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A Case Study:

New antiepileptic agents: structure activity relationships

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ABSTRACT

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

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

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

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

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

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

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

understanding of molecular mechanisms of epilepsy. Another way is to modify already existing drugs and formulations[18]. The efficacy of AEDs is due to the main activities, which include interaction with ion channels or neurotransmitter systems[19-25].

Currently available AEDs have 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 in the brain, and the exact mechanisms of many AEDs remain unknown [26,27]. The new AEDs and anticonvulsant agents have been reviewed during last few years [28-32].

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, which are in different stages of development as potential drugs targeting epilepsy. The newer agents include carabersat analogues, heterocyclic compounds ((arylalkyl)imidazoles, tricyclic indoles, indazoles, arylpiperazine and piperazines, pyrrloidine-2,5-diones, lactams, semi and thiosemicarbazones, thiadiazoles and quinazolin-4(3H)-ones, xanthones, pyridazinone and isatin derivatives), 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 antiepileptic drugs.

New anticonvulsant agents : structure activity relationships:

Heterocyclic analogs of carabersat:

Parent analog of Carabersat is cromakalim (Fig. 1), which is an antihypertensive that acts via relaxation of vascular smooth muscle caused by opening of ATP sensitive K^+ channel. K+ channel opener can easily penetrate CNS and may have therapeutic potential in treatment of seizure [19]. Replacement of the 2-pyrrolidinone group of cromakalim by the fluorobenzoylamino group has introduced anticonvulsant activity[33]. Carabersat, the benzopyran derivative, is a chemically novel AED with a novel mechanism of action and a stereo specific CNS binding site. Carabersat is currently proposed for migraine prophylaxis and in the treatment of epilepsy[34,35]. Compound 270664,the T substituted THIQ was reported as a promising key lead compounds with high affinity at the [3H]-SB-204269 binding site (pK_a 8.9) but was later found to have poor pharmacokinetic properties. In the series of 7 linked THIQ derivatives a new series of 8,8 dimethylnapthyridine compounds are identified in which gem dimethyl group is incorporated to prevent aromatization and replacement of the THIQ benzo ring with pirydyl prevents reduction in hydroxylation and the compound 1 is found to have encouraging pharmacokinetic profile with excellent aqueous stability and good '*in vivo*' activity in preclinical anticonvulsant model in rats[36]. Compound 1 has high affinity at the [3H]-SB-204269 binding site (p*K*i 8.7), suggesting a novel mechanism of action, comparable with carabersat (Fig. 2).

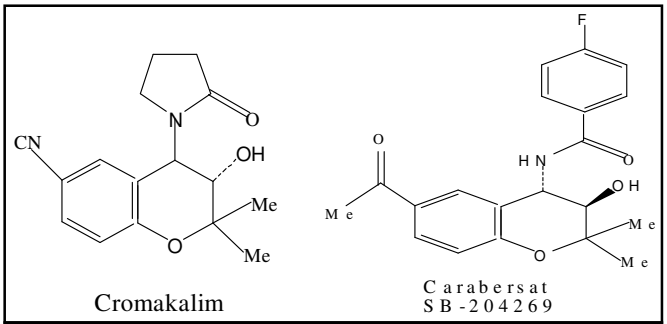


Fig. 1 : The structure of cromakalim and carabersat

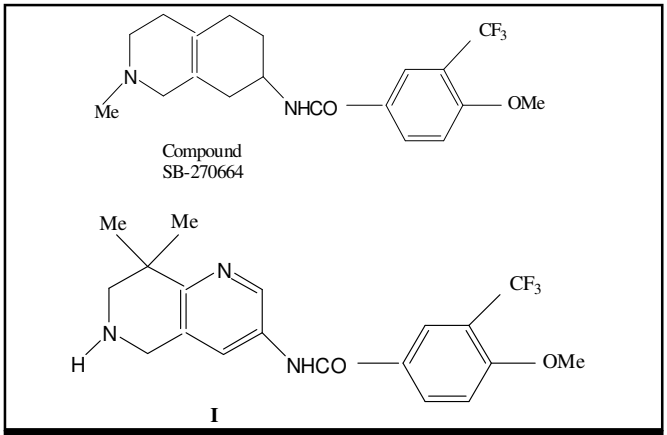


Fig. 2 : Heterocyclic analog of carabersat

Sulphonamides:

Bifunctional 5 membered heterocycles comprised of a sulphonamide and an amide as well as a 1, 3, 4 thiazole nucleus, making a potent Carbonic Anhydrase (CA) inhibitor such as topiramate and zonisamide used as antiepileptic drugs. Acetazolamide, topiramate and zonisamide (Fig. 3) possess a sulphamate moiety, which is essential for their anhydrase inhibition. Several new carbonic anhydrase inhibitors derivatives of sulfonamides have been developed[37,38]. A series of aromatic / heteroaromatic sulfonamides incorporating valproyl and other lipophilic moieties have been found to possess potent

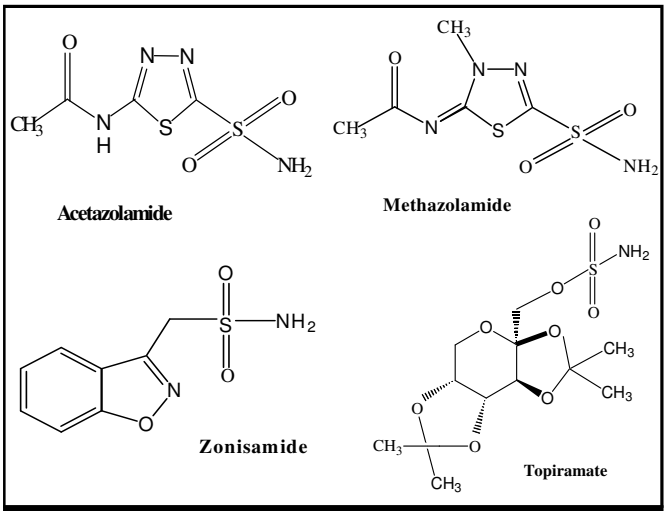


Fig. 3 : Sulfonamide antiepileptic drugs

CA inhibitory properties as well as anticonvulsant *in vivo* effects. The valproyl derivative of acetazolamide 2 was one of the best hCAI and hCAII inhibitors in the series and it exhibited very strong anticonvulsive properties in the MES test in mice. Some lipophilic derivatives such as 5-benzylamido-5-toluenesulfonylamido-, 5-adamantylcarboxamido-, and 5-pivaloylamido1,3,4-thiadiazole-2-sulfonamide show promising in vivo anticonvulsant properties. These compounds serve as interesting leads for developing anticonvulsant or selective cerebrovasodilator drugs[38]. A new series of sulfonamides incorporating adamantyl moieties attached to the scaffolds of aromatic/heteroaromatic sulfonamides have shown good inhibitory potency against two human CA isozymes, compounds 3,4 which also exhibit good protection against electrically induced convulsions (Fig. 4).

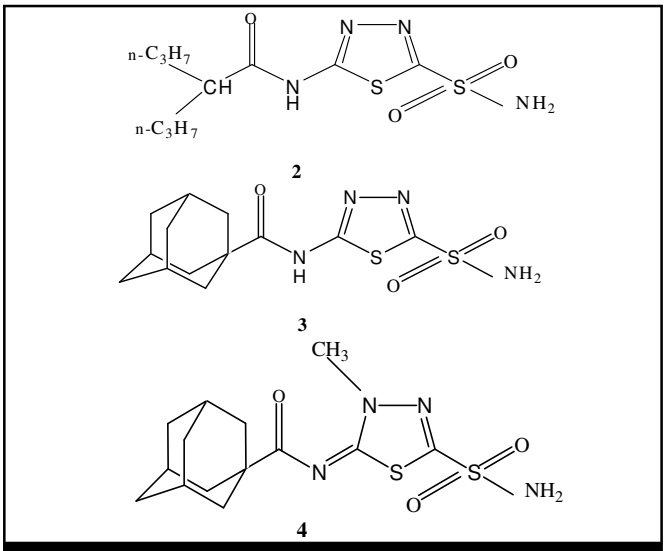


Fig. 4 : Anticonvulsant sulfonamides carbonic anhydrase inhibitors

Amides:

Analogs of γ-vinyl GABA:

Vigabatrin (γ-vinyl GABA) is being proposed as an anticonvulsant agent by acting as inhibitor of GABA aminotransferase [25]. 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[39,40]. Among them, compounds 5 and 6 displayed the most potent anticonvulsive activity and a broader spectrum when compared to vigabatrin (Fig. 5).

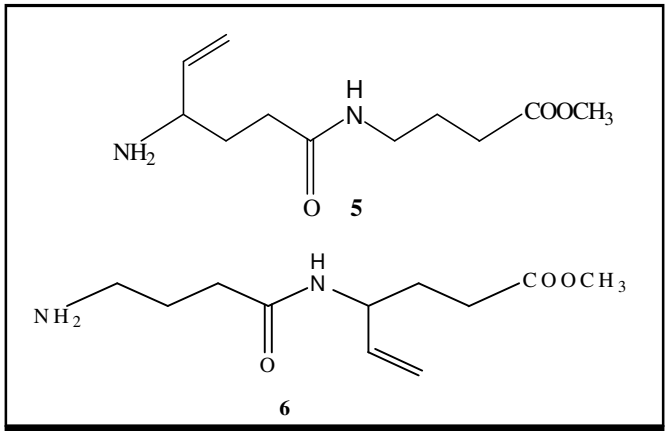


Fig. 5 : Analogs γ-vinyl GABA

N-benzylamides of γ-hydroxy butyric acid:

Derivatives of γ-substituted γ-amino-, γ-phthalimido, γ-acetoxy- and γ-hydroxy butyric acid, such as acids, esters and amides, have been investigated as new potent anticonvulsants[41-50]. It has been shown that α-substituted *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 7 and *N*- (2-chlorobenzylamide) 8 (Fig. 6). Biochemical tests have

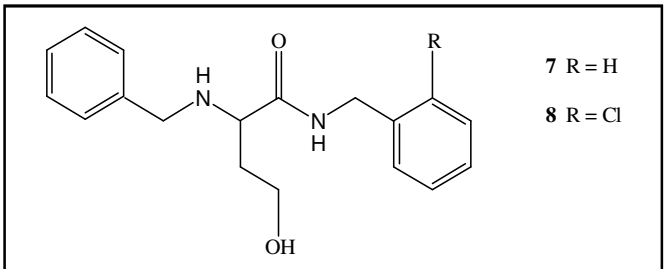


Fig. 6 : α-substituted N benzylamides of γ-hydroxybutric acid

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. The results of pharmacological *in vivo* experiments with the γ -hydroxybutyric acid amide analogues 7 and 8 have shown that the compounds possess variable influence on the CNS in mice[47].

2, 6-dimethylanilides, Carboxamides:

The activity of several 2-piperidinecarboxyamides in the MES test in mice has been reported[51,52]. Using *N*-(2,6-dimethyl) phenyl-2-piperidinecarboxyamide 9 and *N* (α-methylbenzyl) piperidine carboxamide 10 as structural leads (Fig. 7), a variety of analogues have been synthesized and evaluated for anticonvulsant activity in the MES test in mice[53]. The following modifications led to an increase

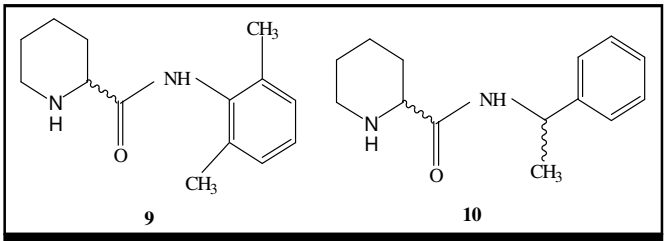


Fig. 7 : Structures of 2-piperidinecarboxamides with activity against MES in mice

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. 8). 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. Pyridine carboxamide 11 and norleucine carboxamide 12 were selected as useful leads in the development of

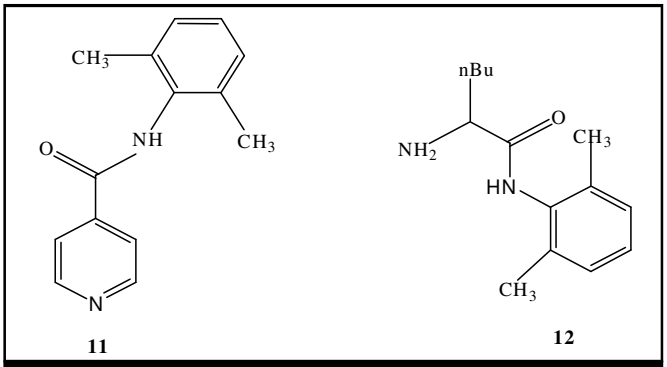


Fig. 8 : Structures of 2, 6-dimenthylanidies, derivatives of carboxamides

compounds with therapeutic potential in the treatment of tonic-clonic and partial seizures in humans. The antiepileptic activity of a series of *N*-aryl-isoxazole carboxamides/*N*-isoxazolylbenzamide analogs has been investigated and a significant antiepileptic activity was predicted[54] (Fig. 9).

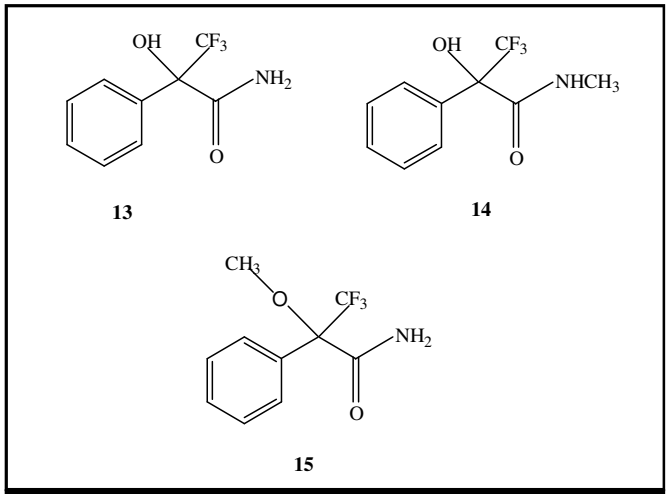


Fig. 9 : Derivatives of hydroxyamides

Hydroxyamides:

Brown and coworkers have evaluated a series of novel hydroxyamides[55,56]. Anticonvulsant testing of these compounds revealed the lead, 3,3,3-trifluoro-2-hydroxy-2-phenyl-propionamide 13, is an active orally available anticonvulsant with similar activity to phenytoin, and its methylated alcohol and amide have shown similar activity. In this new series of compounds, two, 14 and 15, were the most active. Patch clamp electrophysiology studies demonstrated significant tonic blockade of T-type calcium current by compounds 13-15 (Fig. 10) at 1mM.

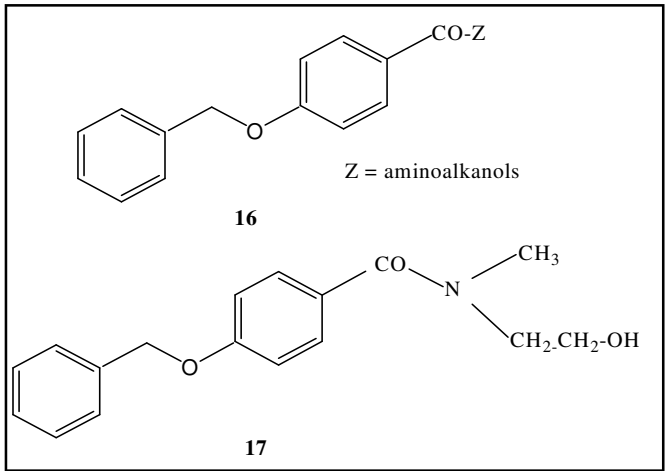


Fig. 10 : Derivatives of 4-(benzyloxy) benzamides

Furthermore, compounds 13 and 14 induced a significant 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.

Alkanolamides:

In the group of alkanolamides (16), the most interesting results were yielded by 2-*N*-methyl amino ethanol derivative (compound 17), which displayed anti-MES activity (i.p. in mice) higher than that for valproate in the same test[57] (Fig. 11).

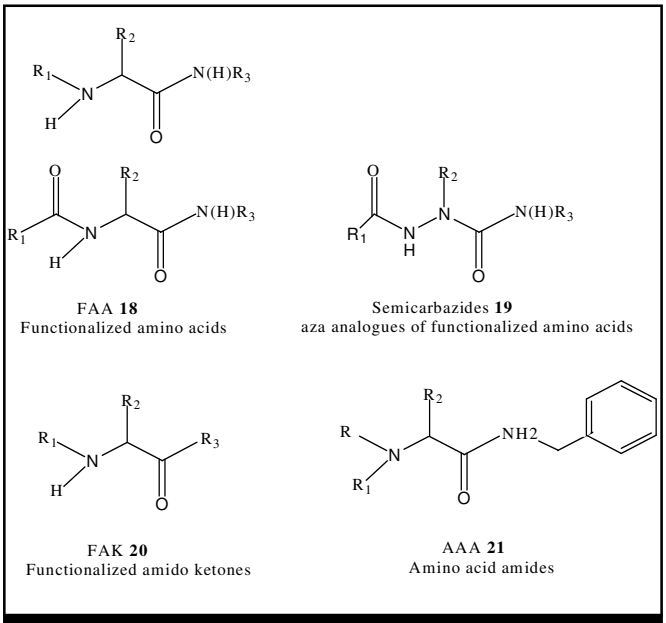


Fig. 11 : The schematic structure of anticonvulsant derivaties of amino acids

Derivatives of amino acids:

Amino acids that are functionalized at both the *N*- and *C* terminal are proven potent anticonvulsant agents[58-83]. In the recent years, Kohn and coworkers have reported on the anticonvulsant activity of a series of functionalized amino acids[58-72]. (FAA) 18 (Fig. 12). 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*-Benzyl-2-acetamidopropionamide 22(Fig. 13) was the parent compound in this series[66]. (*R*)-*N*-benzyl-2-acetamido-3-methoxy-propionamide 10 was selected as the lead compound. Compound 23 (Fig. 13) has now entered phase II clinical trials for the treatment of epilepsy and neuropatic pain. . 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

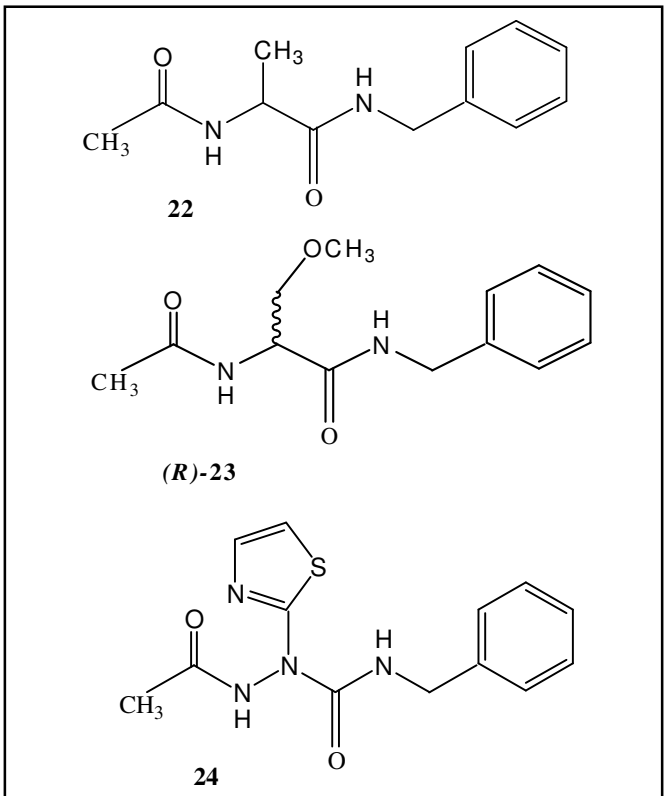


Fig. 12 : Amino acid derivaties

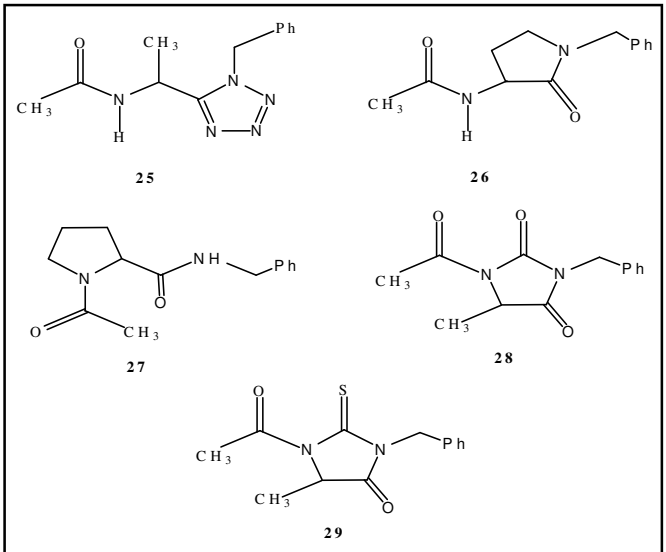
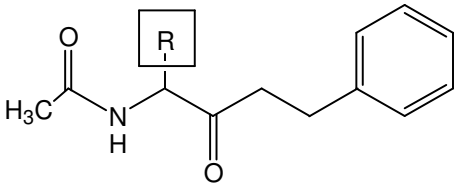


Fig. 13 : Conformationally restricted analogs of anticonvulsant functionalized amino acids (FAA's)

acetamido unit (R1=C (O) CH_3) for potent anticonvulsant activity and showed that either a decrease (*i.e.*, R1 = C (O) H) or increases (*i.e.*, R1 = C (O) CH_2CH_3, C (O)$C(H)CH_3)_2$, $C(O)CCH_3)_3$) in the size of this moiety led to reduced activity. Furthermore, when the acetamido ($CH_3C(O)$ NH) unit in 18 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[66]. Evaluation of aza analogue 19 of functionalized amino acids in both mice (i.p.) and rats (p.o.) showed that the compounds exhibited significant anticonvulsant activities. Of the investigated compounds, 1-acetyl-4-benzyl-2-(thiazol-2-yl)-semicarbazide 24(Fig. 13) displayed moderate-excellent activity in mice (MES i.p. ED50 = 22 mgkg-1, PI = 5.4) and excellent activity in rats (MES p.o. ED50 =6.2 mg kg-1, Tox TD50 > 250) which exceeded that of phenytoin.

Conformationally restricted analogues of anticonvulsant-functionalized amino acids have also been investigated[67]. Four peptidomimetic compounds of parent FAA 22 such as1, 5-disubstituted tetrazole 25, 3-substitued 1-benzylpyrrolidin-2-one 26, proline 27, and (thio) hydantoins 28, 29 as well as peptidomimetic FAA derivatives have been evaluated (Fig. 14).



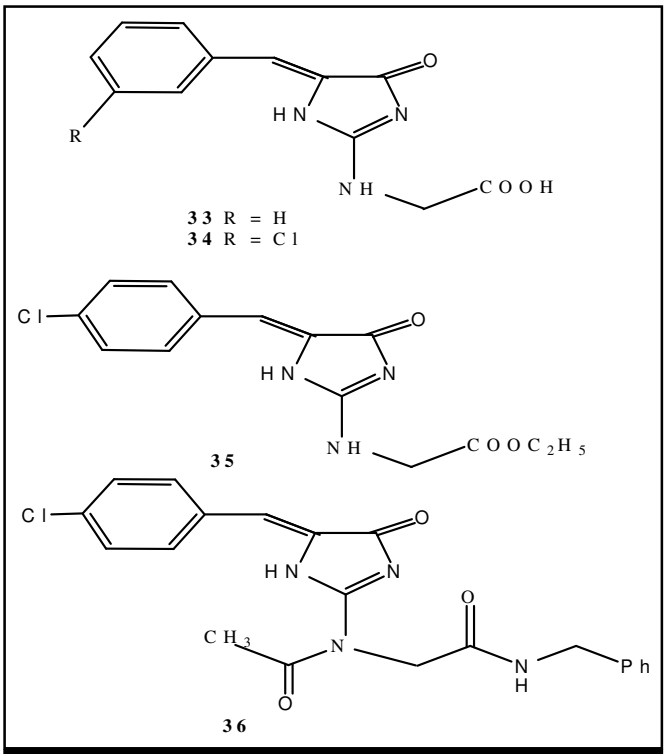
30 R = CH_3
31 R = Ph
32 R = $CH_2.O.CH_3$

Fig. 14 : Functionalized amido ketones (FAK)

Replacing the *N*-terminal amide group in FAA with phenyl ethyl, styryl, and phenyl ethynyl units provided a series of functionalized amido ketones (FAK) 20[71] (Fig. 15). 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 18 to an amino moiety provided amino acid amides (AAA, 21) that are likely to have increased water solubility compared with their FAA 18 counterparts[72].

Some amino acid derivatives have also been studied by Paruszewski and coworkers[73-78]. Amides of *N* substituted natural and a natural amino acids containing benzylamide, 4-fluorobenzylamide, 4-methoxybenzylamide, 2-furfurylamide, phenylethylamide, 3-pirydylmethylamide, buthylamide, isobutylamide,



33 R = H
34 R = Cl

35

36

Fig. 15 : Arylidene-imidazoline-4-one amino acids

usoamylamide moiety as well as esters have been synthesized and evaluated. Among the tested compounds, benzylamide derivatives of b-Ala, Ac-*D*-Pro-BZA and (*R*, *S*)-Me-Tzl-BZA were the most active. Recent studies have demonstrated that some picoline and nicotinic acid benzylamides substituted on the phenyl ring also possess anticonvulsant properties[76-78]. Of these, the most active was the picolinic acid fluorobenzylamide (Pic-FBZA). ED50 of the most effective amide was14.7 mg kg^{-1} (MES), >50 mg kg-1 (scPTZ) and PI < 3.4against MES (rats, i.p.)[76]. SAR studies of alanine derivatives suggested that the structure of this amino acid, especially of fragment N-C$^{\alpha}$-C', is responsible for its action[73].

Derivatives of arylidene imidazoline-4-one amino acids were investigated by Kiec-Kononowicz and Karolak-Wojciechowska[79-80]. Several series of arylidene (aryl)-imidazolidyno-4-one derivatives incorporating glycine, modified glycine or a-alanine and modified a-alanine were studied as a new ligand for the glycine-NMDA binding site (iGluRs) as well as anticonvulsant agents. Selected amino acid derivatives (33-36) presented in Fig. 16 displayed anticonvulsant activity in MES seizure tests at a dosage of 100 mg kg^{-1} or less.

Heterocyclic agents:

(Aryl alkyl) imidazoles:

One of the structurally distinct classes of antiepileptic

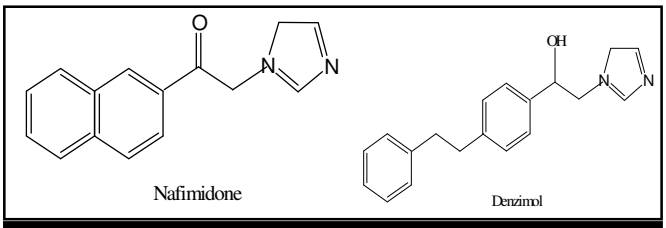


Fig. 16 : Structure of (arylalkyl) imidazole antiepileptic drugs

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) [18]. SAR studies show that anticonvulsant properties of this group are associated with the presence of 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

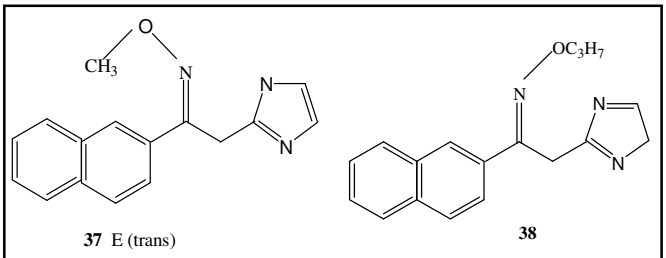


Fig. 17 : Oxime either derivatives of anticonvulsant nafimidone

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[83]. O-Alkylation of nafimidone oxime resulted in new compounds possessing anticonvulsant properties. The o-alkyl substituted compounds (37-38) were found to be more active than o-arylalkyl substituted compounds (Fig. 18).

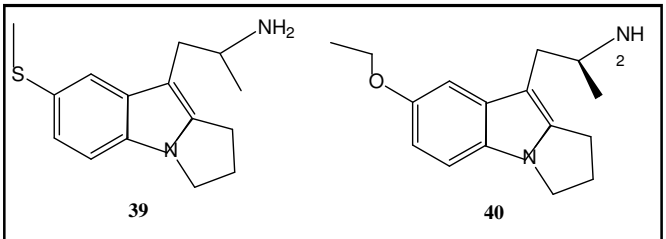


Fig. 18 : Tricyclic indoles

Tricyclic indoles:

Researchers at Vernalis have reported on a series of tricyclic indoles (exemplified by 39 and 40)(Fig. 19) as 5-HT2C agonists, containing a 2-aminopropyl group as a common motif, which is thought to provide improved metabolic stability (reduction of oxidative deamination) and improved selectivity over 5-HT1 receptors[85].

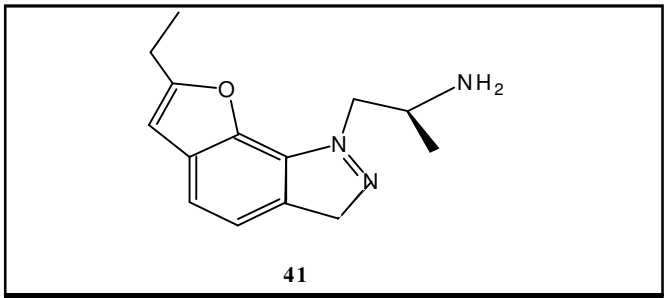


Fig. 19 : Indazole derivatives

Compound 40 is chiral with the S-enantiomer being preferred. This compound displayed good functional selectivity over 5-HT2A with good potency at the 5-HT2C receptors (EC50 (h5-HT2C) = 4nM, 87% of the 5-HT response in a calcium mobilization assay).

Indazole:

A functionally selective and orally active 5-HT2C agonists with the potential to demonstrate antiepileptic effects is the indazole 41 (Fig. 20) which showed functional selectivity in a phosphoinositide hydrolysis assay over 5-HT2A[86].

Arylpiperazines and Piperazine:

The arylpiperazines are known to be 5-HT2C agonists but they are not selective for the 5-HT2C receptors. Many variations on arylpiperazines have been explored in an effort to find potent agonists having promising functional selectivity over the 5-HT2A and 5-HT2B receptors. Biovitrum (formerly part of Pharmacia) has disclosed piperazinylpyazine 42 with excellent affinity (Ki (h5-HT2C) = 8 nM) for the 5-HT2C receptors although no functional data was provided[85].Another constrained arylpiperazine, WAY-161503 43 reported by American Home Product (now Wyeth) is a potent 5-HT2C agonist (EC50 (h5-HT2C) = 8nM, in a functional assay measuring inositol monophosphate formation) with a 2,000-fold functional selectivity over 5-HT2A. Compound 44 and 45 are additional highly selective5-HT2C receptor agonists[85]. Scientists at Vernalis were able to combine the active indole structure and the arylpiperazine template to produce potent ring-constrained analogs exemplified

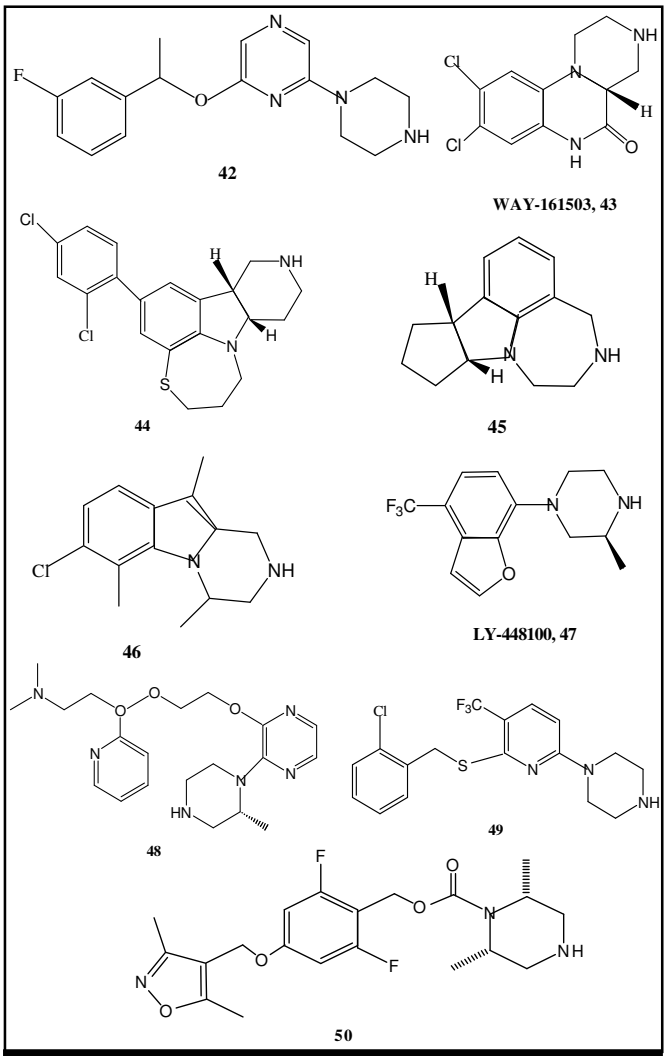


Fig. 20 : Selective 5-HT2C agonists with potential antiepileptic properties

by the tetrahydropyazioindole 46. Compound 46 has an EC50 value of 0.4 nM at the h5-HT2C receptor and is more than 1000-fold selective over 5-HT2A in a calcium mobilization functional assay.

Eli Lilly has reported *in vitro* and *in vivo* profiles of a selective 5-HT2C receptor agonist, LY-448100 47 This compound also exhibited very good oral activity in rats (oral bioavailability= 83%) making it an ideal candidate for further proof of concept as an orally active anticonvulsant[87].

More recently two additional piperazine analogs 48 and 49 were disclosed as potent and selective 5-HT2C agonists. These analogues are claimed to be useful as potential antiepileptics but no supporting *in vivo* data was reported[85]. Hoffmann- la Roche and Vernalis reported a piperazine 50 where the basic nitrogen atom appears to be spatially distant from the aromatic core which possessed good potency and good functional selectivity over the 5-HT2A receptors[85] (Fig. 21).

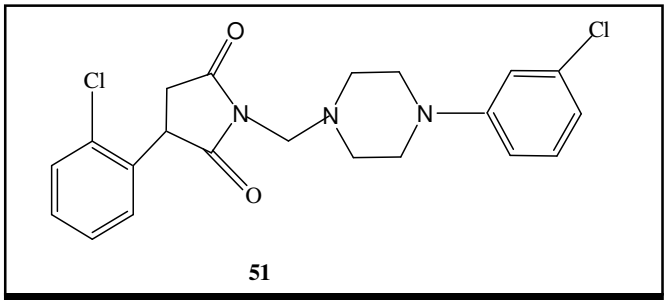


Fig. 21 : Derivatives of 3-arylpyrrolidine-2, 5-dione

Pyrrolidin-2, 5-diones:

A number of 3-phenylpyrrolidine-2, 5-dione derivatives with pyridyl-, aryl- and aminophenyl-moiety at the nitrogen atom, as well as 3-arylpyrrolidine-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[88-92]. Recently, the most potent in the series of N- [(4-arylpiperazin-1-yl) methyl derivatives of 3-arylpyrrolidine-2, 5-dione were compounds 51 and 52 (Fig. 22). SAR studies include following structural

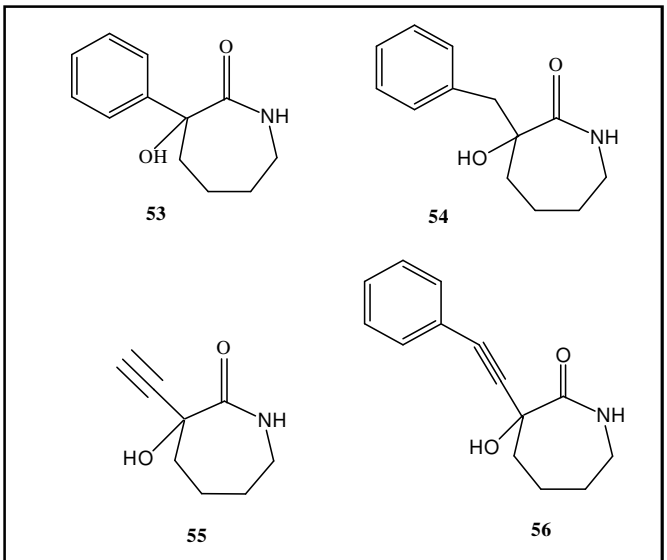


Fig. 22 : Derivatives of α-substituted caprolactams

elements that are required for antiepileptic activity, (a) an aromatic ring of pyrrolidin2-5 dione moiety and a (b) 4-arylpiperazine fragment with selected substitutes at the phenyl ring. The introduction of a spiro cyclopentyl ring at 3-position of pyrrolidin 2-5dione didn't enhance the anticonvulsant activity.

Lactams:

Derivatives of lactams were synthesized and evaluated for antiepileptic activity[93-96]. One of the compounds, α-hydroxy- α-phenylcaprolactam (53) was particularly interesting. I.p. administration of 53 in mice resulted in potent anticonvulsant protection in both anticonvulsant models tested: MES- and scMet-induced convulsions. New synthesized analogues of this compound, α -benzyl- α -hydroxycaprolactam (54), α -ethynyl- α -hydroxycaprolactam (55) and α-hydroxy-α (phenylethynyl) caprolactam (56) (Fig. 23) displayed significant anticonvulsant activity[96].α-benzyl- α hydroxycaprolactam (54) was effective in halting seizures, while α-ethynyl- α -hydroxycaprolactam (55) was a selective inhibitor of petite mal seizures. The potent activity of 56 in all models indicated that the substituted alkynyl caprolactams represent a new anticonvulsant structural class.

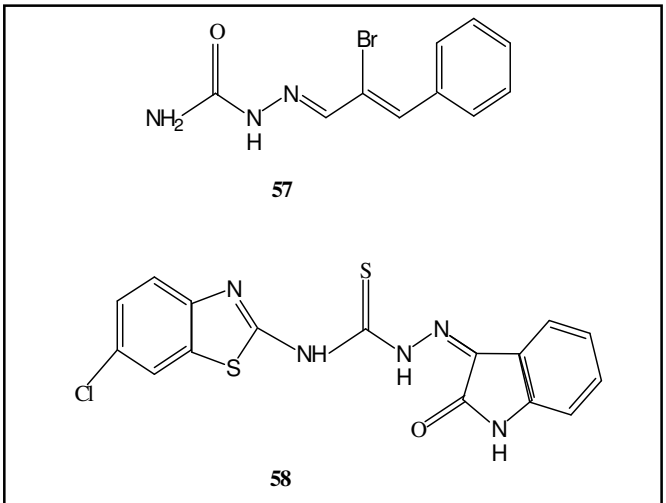


Fig. 23 : Structures of semi-and thiosemicarbazones

Semi- and thiosemicarbazones:

Through the work of Dimmock's and Pandeya's research group[97-108] a number of semicarbazones, thiosemicarbazones, *bis*-carbohydrazones, aryl, arylidene, aryloxyaryl semicarbazones, acetyl hydrazones and oxamoylhydrazones have been synthesized and evaluated for anticonvulsant activity. SAR studies have led to postulating a specific binding site of semicarbazones. The proposed pharmacophoric requirements in the semicarbazone molecules are: (a) aryl binding site with a hydrophobic group; (b) hydrogen bonding domain exemplified by the presence of the –NHCO- grouping; (c) two electron donor systems; (d) hydrophobic binding site whose size determines the type of activity[107]. In the series of aryloxyaryl semicarbazones, molecule 57 was selected as lead (Fig. 24). Recently, compound 58 [4-(6-chlorobenzothiazol-2-yl)-1-(3-isatinimino) thiosemicarbazone] has also shown strong activity in MES seizures and scPTZ screens[107]. Knowing that isatine derivatives possess anticonvulsant properties[109,110] compound 58 was designed as hybrid molecule incorporating a thiosemicarbazone fragment and an isatine molecule.

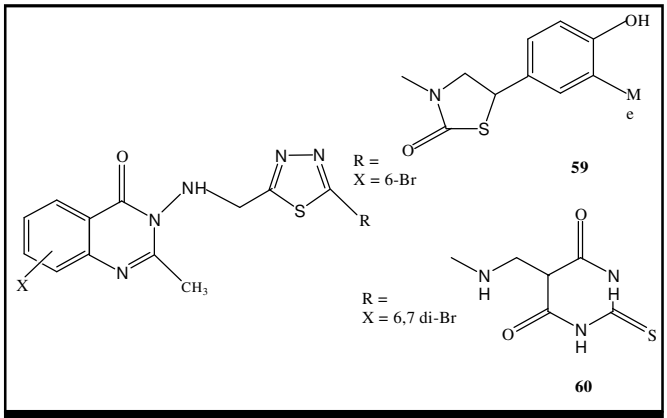


Fig. 24 : Derivatives of thiadiazoly quinazolin-4(3H)-ones

Thiadiazoles and Quinazolin-4 (3H)-ones:

New thiadiazolyl and thiazolidinonyl quinazolin-4 (3*H*)-ones have been synthesized and screened for their anticonvulsant activity comparing with the standard AEDs[111]. These hybrid molecules comprise two fragments, quinazolinone and thiazolidinone, whose derivatives have been found to show anticonvulsant properties[112]. Out of the 30 new hybrid compounds, the most active was 59 (Fig. 25). SAR studies have indicated that compounds having a 3-amino-2-methyl-6-bromoquinazolin- 4(3*H*)-aryl moiety showed more protection than compounds with a 3-amino-2-methyl-quinazolin-4 (3*H*)-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. 25) [113]. Of the compounds studied,

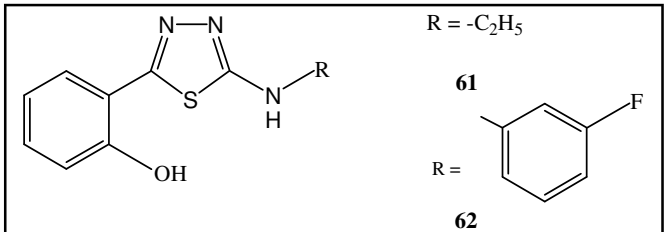


Fig. 25 : 2,5-Disubstituted 1, 3, 4-thiadiazoles

the most active one (60) displayed activity against MES and scPTZ seizure test in mice (i.p.) that was more potent than the standard drug. In the series of 2,5-disubstituted 1,3,4-thiadiazoles, two active anticonvulsant agents (61, 62) have been found[114]. Compounds 61 and 62 (Fig. 26) have shown maximum protection (90 and 70%, respectively) comparative to sodium valproate (80%) in the scPTZ screen.

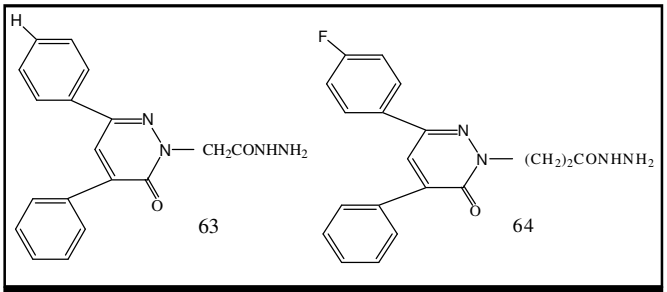


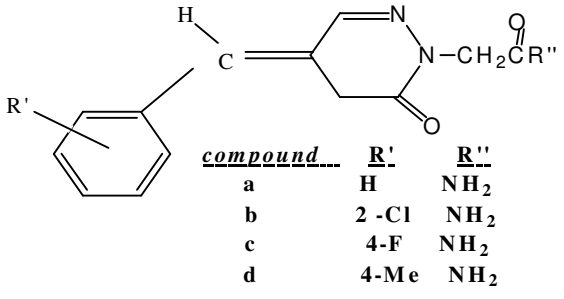
Fig. 26 : Pyridazinone derivatives

Pyridazinones:

Anticonvulsant activity of 4, 6-diaryl-3-pyridazinones or N-ethoxycarbonyl alkyl pyridazinones is also reported[115]. A series of 3-oxo-5-substituted-benzylidene-6-methyl-(4H)-2-pyridazinylacetamides and 2-pyridazinylacetylhydrazides 63 and 64 (Fig. 27) including most of their derivatives showed an anticonvulsant effect better than sodium valproate, a commonly used anticonvulsant agent. The most active compounds in this series are given in (Fig. 28).[116].

Imidooxy compounds:

Imidooxy compounds possess interesting Anticonvulsant activity. Previous results of anticonvulsant activity in several imidooxy carboxylates related to aminooxy acetic acid in young chicks, prompted an in-depth reinvestigation of these analogues in mice. A series of 22 succinimidooxy, phthalimidooxy, and



compound	R'	R''
a	H	NH_2
b	2 -Cl	NH_2
c	4-F	NH_2
d	4-Me	NH_2

Fig. 27 : Different substitutions on pyridazinone derivatives

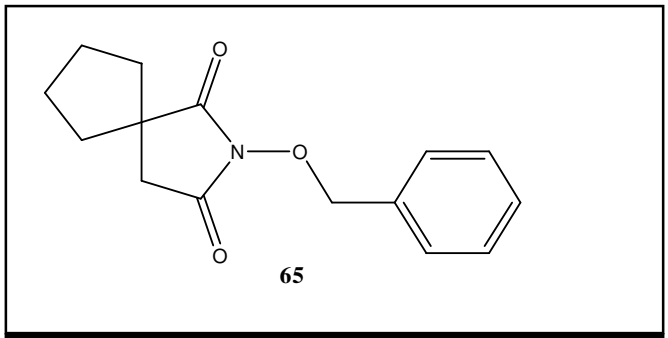


Fig. 28 : N-(benzyloxy)-2-azaspiro [4,4] nonane-1, 3=dione

naphthalimidooxy carboxylates were synthesized by Edafiogho and coworkers, and evaluated for anticonvulsant activity Most interesting results were obtained with N- (benzyloxy)-2-azaspiro [4.4] nonane-1, 3-dione 65 which displayed anti-MES activity and a protective index (TD50/ED50) of >4.5[117].

Conclusion:

Despite the availability of new antiepileptic drugs (AEDs) with novel pharmacological modes of action, the efficacy of the medical therapies in terms of seizure control has not increased significantly over recent years. Nevertheless, there is a continuing need for new AEDs, especially for focal and secondary generalized seizures.

A large portion of the human epilepsies comprises disorders in which the inheritance of two or three susceptibility genes in the same individual is required to produce epilepsy. The protein coded by the mutant gene can suggest new molecules to be targeted by the antiseizure drugs. The available evidence suggests that the combination of AEDs with different modes of action may be more effective than monotherapy. It is therefore conceivable that AEDs with new modes of action, such as 5-HT2C receptor agonism, can improve the effectiveness of medical therapy with respect to seizure control if they are sensibly combined with existing AEDs. Future clinical approval of 5-HT2C agonists as AEDs is expected to be a useful addition to the treatment armamentarium for focal and secondary generalized seizures.

The search for antiepileptic compounds with more selective activity a lower toxicity continues to be an area of intensive investigation in medicinal chemistry. The mechanism of action of new anticonvulsant moieties is still not clear but they can prove useful for the design of future targets and development of new drugs. 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. Pandeya et al, while investigating the semicarbazone series, proposed a new pharmacophore model with four binding sites essential for anticonvulsant activity. These sites are:

– A hydrophobic aryl ring,
– A hydrogen-bonding domain,
– An electron donor acceptor system,
– Another hydrophobic aryl ring responsible for metabolism. (Fig. 29)

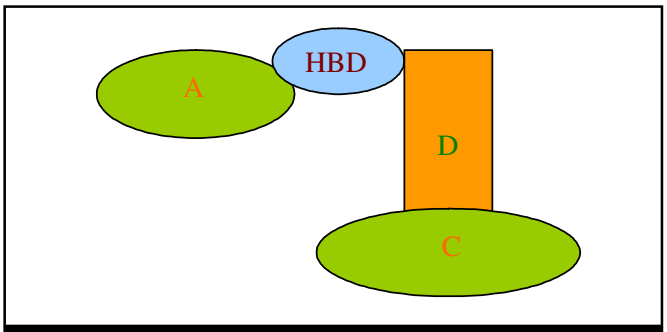


Fig. 29 : Suggested [pharmacophore model of anticovulsant activity. A and C are hydrophobic binding site, HBD is hydrogen-bonding site and D is electron donor group

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.

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REFERENCES

1. **Bell, G.S.** and Sander, J.W. (2002). The epidemiology of epilepsy: The size of the problem. Seizure;11 Suppl A:306-14.
2. **Brown, T.R.,** Holmes and Epilepsy, G.L. (2001). *New Engl. J. Med.*, **344** : 1145-51.
3. **McNamara, J.O.** (1999). Emerging Insights into the genesis of epilepsy. *Nature*, **399** : A15-A22.
4. **Brazil, C.W.** and Pedly, T.A. (1998). Advances in the Medical Treatment of Epilepsy. *Ann. Rev. Med.*, **49** : 135-62.
5. **McCabe, P.H.** (2000). New Anti-Epileptic drugs for the 21st Century. Expert Opinion. *Pharmacother,* **1** : 633-74.
6. **Lopes Lima, J.M.** (2000). The new drugs and strategies to manage epilepsy. *Curr. Pharmac. Design*, **6** : 873-78.
7. **Perucca, E.** (2000). Marketed new antiepileptic drugs: Are they better than old-generation agents? *Ther. Drug Monit.*, 24 : 74-80.
8. **Berk, M.,** Segal, J., Janet, L., Vorster, M. (2001). Emerging options in the treatment of bipolar disorders. *Drugs,* **61** : 1407-14.
9. **Duncan, J.S.** (2002). The promise of new antiepileptic drugs. *British J. Clin. Pharmacol.*, **53** : 123-31.
10. **Eadie, M.J.** (20001). Can anticonvulsant drug therapy 'cure' epilepsy? CNS Drugs, **15**: 679-90.
11. **Szelenyi, I.**, Horvath, K., Howes, J.F. and Mazarati, AM. (2003). The treatment of epilepsy: future possibilities. *Drugs Fut.*, **28**: 925-36.
12. **Regesta, G.** and Tanganelli, P. (1999). Clinical Aspects and Biological Bases of Drug-resistant Epilepsies. *Epilepsy Res.,* **34** : 109-22.
13. **Kwan, P.** (2000). Brodie MJ. Early Identification of Refractory Epilepsies. *New England J. Med.*, **342** : 314-19.
14. **Bruno-Blanch, L.**, Galvez, J. and Garcia-Domenech, R. (2003). Topological virtual screening: A way to find new anticonvulsant drugs from chemical diversity. Bioorg. Med. Chem. Lett., **13** : 2749-54.
15. **Malawska, B.** (2003). Application of pharmacophore models for the design and synthesis of new anticonvulsant drugs. *Mini Rev. Med. Chem.*, **3** : 341-48.
16. **Loscher, W.C.** (2002). Current Status and Future Directions in the Pharmacotherapy of Epilepsy. *Trends. Pharmacol. Sci.*, **23**:113-18.
17. **Bauer, J.** and Reuber, M. (2003). Medical Treatment of Epilepsy. Expert Opinion. *Emerging Drugs,* **8** : 457-67.
18. **Edafiogho, I.** and Scott, KR. (1996). Anticonvulsants. In: Wolff E, John ME, editors. Burger's Medicinal Chemistry and Drug Discovery Vol.3: Therapeutic Agents. 5th ed. Wiley & Sons;1996.p.175-260.
19. **Cosford, N.D.P.**, Meinke, P.T., Stauderman, K.A. and Hess, S.D. (2002). Recent advances in the modulation of voltage-gated ion channels for the treatment of epilepsy. Curr. Drug Targ. CNS & Neur. Dis., **1** : 81-104.
20. **Auberson, Y.P.** (2001). Competitive AMPA antagonism: A novel mechanism for antiepileptic drugs? Drugs Fut., **26** : 463-71.

21. **Jansen, M.** and Dannhardt, G. (2003). Antagonists and agonists at the glycine site of the NMDA receptor for therapeutic interventions. *Eur. J. Med. Chem.*, **38** : 661-70.

22. **Isaac, M.** (2001). The 5-HT2C receptor as a potential therapeutic target for the design of antiobesity and antiepileptic drugs. *Drugs Fut.,* **26** : 383-93.

23. Wiesner, J.B., Ugarkar, B.G., Castellino, A.J., Barankiewicz, J., Dumas, D.P., Gruber, H.E., Foster, A.C. and Erion, M.D. (1999). Adenosine kinase inhibitors as a novel approach to anticonvulsant therapy. *J. Pharmacol. Exp. Ther.*, **289** : 1669-77.

24. **Zorumski, Ch.F.**, Mennerick, S., Isenberg, K.E. and Covey, D.F. (2000). Potential clinical uses of neuroactive steroids. *Curr. Op. Invest. Drugs*, 1:360-369.

25. **Czuczwar, S.J.** and Patsalos, P.N. (2001). The new generation of GABA enhancers. *CNS Drugs,* **15** : 339-50.

26. **Gatti, G.,** Bonomi, I., Jannuzzi, G. and Perucca, E. (2000). The new antiepileptic drugs: Pharmacological and clinical aspects. *Curr. Pharm. Design,* **6** : 839-860.

27. **Nicolson, A.** and Leach, J.P. (2001). Future prospects for the drug treatment of epilepsy. *CNS Drugs,* **15** : 955-68.

28. **Patsalos, P.N.** (1999). Ant-epileptic drugs: Newly licensed and under development. *Curr. Op. Inv. Drugs*, **1** : 549-62.

29. **Saxena, A.K.** and Saxena, M. (1995). Development in anticonvulsants. Progress in Drug Research Ed Jucker, E.Birkhauser verlag Basel Boston Berlin, **44**:185-291.

30. **Cosford, N.D.P.**, McDonald, I.A. and Schweiger, E.J. (1998). Recent progress in antiepileptic drug research. Annual Reports in Medicinal Chemistry Robertson Ed Academic Press, **33** : 61-70.

31. **Martin, L.,** Rabasseda, X., Leeson, R.P. and Casta er, J., (1999). *Pregabalin. Drugs Fut.*, **24**: 862-70.

32. **Hachad, H.**, Ragueneau-Majlessi, I. and Levy, R.H. (2002). New antiepileptic drugs: Review on drug interactions. *Ther. Drug Monit*, **24** : 91-103.

33. **Blackburn, T.P.**, Buckingham, R.E., Chan, W.N., Evans, J.M., Hadley, M.S., Thompson, M., Upton, N., Stean, T.O., Stemp, G. and Vong, A.K. (1995). Stereochemical differentiation of anticonvulsant and antihypertensive effects in (4-fluorobenzoylamino)-benzopyrans. *Bioorg. Med. Chem. Lett.*, **5** : 1163-66.

34. **Chan, W.N.,** Upton, N. and Vong, AK. (1996). Synthesis of novel *trans*-4-(substituted-benzamido)-3,4-dihydro-2*H*-benzo[*b*]pyran-3-ol derivatives as potential anticonvulsant agents with a distinctive binding profile. *J. Med. Chem.*, **39** : 4537-39.

35. **Herdon, H.J.,** Jerman, J.C., Stean, T.O., Middlemiss, D.N., Chan, W.N., Vong, A.K., Evans, J.M., Thompson, M. and Upton, N. (1997). 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. *Brit. J. Pharmacol.,* **121**:1687.

36. **Austin, N.E.,** Hadley, M.S., Harling, J.D., Harrington, F.P., Macdonald, G.J., Mitchell, D.J., Riley, G.J., Stean, T.O., Stemp, G., Stratton, S.C., Thompson, M. and Upton, N. (2003). The design of 8,8-dimethyl[1,6]naphthyridines as potential anticonvulsant agents. *Bioorg. Med. Chem. Lett.*, **13** : 1627-29.

37. **Supuran, C.T.,** Mincione, F., Scozzafava, A., Briganti, F., Mincione, G. and Ilies, M.A. (1998). Carbonic anhydrase inhibitors. Metal complexes of heterocyclic sulfonamides: A new class of strong topical intraocular pressure-lowering agents with potential use as antiglaucoma drugs. *Eur. J. Med. Chem.*, **33** : 247-54.

38. **Ilies, M.A.,** Masereel, B., Rolin, S., Scozzafava, A., Campeanu, G., Cimpeanu, V. and Supuran, C.T. (2004). Carbonic anhydrase inhibitors: Aromatic and heterocyclic sulfonamides incorporating adamantyl moieties with strong anticonvulsant activity. *Bioorg. Med. Chem.*, **12** : 271726.

39. **Kim, Y.,** Zhao, L-X, Kim, T-H, Je, S., Kim, E., Choi, H., Chae, W-G, Park, M., Choi, J., Jahng, Y., Lee, E-S. (2000). Design and synthesis of anticonvulsive agents as g-vinyl GABA-based potential dual acting prodrugs and their biological activities. *Bioorg. Med. Chem. Lett.*, **10** : 609-13.

40. **Zhao, L-X**, Park, J.G., Moon, Y-S, Basnet, A., Choi, J., Kim, E., Jeong, T.C., Jahng, Y., Lee, E-S. (2004). Design, synthesis and anticonvulsive activity of analogs of g-vinyl GABA. *Farmaco,* **59** : 381-88.

41. **Malawska, B.** and Gobaille, S. (1995). Synthesis, physicochemical and pharmacological properties of new *N*-substituted amides of α-piperazine-g-hydroxybutyric acid. *Pharmazie,* **50** : 390-93.

42. **Malawska, B.** and Zejc, A. (1995). Search for new anticonvulsant compounds. Part 1: Synthesis, physicochemical and anticonvulsant properties of new derivatives of α -amino-g-phthalimidobutyric acid. *Pharmazie*, **50** : 722-55.

43. **Mendyk, A.,** Sa at, K., Librowski, T., Czarnecki, T., Malawska, B. (2001). Influence of new g-aminobutyric acid amide derivatives and its phthalimide precursors on the central nervous system activity in mice. *Pol. J. Pharmacol.,* **53** : 689-93.

44. **Malawska, B.**,Kulig, K.,Ciechanowicz-Rutkowska, M.(1999). Search for new anticonvulsant compounds, Part 2: Structure-activity relationship studies of new *N*-substituted amides of α-piperazine-g-hydroxybutyric acid as active anticonvulsants. *Arch. Pharm. Pharm. Med. Chem.*, **330** : 91-99.

45. **Malawska, B.** and Antkiewicz-Michaluk, L. (1999). 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-phenylpiperazine)-GABA. *Pharmazie*, **54** : 239-43.

46. **Malawska, B.,** Kulig, K., Antkiewicz-Michaluk, L., Cliffe, I., Porter, R., Misra, A. (1999). Anticonvulsant activities and voltage-sensitive calcium channels receptor affinity of substituted *N*-benzylamides of g-amino- and g-hydroxybutyric acid. *Arch. Pharm. Pharm. Med. Chem.*, **332** : 167-74.

47. **Sa V at, K.**, Mendyk, A., Librowski, T., Czarnecki, R. and Malawska, B. (2002). Influence of new g-hydroxybutyric acid amide analogues on the central nervous system activity in mice. *Pol. J. Pharmacol.*, **54**:731-36.

48. **Malawska, B.**, Kulig, K. and Bendieck, E. (2003). Comparison of chromatographically determined values of the lipophilicity of anticonvulsant active *N*-substituted amides of α-arylalkylamine-g-hydroxybutyric acid with values estimated by computational methods. *J. Planar Chromatogr*, **16** : 390-95.

49. **Malawska, B.** (2001). Searching of -amino- and g-hydroxybutyric acid analogues with expected anticonvulsant activity (Polish). *Wiad. Chem.*, **55**:377-402.

50. **Malawska, B.**, Kulig, K., Spiewak, A. and Stables, J.P. (2004). Investigation into new anticonvulsant derivatives of α -subsituted *N*-benzylamides of g-hydroxy- and g-acetoxybutyric acid. Part.5: Search for new anticonvulsant compounds. *Bioorg. Med. Chem.*, **12**:625-32.

51. **Hinko, C.N.**, Crider, A.M., Kliem, M.A., Steinmiller, C.I., Seo, T.H., Ho, B., Venkatarangan, P., El-Assadi, A.A., Chang, H., Burns, C.M., Tietz, E.I., Andersen, P.H. and Klitgaard, H. (1996). Anticonvulsant activity of novel derivatives of 2- and 3 piperidinecarboxylic acid in mice and rats. *Neuropharmacology,* **35** : 1721-35.

52. **Ho, B.**, Venkatarangan, P., Cruse, S.F., Hinko, C.N., Andersen, P.H., Crider, A.M., Adloo, A.A., Roane, D.S. and Stables, J.P. (1998). Synthesis of 2-piperidinecarboxylic acid derivatives as potential anticonvulsants. *Eur. J. Med. Chem.,* **33** : 23-31.

53. **Ho, B.**, Crider, A.M. and Stables, J.P. (2001). Synthesis and structure-activity relationships of potential anticonvulsants based on 2-piperidinecarboxylic acid and related pharmacophores. *Eur. J. Med. Chem.*, **36** : 265-86.

54. **Goel, A.** and Madan, A.K. (1995). Structure-activity study of antiepileptic*N*-aryl-isoxazolecarboxamides/*N*-isoxazolylbenzamide analogs using Wiener's topological index. *Stru. Chem.*, **2** : 155-59.

55. **Brown, M.L.Z.C.C.**, Van Dyke, C.C., Brown, G.B., Brouillette, W.J. (1999). Comparative molecular field analysis of hydantoin binding to the neuronal voltage-dependent sodium channel. *J. Med. Chem.*, **42**:1537-45.

56. **Schenck, H.A.**, Lenkowski, P.W., Choudhury-Mukherjee, I., Ko, S-H, Stables, J.P., Patel, M.K., Brown, M.L. (2004). Design, synthesis and evaluation of novel hydroxyamides as orally available anticonvulsants. *Bioorg. Med. Chem.,* **12** : 979-93.

57. **Marona, H.** and Szneler, E. (2003). Preliminary evaluation of anticonvulsant activity of some 4-(benzyloxy)-benzamides. *Acta Pol. Pharm. Drug-Res.*, **60** : 477-80.

58. **Conley, J.D.** and Kohn, H. (1987). Functionalized DL-amino acid derivatives. Potent new agents for the treatment of epilepsy. *J. Med. Chem.*, **30**:567-74.

59. **Kohn, H.,** Conley, J.D. and Leander, J.D. (1988). Marked stereospecificity in a new class of anticonvulsants. *Brain Res.*, **457**: 371-75.

60. **Kohn, H.**, Sawhney, K.N., LeGall, P., Conley, J.D., Robertson, D.W. and Leander, J.D. (1990). Preparation and anticonvulsant activity of a series of functionalized α-aromatic and α-heteroaromatic amino acids. *J. Med. Chem.*, **33** : 919-26.

61. **Kohn, H.**, Sawhney, K.N., LeGall, P., Robertson, D.W. and Leander, J.D. (1991). Preparation and anticonvulsant activity of a series of functionalized á-heteroaromatic-substituted amino acids. *J. Med. Chem.*, **34** : 2444-52.

62. **Kohn, H.,** Sawhney, K.H., Bardel, P., Robertson, D.W. and Leander, J.D. (1993). Synthesis and anticonvulsant activities of α-heteroaromatic-α-acetamido-N-benzylacetamide derivatives. *J. Med. Chem.*, **36** : 3350-60.

63. **Bardel, P.**, Bolanos, A. and Kohn, H. (1994). Synthesis and anticonvulsant activities of α-acetamido-N-benzylacetamide derivatives containing an electron-deficient α-heteroaromatic substituent. *J. Med. Chem.*, **37** : 4567-71.

64. **Kohn, H.**, Sawhney, K.N., Robertson, D.W. and Leander, J.D. (1994). Anticonvulsant properties of N-substituted α, α -diamino acid derivatives. *J. Pharm. Sci.*, **83**:689-91.

65. **Choi, D.,** Stables, J.P. and Kohn, H. (1996). Synthesis and anticonvulsant activities of N-benzyl-2-acetamidopropionamide derivatives. *J. Med. Chem.*, **39** : 1907-16.

66. **Andurkar, S.V.,** Stables, J.P. and Kohn, H. (1999). The anticonvulsant activities of N-benzyl-3-methoxypropionamides. *Bioorg. Med. Chem.*, **7** : 2381-89.

67. **Le Tiran, A.**, Stables, J.P. and Kohn, H. (2001). Functionalized amino acid anticonvulsants: Synthesis and pharmacological evaluation of conformationally restricted analogues. *Bioorg. Med. Chem.*, **9** : 2693-708.

68. **Andurkar, S.V.,** Beguin, C., Stables, J.P., Kohn, H. (2001). Synthesis and structural studies of aza analogues of funcionalized amino acids: New anticonvulsant agents. *J. Med. Chem.*,**44** : 1475-78.

69. **Le, Tiran, A.**, Stables, J.P. and Kohn, H. (2002). Design and evaluation of affinity labels of functionalized amino acid anticonvulsants. *J. Med. Chem.*, **45**:4762-73.

70. **Shen, M.,** Le, Tiran, A., Xiao, Y., Golbraikh, A., Kohn, H. and Tropsha, A. (2002). Quantitative structure-activity relationships analysis of funcionalized amino acid anticonvulsant agents using k nearest neighbor and simulated annealing PLS methods. *J. Med. Chem.*, **45** : 2811-23.

71. **Beguin, C.**, Andurkar, S.V., Jin, A.Y., Stables, J.P., Weaver, D.F. and Kohn, H. (2003). Functionalized amido ketones: New anticonvulsant agents. *Bioorg. Med. Chem.*, **11** : 4275-85.

72. **Beguin, C.**, LeTiran, A., Stables, J.P., Voyksner, R.D. and Kohn, H. (2004). *N*-Substituted amino acid *N'*-benzylamides: Synthesis, anticonvulsant, and metabolic activities. *Bioorg. Med. Chem.*, **12** : 3079-96.

73. **Paruszewski, R.**, Rostafinska-Suchar, G., Strupinska, M, Jaworski, P., Stables, J.P. (1996). Synthesis and anticonvulsant activity of some amino amid derivatives. Part 1: Alanine derivatives. *Pharmazie,* **51** : 145-48.

74. **Paruszewski, R.**, Rostafinska-Suchar, G., Strupinska, M., Jaworski, P., Winiecka, I., Stables, J.P. (1996). Synthesis and anticonvulsant activity of some amino amid derivatives. Part 2: Derivatives of Gly, Ala, Leu, Pro, Trp, Phe(4Cl), Ala(á-Me). *Pharmazie*, **51** : 212-15.

75. **Paruszewski, R.,** Rostafinska-Suchar, G., Strupinska, M., Winiecka, I. and Stables, J.P. (2000). Synthesis and anticonvulsant activity of some amino amid derivatives. Part 3: Derivatives of Ala. Arg, Tzl, Gly and χ Abu. *Pharmazie,* **55** : 27-30.

76. **Paruszewski, R.**, Strupinska, M., Stables, J.P., Swiader, M., Czuczwar, S., Kleinrock, Z. and Turski, W. (2001). Amino acid derivatives with anticonvulsant activity. *Chem. Pharm. Bull.*, **49**:629-31.

77. **Paruszewski, R.**, Strupinska, M., Rostafinska-Suchar, G., Stables, J.P. (2003). Anticonvulsant activity of benzylamides of some amino acids and heterocyclic acids. *Prot. Pept. Lett.*, **10** : 475-82.

78. **Paruszewski, R.**, Rostafinska-Suchar, G., Strupinska, M. and Stables, J.P. (2004). The Fourth Multidisciplinary Conferences on Drug Research, Gdan´sk-Sobieszewo, Book of abstract, p-129.

79. **Kiec-Kononowicz, K.**, Karolak-Wojciechowska, J. and Handzlik, J. (1998). Glycine derivatives of imidazolones as potential ligands of glycine binding site of NMDA receptors. *Acta Pol. Pharm. Drug. Res.*, **55** : 381-88.

80. **Kiec-Kononowicz, K.** and Karolak-Wojciechowska, J. Structure and activity studies on glycine receptor ligands. Diphenyl imidazolin-4- one glycinamides. *Acta Pol. Pharm. Drug Res.*, **55**:389-97.

81. **Karolak-Wojciechowska, J.**, Kiec-Kononowicz, K. and Mrozek, A. (2001). Structure and activity studies of glycine receptor ligands. Structural remarks on arylidene-imidazoline-4-one glycinates and glycinamides. *J. Mol. Struct.*, **597** : 73-81.

82. **Karolak-Wojciechowska, J.**, Mrozek, A., Kiec-Kononowicz, K. and Handzlik, J. Structure and activity studies of glycine receptor ligands. Arylidene-imidazoline-4-one aminoacids. *J. Mol. Srtuct.*, **649** : 25-36.

83. **Tan, C.Y.K.**, Wainman, D. and Weaver, D.F. (2003). *N*-, α-, and β-Substituted 3aminopropionic acids: Design, syntheses and antiseizure activities. *Bioorg. Med. Chem.*, **11**: 113-21.

84. **Karakurt, A.,** Dalkara, S., Ozalp, M., Ozbey, S., Kendi, E. and Stables, J.P. (2001). Synthesis of some1-(2-naphthyl)-2-(imidazole-1-yl)ethanone oxime and oxime ether derivatives and their anticonvulsant and antimicrobial activities. *Eur. J. Med. Chem.*, **36**:421-33.

85. **Bishop, M.J.** and Nilsson, B.M. (2003). New 5-HT2C-receptor agonist expert opinion. *Ther. Patent,* **13** : 1691-1705.

86. **Kimura, Y.,** Hatanaka, K., Naitou, Y., Maeno, K., Shimada, I., Koakutsu, A., Wanibuchi, F. and Yamaguchi, T. (2004). Pharmacological profile of YM348, a novel, potent and orally active 5-HT2Creceptor agonist. *Eur. J. Pharmacol.,* **483** : 37-43.

87. **Bickerdike, M.J.** (2003). 5-HT2C receptor agonists as potential drugs for the treatment of obesity. *Curr. Top. Med. Chem.*, **3** : 885-97.

88. **Zejc, A.,** Obniska, J., Wilimowski, M., Rutkowska, M., Witkowski, J., Barczynska, L., Kedzierska-Gozdzik, L., Wojewodzki, W., Orzechowska-Juzwenko, K., Plawiak, T., Dus, E., Gryska, J. and Gliniak, M. (1990). Synthesis and anticonvulsant properties of some arylsuccinate methylpyridylimides. *Pol. J. Pharmacol. Pharm.*, **42**:69-77.

89. **Obniska, J.,** Kulig, K. and Zejc, A. (1998). Synthesis and anticonvulsant properties of new *N*-piperazinylalkyl imides of succinic acid. *Acta Pol. Pharm. Drug. Res.*, **55** : 223-31.

90. **Obniska, J.,** Zejc, A. and Karolak-Wojciechowska, J. (1999). Synthesis and anticonvulsant properties of new *N*-pyridyl derivatives of 3-phenyland 3,3-diphenyl-succinimides. *Farmaco,* **54** : 423-29.

91. **Obniska, J.**, Zejc, A. and Zagorska, A. (2002). Synthesis and anticonvulsant properties of new 1-phenyl and 1-phenylamino-3-phenylpyrrolidine-2,5-dione derivatives. *Acta Pol. Pharm. Drug Res.*, **59**: 209-13.

92. **Obniska, J.** and Zagorska, A. (2003). Synthesis and anticonvulsant properties of new *N*-[(4-arylpiperazin-1-yl)-methyl] derivatives of 3-aryl pyrrolidine-2,5-dione and 2-aza-spiro[4.4]nonane-1,3-dione. *Farmaco*,**58**:1227-34.

93. **Brouillette, W.J.** and Grunewald, G.L. (1984). Synthesis and anticonvulsant activity of some substituted lactams and amides. *J. Med. Chem.*, **27** : 202-06.

94. **Reddy, P.A.**, Hsiang, B.C.H., Latifi, T.N., Hill, M.W., Woodward, K.E., Rothman, S.M., Ferrendelli, J.A. and Covey, D.F. (1996). 3,3-dialkyland 3-alkyl-3-benzyl-substituted 2-pyrrolidinones: A new class of anticonvulsant agents. *J. Med. Chem.*, **39**: 1898-1906.

95. **Reddy, P.A.**, Woodward, K.E., McIlheran, S.M., Hsiang, B.C.H., Latifi, T.N., Hill, M.W., Rothman, S.M., Ferrendelli, J.A. and Covey, D.F. (1997). Synthesis and anticonvulsant activities of 3,3-dialkyl- and 3-alkyl-3-benzyl-2-piperidinones (δvalerolactams) and hexahydro- 2H-azepin-2-ones (ε-caprolactams). *J. Med. Chem.*, **40** : 44-49.

96. **Grimm, J.B.**, Stables, J.P., Brown, M.L. (2003). Design, synthesis, and development of novel caprolactam anticonvulsants. *Bioorg. Med. Chem.*, **11**: 4133-41.

97. **Dimmock, J.R.**, Sidhu, K.K., Tumber, S.D., Basran, S.K., Chen, M., Quail, J.W., Yang, J., Rozas, I., Weaver, D.F. (1995). Some aryl semicarbazones possessing anticonvulsant activities. *Eur. J. Med. Chem.*, **30**:287-301.

98. **Dimmock, J.R.**, Pandeya, S.N., Quail, J.W., Pugazhenthi, U., Allen, T.M., Kao, G.Y. and Balzarini, J. (1995). DeClercq, E. Evaluation of the semicarbazones, thiosemicarbazones and bis-carbohydrazones of some aryl alicyclic ketones for anticonvulsant and other biological properties. *Eur. J. Med. Chem.*, **30** : 303-14.

99. **Dimmock, J.R.**, Puthucode, R.N., Smith, J.M., Hetherington, M., Quail, J.W., Pugazhenthi, U., Lecher, T. and Stables, J.P. (1996). (Aryloxy)aryl semicarbazones and related compounds: A novel class of anticonvulsant agents possessing high activity in the maximal electroshock screen. *J. Med. Chem.,* **39**:3984-97.

100. **Puthucode, R.,** Pugazhenthi, U., Quail, J.W., Stables, J.P. and Dimmock, J.R. (1998). *Eur. J. Med. Chem.*, **33**:595-607.

101. **Pandeya, S.N.**, Ponnilavarasan, I., Pandey, A., Lakhan, R. and Stables, J.P. (1999). Evaluation of *p*-nitrophenyl substituted semicarbazones for anticonvulsant properties. *Pharmazie,* **54** : 923-25.

102. **Dimmock, J.R.**, Vashishtha, S.C. and Stables, J.P. (2000). Anticonvulsant properties of various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. *Eur. J. Med. Chem.*, **35** : 241-48.

103. **Pandeya, S.N.**, Yogeeswari, P. and Stables, J.P. (2000). Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones. *Eur. J. Med. Chem.*, **35** : 879-86.

104. **Pandeya, S.N.**, Mishra, V., Ponnilavarasan, I. and Stables, J.P. (2000). Anticonvulsant activity of *p*-chlorophenyl substituted aryl semicarbazones – The role of primary terminal amino group. *Pol. J. Pharmacol.*, **52** : 283-90.

105. **Dimmock, J.R.**, Vashishtha, S.C., Stables, J.P. (2000). Ureylene anticonvulsants and related compounds. *Pharmazie,* **55** : 490-94.

106. **Pandeyam, S.N.**, Manjula, H. and Stables, J.P. (2001). Design of semicarbazones and their bio-isosteric analogues as potential anticonvulsants. *Pharmazie,* **56** : 121-24.

107. **Yogeeswari, P.**, Sriram, D., Sunil, J.L.R., Kumar, S.S., Stables, J.P. (2002). Anticonvulsant and neurotoxicity evaluation of some 6- chlorobenzothiazolyl-2-thiosemicarbazones. *Eur. J. Med. Chem.*, **37** : 231-36.

108. **Pandeya, S.N.,** Agarwal, A.K., Singh, A. and Stables, J.P. (2003). Design and synthesis of semicarbazones and their bio-isosteric analogues as potent anticonvulsants: The role of hydrogen bonging. *Acta Pharm.*, **53**:15-24.

109. **Popp, F.D.** (1984). Potential anticonvulsants.IX.Some isatin hydrazones and related compounds. *J. Heteroc Chem.*, **21** : 1641-45.

110. **Pandeya, S.N.**, Sriram, D., Yogeeswari, P., Stables, J.P. (2001). Anticonvulsant and neurotoxicity evaluation of 5-(un)-substituted isatin-imino derivatives. *Pharmazie,* **56** : 875-76.

111. **Srivastava, A.V.K.** and Kumar, A. (2002). Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3*H*)-ones as potential anticonvulsant agents. *Eur. J. Med. Chem.*, **37** : 873-82.

112. **Chapleo, C.B.,** Mayer, M., Myer, P.L., Saville, J.F., Smith, A.C.B., Stilling, M.R., Tulloch, I.F., Walter, D.S. and Welbourn, A.P. (1987). Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 1. Hydrazines *J. Med. Chem.*, **29** : 2273-80.

113. **Srivastava, A.V.K.** and Kumar, A. (20004). Synthesis of some newer derivatives of substituted quinazolinonyl-2-oxo/thiobarbituric acid as potent anticonvulsant agents. *Bioorg. Med. Chem.*, **12** : 1257-64.

114. **Dogan, H.N.,** Duran, A., Rollas, S., Sener, G., Uysal, M.K. and Gulen, D. (2002). Synthesis of new 2,5-disubstituted-1,3,4-thiadiazoles and preliminary evaluation of anticonvulsant and antimicrobial activities. *Bioorg. Med. Chem.*, **10** : 2893-98.

115. **Coudert, P.,** Rubat, C., Couquelet, J., Fialip, J., Bastide, P. and Privat, A.M. (1989). Synthèse et recherche d'une activité anti-convulsivante dans une nouvelle série de diaryl-4,6 pyridazinones-3 *N*-substituées. *Eur. J. Med. Chem.*, **24**: 551-55.

116. **Rubat, C.**, Coudert, P., Refouvelet, B., Tronche, P., Bastide, P. and Bastide, P. (1990). Anticonvulsant Activity of 3-Oxo-5-substituted Benzylidene-6-methyl-(4H)-2-pyridazinylacetamides and 2-Pyridazinylacetylhydrazides. *Chem. Pharm. Bull.*, **38**(11):3009-13.

117. **Bihzad, S.**, Al-Zaid, B. and Edafiogho, I.O. (2002). Phthalimidooxy compound (E49) as a potential anticancer agent. Seventh Annual Health Sciences Poster Day, p.181.

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