0.05) at -60 mV, however the blockade was not strong enough to conclude that this was its principal mechanism of action. A biotransformation pathway for enaminones was also investigated [134]. The pharmacokinetic evaluation of 68 indicated that the carboalkoxy substituent converted in a two step reaction involving deesterification and decarboxylation to a second active enaminone metabolite 69 (Fig. 27). The 5-methyl ketone (69) in the MES screens displayed an ED\textsubscript{50} value of 40.4 mg kg\textsuperscript{-1} and TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 49.6; methyl ester (71), ED\textsubscript{50} 68.9 mg kg\textsuperscript{-1} i.p. in mice, TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 7.3, and tert-buthyl ester (72), ED\textsubscript{50} 28.1 mg kg\textsuperscript{-1} p.o. in rats, TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 17.8. Sodium channel binding studies, as well as evaluations against pentylenetetrazol, bicuculline, and picrotoxin on isoxazole 70 were all negative, leading to an unknown mechanism of action. X-ray diffraction patterns of a representative of the 3-amino series of isoxazoles displayed the existence of intramolecular hydrogen bonding of nitrogen to the vinylic proton in the cyclohexane ring, providing a pseudo-three ring.

The anticonvulsant activity of a series of enaminone-derived isoxazoles provided a potent, orally active class of compounds [131]. Two series of enaminones possessing the isomeric 5-methyl-substituted isoxazoles and 3-methylsubstituted isoxazoles revealed both similarities and differences with regard to anticonvulsant activity (Fig. 28). The most potent anti-MES were three compounds in the 3-amino series: ethyl ester 70 (ethyl 4-(5-methyl-3-isoxazolyl) amino]-6-methyl-2-oxo-3-cyclohexene-1-carboxylate), ED\textsubscript{50} 68.9 mg kg\textsuperscript{-1}, p.o. in rats TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 49.6; methyl ester (71), ED\textsubscript{50} 68.9 mg kg\textsuperscript{-1} i.p. in mice, TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 7.3, and tert-buthyl ester (72), ED\textsubscript{50} 28.1 mg kg\textsuperscript{-1} p.o. in rats, TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 17.8. Sodium channel binding studies, as well as evaluations against pentylenetetrazol, bicuculline, and picrotoxin on isoxazole 70 were all negative, leading to an unknown mechanism of action. X-ray diffraction patterns of a representative of the 3-amino series of isoxazoles displayed the existence of intramolecular hydrogen bonding of nitrogen to the vinylic proton in the cyclohexane ring, providing a pseudo-three ring.

Fig. (24). Derivatives of xanthone.

The anticonvulsant activity of a series of enaminone-derived isoxazoles provided a potent, orally active class of compounds [131]. Two series of enaminones possessing the isomeric 5-methyl-substituted isoxazoles and 3-methylsubstituted isoxazoles revealed both similarities and differences with regard to anticonvulsant activity (Fig. 28). The most potent anti-MES were three compounds in the 3-amino series: ethyl ester 70 (ethyl 4-(5-methyl-3-isoxazolyl) amino]-6-methyl-2-oxo-3-cyclohexene-1-carboxylate), ED\textsubscript{50} 68.9 mg kg\textsuperscript{-1}, p.o. in rats TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 49.6; methyl ester (71), ED\textsubscript{50} 68.9 mg kg\textsuperscript{-1} i.p. in mice, TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 7.3, and tert-buthyl ester (72), ED\textsubscript{50} 28.1 mg kg\textsuperscript{-1} p.o. in rats, TD\textsubscript{50} > 500 mg kg\textsuperscript{-1}, PI > 17.8. Sodium channel binding studies, as well as evaluations against pentylenetetrazol, bicuculline, and picrotoxin on isoxazole 70 were all negative, leading to an unknown mechanism of action. X-ray diffraction patterns of a representative of the 3-amino series of isoxazoles displayed the existence of intramolecular hydrogen bonding of nitrogen to the vinylic proton in the cyclohexane ring, providing a pseudo-three ring.

Fig. (26). Structures of anticonvulsant enaminones.
The presented review summarizes ongoing medicinal chemistry investigations in search for new anticonvulsant compounds. Many of the compounds presented in this review have been evaluated by the ADD Program. Their anticonvulsant activity has been confirmed through in vivo screening tests, although for many compounds the precise mechanism of action is still not known. Some of the newer anticonvulsant agents represent structural modifications of pre-existing compounds, while others have been developed with the specific objective of modifying targets. These new agents belong to several different chemical classes. Some of them represent compounds bearing five-membered or other heterocyclic rings in their structure; additionally, numerous studies have demonstrated that derivatives of amino acids can function as potential new anticonvulsant agents. The most common structural elements of many active compounds are an amide bond (particularly a benzylamide group) and the presence of at least one aryl unit. New data has also confirmed that the lipophilicity of new active molecules is an important factor affecting their anticonvulsant potency. These new agents can be used for the design of future targets and development of new drugs. The discovery of a number of active leads may also ultimately help elucidate the mechanism of action of these new anticonvulsants.

**ABBREVIATIONS**

| AED      | = | Antiepileptic drug |
| ASP      | = | The Anticonvulsant Screening Project |
| ADD      | = | Antiepileptic Drug Development program |
| MES      | = | Maximal electroshock |
| scPTZ    | = | Subcutaneous pentylenetetrazole |
| scMet    | = | Subcutaneous metrazol |
| GABA     | = | γ-aminobutyric acid |
| THIQ     | = | Tetrahydroisoquinoline |
| MEST     | = | Maximal electroshock threshold |
| ED<sub>50</sub> | = | The median effective dose |
| TD<sub>50</sub> | = | The median toxic dose |
| PI       | = | Protective index |
| PI<sub>i.p.</sub> | = | Intraperitoneally |
| p.o.     | = | Orally |
| BIC      | = | Bicuculline |
| PCR      | = | Picrotoxin |
| SAR      | = | Structure-activity-relationships |
| FAA      | = | Functionalized amino acid |
| FAK      | = | Functionalized amindo ketones |
| AAA      | = | Amino acid amides |

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**Fig. (27).** A biotransformation pathway of enaminone 68.

**Fig. (28).** The isoxazolylamino enaminones.
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid

NMDA = N-methyl-D-aspartate

REFERENCES

[1] Bell, G.S.; Sander, J.W. The epidemiology of epilepsy: The size of the problem. Seizure 2002, 11 (Suppl. A), 306-314.

[2] Lopes Lima, J.M. The new drugs and strategies to manage epilepsy. Curr. Pharmaceut. Design 2000, 6, 873-878.

[3] Penacca, E. Marketed new antiepileptics: Are they better than old-generation agents? Ther. Drug Monit. 2002, 24, 74-80.

[4] Berk, M.; Segal, J.; Janet, L.; Vorster, M. Emerging options in the treatment of bipolar disorders. Drugs 2001, 61, 1407-1414.

[5] Duncan, J.S. The promise of new antiepileptic drugs. Br. J. Clin. Pharmacol. 2002, 53, 123-131.

[6] Edadie, M.J. Can anticonvulsant drug therapy ‘cure’ epilepsy? CNS Drugs 2001, 15, 679-690.

[7] Szelényi, I.; Horvath, K.; Howes, J.F.; Mazarati, A.M. The treatment of epilepsy: future possibilities. Drugs Fut. 2003, 28, 924-936.

[8] Bruno-Blanch, L.; Gálvez, J.; García-Domenech, R. Topological virtual screening: A way to find new anticonvulsants from chemical diversity. Bioorg. Med. Chem. Lett. 2003, 13, 2749-2754.

[9] Malawska B.: Application of pharmacophore models for the design and synthesis of new antiepileptic drugs. Mini Rev. Med. Chem. 2003, 3, 341-348.

[10] Edfogo, I.; Scott, K.R. Anticonvulsants. Burger’s Medicinal Chemistry and Drug Discovery, Fifth Ed. Vol. 3: Therapeutic Agents, Ed. Wolff, M.E. John Wiley & Sons, Inc, 1999, 26, 197-250.

[11] Cosford, N.D.P.; McDonald, I.A.; Schweiger, E.J. Recent progress in antiepileptic drug research. In Annual Reports in Medicinal Chemistry, Ed. Levy, R.H.; Mattson, R.H.; Meldrum, B.; Penry J.K.; Dreifuss, F.E. Eds. New York: Raven Press 1989, 85-102.

[12] Sneed, O.C. Pharmacological models of generalized absence seizures in rodents. J. Neural. Transm. (Suppl) 1992, 35, 7-19.

[13] Chan, W.N.; Upton, N.; Vong, A.K. Synthesis of novel trans-4-(substituted-benzamido)-3,4-dihydro-2H-benzo[b]pyran-3-ol derivatives as potential anticonvulsant agents with a distinctive binding profile. Med. Chem. 1996, 19, 4537-4539.

[14] Herdon, H.J.; Jerman, J.C.; Stein, T.O.; Middlemiss, D.N.; Chan, W.N.; Vong, A.K.; Evans, J.M.; Thompson, M.; Upton, N. Characterization of the binding of [3H]-SB-204269, a radiolabelled form of the new anticonvulsant SB-204269 (carabersat), to a novel binding site in rat brain membranes. Br. J. Pharmacol. 1997, 121, 1687.

[15] Cosford, N.D.P.; McDonald, I.A.; Schweiger, E.J. Recent progress in antiepileptic drug research. In Annual Reports in Medicinal Chemistry, Ed. Levy, R.H.; Mattson, R.H.; Meldrum, B.; Penry J.K.; Dreifuss, F.E. Eds. New York: Raven Press 1989, 85-102.

[16] Sneed, O.C. Pharmacological models of generalized absence seizures in rodents. J. Neural. Transm. (Suppl) 1992, 35, 7-19.

[17] Chan, W.N.; Upton, N.; Vong, A.K. Synthesis of novel trans-4-(substituted-benzamido)-3,4-dihydro-2H-benzo[b]pyran-3-ol derivatives as potential anticonvulsant agents with a distinctive binding profile. Med. Chem. 1996, 19, 4537-4539.

[18] Herdon, H.J.; Jerman, J.C.; Stein, T.O.; Middlemiss, D.N.; Chan, W.N.; Vong, A.K.; Evans, J.M.; Thompson, M.; Upton, N. Characterization of the binding of [3H]-SB-204269, a radiolabelled form of the new anticonvulsant SB-204269 (carabersat), to a novel binding site in rat brain membranes. Br. J. Pharmacol. 1997, 121, 1687.

[19] Austin, N.E.; Hadley, M.S.; Harling, J.D.; Herdon, H.J.; Jerman, J.C.; Orlek, B.S.; Stein, T.O.; Thompson, M; Upton, N; Ward, R.W. Identification of a series of 1,2,3,4-tetrahydroisoquinoliny1-benzamides with potential anticonvulsant activity. Bioorg. Med. Chem. Lett. 1998, 8, 2903-2906.

[20] Chan, W.N.; Hadley, M.S.; Harling, J.D.; Herdon, H.J.; Jerman, J.C.; Orlek, B.S.; Stein, T.O.; Thompson, M; Upton, N; Ward, R.W. Evaluation of a series of anticonvulsant 1,2,3,4-tetrahydroisoquinoliny1-benzamides. Bioorg. Med. Chem. 2000, 8, 2085-2094.

[21] Austin, N.E.; Hadley, M.S.; Harling, J.D.; Harrington, F.P.; Macdonald G.J.; Mitchell, D.J.; Riley, G.J.; Stein, T.O.; Stemp, G.; Statron, S.C.; Thompson, M; Upton, N. The design of 8,8-dimethyl[1,6]naphthyridines as potential anticonvulsant agents. Bioorg. Med. Chem. Lett. 2003, 13, 1627-1629.

[22] Supuran, C.T.; Scozzafava, A. Carbonic anhydrase inhibitors. Curt. Med. Chem.-Imm., Endoc. & Metab. Agents 2001, 1, 61-97.

[23] Shank, R.P.; Gardocki, J.F.; Vaught, J.L.; Davis, C.B.; Schupsky, J.J.; Raffa, R.B.; Dodgson, S.J.; Nortey, S.O.; Marianno, B.E. Topiramate: preclinical evaluation of strucrally novel anticonvulsant. Epilepsia 1994, 35, 450-460.

[24] Sabers, A.; Gram, L. Newer anticonvulsants: Comparative review of drug interactions and adverse effects. Drugs 2000, 60, 23-33.

[25] Supuran, C.T.; Minicione, F.; Scozzafava, A.; Briganti, F.; Mincione, G.; Ilies, M.A. Carbonic anhydrase inhibitors. Metal complexes of heterocyclic sulfonamides: A new class of strong anticonvulsant agents. Eur. J. Med. Chem. 2000, 35, 23-33.
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[45] Masereel, B.; Rolin, S.; Abbate, F.; Scozzafava, A.; Supuran, C.T. Carbolic anhydride inhibitors: Anticonvulsant sulfonylamides incorporating valproyl and other lipophilic moieties. J. Med. Chem. 2002, 45, 312-320.

[46] Illies, M.A.; Masereel, B.; Rolin, S.; Scozzafava, A.; Cimpeanu, G.; Cimpeanu, V.; Supuran, C.T. Carbolic anhydride inhibitors: aromatic and heterocyclic sulfonylamides incorporating adamantyl moieties with strong anticonvulsant activity. Bioorg. Med. Chem. 2004, 12, 2717-2726.

[47] Conley, J.D.; Kohn, H. Functionalized DL-amino acid derivatives. Potent new agents for the treatment of epilepsy. J. Med. Chem. 1987, 30, 567-574.

[48] Kohn, H.; Conley, J.D.; Leander, J.D. Marked stereospecificity in a new class of anticonvulsants. Brain Res. 1988, 457, 371-375.

[49] Kohn, H.; Sawhney, K.N.; LeGall, P.; Conley, J.D.; Robertson, D.W.; Leander, J.D. Preparation and anticonvulsant activity of a series of functionalized α-aminic and α-heteroaromatic amino acids. J. Med. Chem. 1990, 33, 919-926.

[50] Kohn, H.; Sawhney, K.N.; LeGall, P.; Robertson, D.W.; Leander, J.D. Synthesis and anticonvulsant activities of N-substituted α,α-diamino acid derivatives. J. Pharm. Sci. 1994, 83, 689-691.

[51] Choi, D.; Stables, J.P.; Kohn, H. Synthesis and anticonvulsant activities of N-benzyl-2-acetamidopropionamide derivatives. J. Med. Chem. 1996, 39, 1907-1916.

[52] Andurkar, S.V.; Stables, J.P.; Kohn, H. The anticonvulsant activities of N-benzyl-3-methoxypropionamides. Bioorg. Med. Chem. 1999, 7, 2381-2389.

[53] Le Tiran, A.; Stables, J.P.; Kohn, H. Functionalized amino acid anticonvulsants: Synthesis and pharmacological evaluation of conformationally restricted analogues. Bioorg. Med. Chem. 2001, 9, 2693-2708.

[54] Andurkar, S.V.; Béguin, C.; Stables, J.P.; Kohn, H. Synthesis and structural studies of aza analogues of functionalized amino acids: New anticonvulsant agents. J. Med. Chem. 2002, 45, 4762-4773.

[55] Shen, M.; Le Tiran, A.; Xiao, Y.; Golbraikh, A.; Kohn, H.; Tropsha, A. Quantitative structure-activity relationships analysis of functionalized amino acid anticonvulsant agents using k nearest neighbor and simulated annealing PLS methods. J. Med. Chem. 2002, 45, 2811-2823.

[56] Béguin, C.; Andurkar, S.V.; Jin, A.Y.; Stables, J.P.; Weaver, D.F.; Kohn, H. Functionalized amino ketones: New anticonvulsant agents. Bioorg. Med. Chem. 2003, 11, 4275-4285.

[57] Béguin, C.; LeTiran, A.; Stables, J.P.; Voyer, R.D.; Kohn, H. N-Substituted amino acid N'-benzylamides: Synthesis, anticonvulsant, and metabolic activities. Bioorg. Med. Chem. 2004, 12, 3079-3096.

[58] Paruszewski, R.; Rostafinska-Suchar, G.; Strupinski, M.; Jaworski, P.; Stables, J.P. Synthesis and anticonvulsant activity of some amino acid derivatives. Part 1: Alanine derivatives. Pharmazie 1996, 51, 145-148.

[59] Paruszewski, R.; Rostafinska-Suchar, G.; Strupinski, M.; Jaworski, P.; Winiecka, I.; Stables, J.P. Synthesis and anticonvulsant activity of some amino acid derivatives. Part 2: Derivatives of Gly, Ala, Leu, Pro, Trp, Phe(4Cl), Ala(α-Me). Pharmazie 1996, 51, 212-215.

[60] Paruszewski, R.; Rostafinska-Suchar, G.; Strupinski, M.; Winiecka, I.; Stables, J.P. Synthesis and anticonvulsant activity of some amino acid derivatives. Part 3: Derivatives of Ala, Arg, Tle, Gly and γ-Abu. Pharmazie 2000, 55, 27-30.

[61] Paruszewski, R.; Strupinska, M.; Stables, J.P.; Swiader, M.; Czuczwar, S.; Kleinrock, Z.; Turski, W. Amino acid derivatives with anticonvulsant activity. Chem. Pharm. Bull. 2001, 49, 629-631.

[62] Paruszewski, R.; Strupinska, M.; Rostafinska-Suchar, G.; Stables, J.P. Anticonvulsant activity of benzamides of some amino acids and heterocyclic acids. Prog. Pept. Lett. 2003, 10, 475-482.

[63] Malawska, B.; Kulig, K.; Sypiewak, A.; Stables, J.P.; Winiecka, I.; Stables, J.P. The Fourth Multidisciplinary Conferences on Drug Research, Gdansk-Sobieszewo, Book of abstract, 2004, P-129.

[64] Malawska, B.; Kiec-Kononowicz, K.; Karolak-Wojciechowska, J.; Handzlik, J. Glycine derivatives of imidazolones as potential ligands of glycine binding site of NMDA receptors. Acta Pol. Pharm.-Drugs Res. 1998, 55, 381-388.

[65] Malawska, B.; Kiec-Kononowicz, K.; Karolak-Wojciechowska, J. Structure and activity studies on glycine receptor ligands. Diphenyl imidazol-4-one, 3-acylimidazolines, Acta Pol. Pharm.-Drug Res. 1998, 55, 389-397.

[66] Malawska, B.; Gobaille, S. Synthesis, physicochemical and pharmacological properties of new N-substituted amides of α-piperazine-γ-hydroxybutyric acid. Pharmazie 1995, 50, 390-393.

[67] Malawska, B.; Zejc, A. Search for new anticonvulsant compounds. Part 1: Synthesis, physicochemical and anticonvulsant properties of new derivatives of α-amino-γ-phenylmethylidobutycarboxylic acid. Pharmazie 1995, 50, 722-755.

[68] Malawska, B.; Librowski, T.; Czarnecki, T.; Malawska, B. Influence of new γ-amino-γ-phenylbutyric acid amides and its phthalimide precursors on the central nervous system activity in mice. Pol. J. Pharmacol. 2001, 53, 689-693.

[69] Malawska, B.; Kulig, K.; Cieszanowicz-Rutkowska, M. Search for new anticonvulsant compounds, Part 2: Structure-activity relationships studies of new N-substituted amides of α-piperazine-γ-hydroxybutyric acid as active anticonvulsants. Arch. Pharm. Pharm. Med. Chem. 1997, 330, 91-99.

[70] Malawska, B.; Antkiewicz-Michaluk, L. Search for new anticonvulsant compounds, Part 3. Synthesis, physicochemical properties, anticonvulsant activities and voltage-sensitive calcium channels affinity of N-substituted amides of α-4-phenoxy(piperazinyl)-γ-hydroxybutyric acid. Pharmazie 1999, 54, 239-243.

[71] Malawska, B.; Kulig, K.; Antkiewicz-Michaluk, L.; Cline, I.; Porter, R.; Misra, A. Anticonvulsant activities and voltage-sensitive calcium channels receptor affinity of substituted N-benzylamides of γ-amino- and γ-hydroxybutyric acid. Arch. Pharm. Pharm. Med. Chem. 1999, 332, 167-174.

[72] Malawska, B.; Kulig, K.; Czarnecki, T.; Malawska, B. Influence of new γ-hydroxybutyric acid amides analogues on the central nervous system activity in mice. Pol. J. Pharmacol. 2002, 54, 731-736.

[73] Malawska, B.; Kulig, K.; Kiec-Kononowicz, K.; Karolak-Wojciechowska, J. Anticonvulsant compounds with improved anticonvulsant activity (Polish). Wed. Chem. 2001, 55, 377-402.

[74] Malawska, B.; Kulig, K. Spiewak, A.; Stables, J.P. Investigation into new anticonvulsant derivatives of α-substituted N-benzylamides
of γ-hydroxy- and γ-acetoxybutyric acid. Part 5: Search for new anticonvulsant compounds. Bioorg. Med. Chem. 2004, 12, 625-632.

[85] Hinko, C.N.; Crider, A.M.; Klem, M.A.; Steinnmiller, C.I.; Seo, T.H.; Ho, B.; Venkataraman, P.; El-Assaad, A.A.; Chang, H.; Burns, C.M.; Tietz, E.L.; Andersen, P.H.; Kittigard, H. Anticonvulsant activity of novel derivatives of 2- and 3-piperidinocarboxylic acid in mice and rats. Neuropharmacology 1996, 35, 1721-1735.

[86] Ho, B.; Venkataraman, P.; Cruse, S.F.; Hinko, C.N.; Andersen, P.H.; Crider, A.M.; Adloo, A.A.; Roane, D.S.; Stables, J.P. Synthesis of 2-piperidinocarboxylic acid derivatives as potential anticonvulsants. Eur. J. Med. Chem. 1998, 33, 23-31.

[87] Ho, B.; Crider, A.M.; Stables, J.P. Synthesis and structure-activity relationships of potential anticonvulsants based on 2-piperidinocarboxylic acid and related pharmacophores. Eur. J. Med. Chem. 2001, 36, 265-286

[88] Brown, M.L.Z.C.C.; Van Dyke, C.C.; Brown, G.B.; Brouillette, W.J. Comparative molecular field analysis of hydantoin binding to the neuronal voltage-dependent sodium channel. J. Med. Chem. 1999, 42, 1537-1545.

[89] Schenck, H.A.; Lenkowski, P.W.; Choudhury-Mukherjee, I.; Ko, S.-H.; Stables, J.P.; Patel, M.K.; Brown, M.L. Design, synthesis and evaluation of novel hydroxamides as orally available anticonvulsants. Bioorg. Med. Chem. 2004, 12, 979-993.

[90] Marona, H.; Szneler, E. Preliminary evaluation of anticonvulsant activity of some 4-(benzylxoy)-benzamides. Acta Pol. Pharm-Drug Res. 2003, 60, 477-480.

[91] Karakurt, A.; Dalkara, S.; Ozalp, M.; Ozbay, S.; Kendi, E.; Stables, J.P. Synthesis of some 1-(2-naphthyl)-2-(imidazol-1-yl)ethanone oxime and oxime ether derivatives and their anticonvulsant and antimicrobial activities. Eur. J. Med. Chem. 2001, 36, 421-433.

[92] Zejc, A.; Obniska, J.; Wilimowski, M.; Rutkowska, M.; Witkowska, J.; Barczyńska, L.; Kędzierska-Góździk, L.; Wojewódzki, W.; Orzechowska-Juzwenko, K.; Pławiak, T.; Dus, E.; Gryska, J.; Gliński, M. Synthesis and anticonvulsant properties of some arylocyanuric methylpyridylimides. Pol. J. Pharmacol. Pharm. 2000, 52, 283-290.

[93] Dimmock, J.R.; Vashishtha, S.C.; Stables, J.P. Anticonvulsant properties of various acetyloxidines, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. Eur. J. Med. Chem. 2000, 35, 241-248.

[94] Pandeya, S.N.; Yogeesswari, P.; Stables, J.P. Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones. Eur. J. Med. Chem. 2000, 35, 879-886.

[95] Pandeya, S.N.; Mishra, V.; Poninalvarasan, I.; Stables, J.P. Anticonvulsant activity of p-chlorophenyl substituted aryl semicarbazones – The role of primary terminal amino group. Pol. J. Pharm. 2000, 52, 283-290.

[96] Dimmock, J.R.; Vashishtha, S.C.; Stables, J.P. Ureylene anticonvulsants and related compounds. Pharmazie 2000, 55, 490-494.

[97] Pandeya, S.N.; Manjula, H.; Stables, J.P. Design of semicarbazones and their bio-isosteric analogues as potential anticonvulsants. Pharmazie 2001, 56, 121-124.

[98] Yogeesswari, P.; Sriram, D.; Sunil Jit, L.R.; Kumar, S.S.; Stables, J.P. Anticonvulsant and neurotoxicity evaluation of some 6-chlorobenzothiazolyl-2-thiosemicarbazones. Eur. J. Med. Chem. 2002, 37, 231-236.

[99] Pandeya, S.N.; Agarwal, A.K.; Singh, A.; Stables, J.P. Design and synthesis of semicarbazones and their bio-isosteric analogues as potent anticonvulsants: The role of hydrogen bonding. Acta Pharm. 2003, 53, 15-24.

[100] Popp, F.D. Potential anticonvulsants. IX. Some isatin hydrazines and related compounds. J. Heteroc. Chem. 1984, 21, 1641-1645.

[101] Pandeya, S.N.; Sriram, D.; Yogeesswari, P.; Stables, J.P. Anticonvulsant and neurotoxicity evaluation of 5-(un)-substituted isatin-imino derivatives. Pharmazie 2001, 56, 875-876.

[102] Srivastava, A.V.K.; Kumar, A. Synthesis of newer thiazolizyl and thiazolidinolin quinazolin-4(3H)-ones as potential anticonvulsant agents. Eur. J. Med. Chem. 2002, 37, 873-882.

[103] Chapleo, C.B.; Mayer M.; Myer, P.L.; Saville, J.F.; Smith, A.C.B.; Stilling, M.R.; Tulloch, I.F.; Walter, D.S.; Welbourn, A.P.; Stables, I.; 1,3,4-thiadiazoles with anticonvulsant activity. 1. Hydrazines J. Med. Chem. 1986, 29, 2273-2280.

[104] Srivastava, A.V.K.; Kumar, A.; Synthesis of some newer derivatives of substituted quinazolin-2-oxothiobarbatic acid as potent anticonvulsant agents. Bioorg. Med. Chem. 2004, 12, 1257-1264.

[105] Dogan, H.N.; Duran, A.; Rollas, S.; Sener, G.; Uyusl M.K.; Gülen, D. Synthesis of new 2,5-disubstituted-1,3,4-thiadiazoles and preliminary evaluation of anticonvulsant and antimicrobial activities Bioorg. Med. Chem. 2002, 10, 2893-2898.

[106] Marona, H.; Górkza, Z.; Szneler, E. Aminoalkanolic derivatives of xanthon with potential antipiepleptic activity. Pharmazie 1998, 53, 219-223.

[107] Marona, H.; Evaluation of some 2-substituted derivatives of xanthon for anticonvulsant properties. Pharmazie 1998, 53, 405-409.

[108] Marona, H.; Synthesis and anticonvulsant effects of some aminolocanolic derivatives of xanthon. Pharmazie 1998, 53, 672-676.

[109] Marona, H.; Pękala, E.; Filipek, B.; Maciej, D.; Szneler, E. Pharmacological properties of some aminolocanolic derivatives of xanthon. Pharmazie 2001, 56, 567-572.

[110] Jastrzębska-Wisieńk, M.; Librowski, T.; Czarnecki, T.; Marona, H.; Nowak, G. Central activity of some xanthone derivatives with chiral center in some pharmacological tests in mice. Pol. J. Pharmacol. 2003, 55, 461-465.

[111] Sridhar, S.K.; Pandeya, S.; Stables, J.P.; Ramesh, A. Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur. J. Pharm. Sci. 2002, 16, 129-132.
Sridhar, S.K.; Ramesh, A. Synthesis and pharmacological activities of hydrazones, Schiff and Mannich bases of isatin derivatives. Biol. Pharm. Bull. 2001b, 24, 1149-1152.

Verma, M.; Pandeya, S.N.; Singh, K.N.; Stables, J.P. Anticonvulsant activity of Schiff bases of isatin derivatives. Acta Pharm. 2004, 54, 49-56.

Alexander, M.S.; Stables, J.P.; Ciechanowicz-Rutkowska, M.; Hursthouse, M.B.; Hibbs, D.E.; Edafiogho, I.O.; Moore, V.A.; Scott, K.R. Spiranes 6. Ring A homologues of N-benzyloxy-2-azaspiro[4,4]nonane-1,3-dione. Synthesis, X-ray analysis and anticonvulsant evaluation. Eur. J. Med. Chem. 1996, 31, 787-795.

Foster, J.E.; Nicholson, J.M.; Butcher, R.; Stables, J.P.; Edafiogho, I.O.; Goodwin, A.M.; Henson, M.C.; Smith, C.A.; Scott, K.R. Synthesis, characterization and anticonvulsant activity of enaminones. Part 6: Synthesis of substituted vinylc benzamides as potential anticonvulsants. Bioorg. Med. Chem. 1999, 7, 2415-2425.

Eddington, N.D.; Cox, D.S.; Roberts, R.R.; Stables, J.P.; Powell, C.B.; Scott, K.R. Enaminones-versatile therapeutic pharmacophores. Further advances. Curr. Med. Chem. 2000, 7, 417-436.

Cox, D.S.; Scott, K.R.; Gao, H.; Eddington, N.D. Influence of multidrug resistance (MDR) proteins at the blood-brain barrier on the transport and brain distribution of enaminone anticonvulsants. J. Pharm. Sci. 2001, 90, 1540-1552.

Eddington, N.D.; Cox, D.S.; Roberts, R.R.; Butcher, R.J.; Edafiogho, I.O.; Stables, J.P.; Cooke, N.; Goodwin, A.M.; Smith, C.A.; Scott, K.R. Synthesis and anticonvulsant activity of enaminones. 4. Investigation on isoxazole derivatives. Eur. J. Med. Chem. 2002, 37, 635-648.

Edafiogho, I.O.; Phillips, O.A.; Abdel-Hamid, M.; Ali, A.A.M.; Matowe, W.C.; El-Hashim, A.; Kombian, S.B. Ultraviolet spectroscopy of anticonvulsant enaminones. Bioorg. Med. Chem. 2002, 10, 593-597.

Cox, D.S.; Scott, K.R.; Gao, H.; Eddington, N.D. Effect of P-Glycoprotein on the pharmacokinetics and tissue distribution of enaminone anticonvulsants: analysis by population and physiological approaches J. Pharmacol. Exp. Ther. 2002, 302, 1096-1104.

Eddington, N.D.; Cox, D.S.; Khurana, M.; Salama, N.N.; Stables, J.P.; Harrison, S.J.; Negussie, A.; Taylor, R.S.; Tran, U.Q.; Moore, J.A.; Barrow, J.C.; Scott, K.R. Synthesis and anticonvulsant activity of enaminones Part 7. Synthesis and anticonvulsant evaluation of ethyl 4-[(substituted phenyl)amino]-6-methyl-2-oxocyclohex-3-ene-1-carboxylates and their corresponding 5-methylcyclohex-2-ene derivatives. Eur. J. Med. Chem. 2003, 38, 49-64.