On Chemical Structures with Potent Antiepileptic/Anticonvulsant Profile

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Abstract: Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. There has been a considerable interest in the development of many antiepileptic and anticonvulsant agents for controlling epilepsy with fewer side effects and improvement of quality of life. Since the terms antiepileptics /anticonvulsants are used interchangeably, this article reviews their classification according to the chemical structure into: hydantoins, oxazolidinediones, succinimides, barbiturates, amides, benzodiazepines, valproic acid and its derivatives, GABA-analogues, cycloalkanes, semicarbazones, γ butyrolactones (GBLs), imidaquinazolines and pyrrolidine derivatives as well as miscellaneous compounds. In addition, the review discusses the different mechanisms of action of antiepileptic and anticonvulsant agents.

Keywords: Epilepsy, Mechanism of action of antiepileptics, Antiepileptics, Anticonvulsants.

I. INTRODUCTION

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures [1,2]. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain [3]. About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries [4]. Epilepsy is more likely to occur in young children or people over the age of 65 years; however it can occur at any time [5]. Genetic, congenital, and developmental conditions are mostly associated with epilepsy among younger patients. Tumors, head trauma and central nervous system infections may result in epileptic seizures at any age. The prevalence of active epilepsy is in the range 5–10 per 1000 people. Epilepsy's approximate annual incidence rate is 40–70 per 100,000 in industrialized countries and 100–190 per 100,000 in resource-poor countries; socioeconomically deprived people are at higher risk. In industrialized countries the incidence rate decreased in children but increased among the elderly during the three decades prior to 2003, for reasons not fully understood [6]. Beyond symptoms of the underlying diseases that can cause certain epilepsies, people with epilepsy are at risk for death from four main problems: status epilepticus (most often associated with anticonvulsant noncompliance), suicide associated with depression, trauma from seizures, and sudden unexpected death in epilepsy (SUDEP) [7-10]. Epilepsy is usually controlled, but not cured, with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizures control [11, 12]. Thus introduction of new antiepileptics and anticonvulsants is persistence aiming to achieve the best medications with fewer side effects.

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II. TYPES OF EPILEPTIC STATE SEIZURES

1. Partial (Focal) Seizures

This type of seizures involves only part of one lobe of one hemisphere. The symptoms depend on the site of the neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Consciousness is usually preserved. A diagnosis may classify partial seizures as simple and complex seizures:

a. Simple Partial

In this type of seizures the electrical discharge does not spread and patient does not lose consciousness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also shows sensory distortious. This activity may spread.

b. Complex Partial

These seizures may occur at any age and exhibit complex sensory hallucinations, mental distortion and loss of consciousness. Motor dysfunction may involve chewing movements, diarrohea and/or urination.

Simple partial seizure activity may spread and become complex which may later develop into a secondary generalized convulsion [13].

2. Generalized Seizures

This type of seizures may begin locally, producing abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or non convulsive and the patient usually has an immediate loss of consciousness. Generalized seizures can be classified into:

a. Tonic-Clonic Seizures

Seizures result in loss of consciousness followed by tonic (continuous contractions) and clonic (rapid contraction and

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relaxation) phases. The seizures may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

b. Abscense Seizures

These seizures involve a brief, abrupt and self-limited loss of consciousness. The patient stares and exhibits rapid, eye-blinking which lasts three to five seconds, that generally occurs in patients at three to five years of age and lasts until puberty or beyond.

c. Myoclonic Seizures

These seizures consist of short episodes of muscle contractions that may reoccur for several minutes. They exhibit a brief jerk of the limbs.

d. Febrile Seizures

Young children may develop seizures with illness accompanied by high fever. The febrile seizures consist of generalize tonic-clonic convulsions of short duration and do not nessearily lead to diagnosis of epilepsy.

e. Satus Epileticus

In such condition, two or more seizures recur without recovery of full cosciousness between them. Status epileticus is life threatening and requires emergency treatment [13].

3. Lennox-Gastaut Syndrom

It is a particular severe and intractable type of epilepsy that occurs in children. This type is associated with progressive mental retardation which is possibly a reflection of excitotoxic neurodegeneration [14].

Thus it is noteworthy that many of the current antiepileptic drugs were developed empirically on the basis of their activity in animal models. However, the ultimate goal of the antiepileptics is to prevent the paroxysmal discharge without affecting normal transmission [15].

III. ANTIEPILEPTIC AND ANTICONVULSANT AGENTS

It is worth mentioning that the two terms, antiepileptics and anticonvulsants are used interchangeably. An antiepileptic drug is a drug used clinically to control epilepsy in human. On the other hand the term anticonvulsant designates an agent that blocks experimentally produced seizures in laboratory animals [14].

1. Mechanisms of Action of Antiepileptic Drugs

The general effect of antiseizure drugs is to supress repitetive action potential in epileptic foci in the brain. There are various mechanisms that are involved in achieving this effect. Four main mechanisms appear to be important in the action of antiepileptic drugs [16], which are going to be discussed hereunder:

a. Enhancement of GABA Action

γ Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the vertebrate central nervous system [17]. GABA interacts with three different receptor classes, the $GABA_A$, $GABA_B$ and $GABA_C$ receptors [18]. Many anticonvulsant drugs are reported to act by increasing the GABA level in the brain or by enhancing the inhibitory effect of $GABA_A$-receptors. GABA aminotransferase enzyme was found to play an important role in degradation of GABA mediator, by its deamination-oxidation into the succinic semialdehyde that will be converted by another enzyme-succinic semialdehyde dehydrogenase(SSAD)-into succinic acid. In another words, GABA aminotransferase would decrease GABA level [19], Fig. (**1**) [20]. Accordingly, the GABA aminotransferase enzyme would be considered as a target for the discovery of novel anticonvulsant agents. This enzyme was isolated as crystal structures with the anticonvulsant agents e.g. gabapentin and vigabatrin and is available in protein data bank (PDB). However, other drugs that may facilitate the inhibitory actions of GABA include felbamate, topiramate and valproic acid.

b. Inhibition of Sodium-Channel

This mechanism involves the antiepileptic drugs which affect membrane excitability by interaction with ionotropic receptors and exert action on voltage-dependent sodium-channels. The latter carry the inward membrane current necessary for the generation of action potential. Drugs activity through such mechanism block preferentially the excitation of cells that are firing repetitively during the

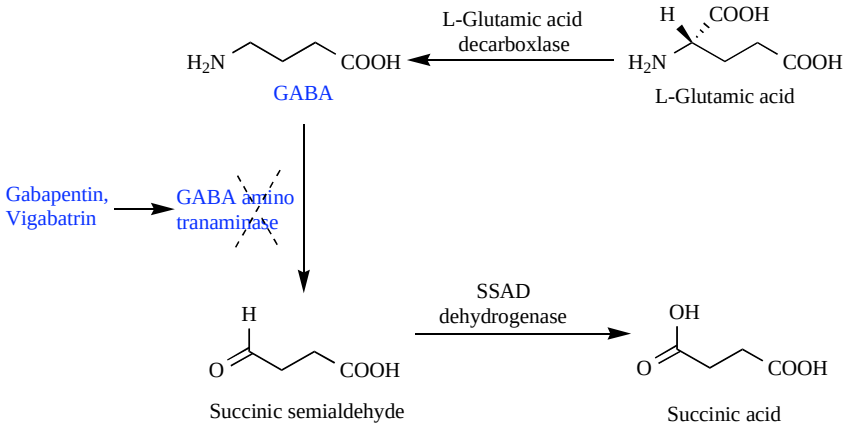


Fig. (1). Schematic diagram of biosynthesis and metabolism of GABA [20].

epileptic seizures e.g. phenytoin, carbamazepine, valproic acid and lamotrigine and the higher the frequency of firing, the greater the block produced. Depolarization of neurons increases the proportion of sodium-channels in the inactivated state. Antiepileptic drugs bind preferentially to channels in this state, preventing them from returning to the activated state, and thus reducing the number of functional channels available to generate seizures [21].

c. Inhibition of Calcium-Channels

Here the drug used in epileptic episodes affects other aspect of membrane function, that is the calcium-channel, which could also interfere with membrane excitability and synaptic function e.g. phenytoin which does not only use-dependant block of sodium channels but also affects calcium-channels.

Several antiepileptic drugs inhibit low-threshold (T-type) calcium-current, especially in thalamic neurons that act as pacemakers to generate the rythmic cortical discharge e.g. ethosuximide, valproic acid. Gabapentin may act on L-type calcium-channels, but whether this is important for its antiepileptic properties is still uncertain [21].

d. Blocking Glutamate G-Protien-Coupled Metabotropic Receptors

Glutamic acid is considered the main excitatory neurotransmitter in the CNS. Thus other mechanisms that may operate with some anticonvulsants are inhibition of glutamate release and block glutamate G-protien-coupled metabotropic receptors. e.g. pregabalin [22].

2. Classes of Antiepileptic and Anticonvulsant Agents

Antiepileptic drugs are chemical compounds (c.f. Table **1**) that are used in controlling seizures and are classified according to their chemical classes.

a. Hydantoins

Hydantoins which are considered as cyclic imides, are a major class which involves drugs that possess pronounced anticonvulsant property [14].

Phenytoin (Epanutin ®, **1**), is the oldest non-sedative antiseizures drug. It is the most important member of this group which is used to treat partial and generalized epilepsy. It is highly effective in reducing the intensity and duration of electrically induced convulsions in mice. It alters sodium, potassium and calcium conductance, membrane potentials and the concentrations of amino acids and the neurotransmitters norepinephrine, acetyl choline and gamma-amino butyric acid (GABA). The usual adult dose range is 200-600mg/day and the therapeutic plasma level of phenytoin is 10-20 mcg/mL [23, 24].

Many congeners of phenytoin have been synthesized including ethotoin (Peganone®, **2**). This drug is an antiepileptic agent employed against generalized seizures, but usually on an adjunctive basis owing to its low potency. Generally, removal of one substitution in carbon 5 decreases the potency [15, 25]. Ethotoin may be recommended for hypersensitive patients to phenytoin, however larger doses are required.

The phenytoin prodrug fosphenytoin (Pro-Epanutin®, **3**) is used as an alternative of phenytoin for parentral use. This phosphate ester pro-drug is rapidly metabolised to phenytoin in plasma within 8-15 minutes [26, 27].

Mephenytoin (Mesantoin®, **4**) demonstrates a prodrug that is metabolically N-dealkylated to 5-ethyl-5-phenyl hydantoin which is believed to be the active agent. Mephenytoin has a spectrum of activity similar to that of phenytoin and with the same adult dose range The therapeutic level for mephentoin ranges from 5-16 mcg/mL, while levels above 20 mcg/mL are considered toxic [23, 28].

Oba *et al.* [29] prepared the thiohydantoin albutoin **(5)** which exhibited antiseizures activity. Its maximum recommended therapeutic adult dose is 40.0 mg / kg b.wt/day, orally.

The spirocyclic hydantoin tetrantoin **(6)** was found to inhibit and prevent convulsions occurring through maximum electric shock test with approximate ED_{50} of 54mg / kg [30].

In 2004, Thenmozhiyal *et al.* [31], disclosed that the phenyl methylenehydantoins substituted with 2,4- dimethyl **7a** and 2,4,6-trimethyl **7b** groups at the phenyl ring. This drug exhibit good anticonvulsant profile with $ED_{MES(2.5)}$ 39 ± 4 and 28 ± 2mg / kg , respectively using (MES).

In 2011, Obniska *et al*. [32] synthesized new N-Mannich bases derived from 5-cyclopropyl-5-phenyl-hydantoins of which the most active compound was 3-[(4-phenylpiprazine-1-yl)-methyl]-5-cyclopropyl-5-phenyl-imidazolidine-2, 4-dione **(8)** with the ED_{50} value of 5.29 mg/kg in the MES test.

b. Oxazolidinediones

The oxazolidinedione system is considered as a hydantoin bioisostere. Four main drugs that bear this skeleton are known:

Trimethadione (Tridione®, **9**), was the first drug introduced specifically for treating absence seizures [33]. Trimethadione is important as a prototype structure for anti-absence drugs. The drug is metabolized by N-demethylation to the putative active metabolite dimethadione **(10),** which is a water-soluble compound that shows low lipophilicity and it is excreted as such without further metabolism. Plasma levels above 20 mcg/mL and a dose of 30 mg/kg/day is necessary to achieve this level in adult [34, 35]. Furthermore, replacing one methyl group of C-5 side-chain by an allyl one afforded aloxidone **(11)**, which is also effective as anticonvulsant [36, 37].

The C-5 side chain homologue of **9**, paramethadione (Paradione®, **12**) displays similar activity and side effects. The N-demethylated metabolite, which is excreted slowly, is thought to be the active drug. The usual adult dose range is 0.9g - 2.5g/day [38].

c. Succinimides

The structurally bioisosteric succinimides which are pyrrolidine -2,5-diones, where the $-CH_2-$ replaces the -NH- and -O- in hydantoins and oxazolidinediones, respectively, were a logical choice for synthesis and evaluation as antiepileptic drugs [14]. Ethosuximide (Zarontin ®, **13**) is the

most popular and widely used representative drug of this group. It conforms very well to act as anti-absence drug. Ethosuximide is more active and less toxic than trimethadione. Consequently, it has emerged as the drug of choice for typical absence seizures. Ethosuximide has an important effect on calcium currents, reducing the low-threshold (T-type) current. Therapeutic level of 60-100 mcg/mL can be achieved in adults with doses of 750-1500 mg/day [39].

Also, phensuximde (Melontin ®, **14**) is used primarily against absence seizures, due to its low potency. The phenyl substituent confers some activity against generalized tonic-clonic and partial seizures. N-demethylation of **14** occurs to yield the putative active metabolite. Both phensuximide and its N-demethylated metabolite are inactivated by *p*-hydroxylation and conjugation [40, 41]. Methsuximide (Celontin ®, **15**), is another example of this group which has some use against absence and complex partial seizures. The usual maximum daily dose is 300-1200 mg/day and the target serum concentration range is 10-40mcg/mL [40, 42].

Furthermore, It was reported that the succinimide congener suclophenide (**16**) displayed pronounced anticonvulsant activity against maximum electric shock seizures test with ED_{50} = 18 mg/kg, orally [43, 44].

Kamiński *et al*. [45] have synthesized a series of new N-phenyl amino derivatives of 2-azaspiro[4,4]nonane –1,3-dione.The most active compound was N-[(2,4-dichloro-phenylamino]-2-azaspiro[4,4]nonane-1,3-dione (**17**),which exhibited antiseizure properties in the (MES) at dose of 100mg/kg in mice.

In the same vein, Kamiński and Obniska [46] have developed new anticonvulsants of substituted N-phenylamino pyrrolidine-2, 5- diones and hexahydro-isoindole-1, 3-diones of which N-phenylamino-3,3-dimethyl-pyrrolidine-2,5-dione (**18**) showed ED_{50} value of 69.89 mg/kg in rats by MES test.

d. Barbiturates

Phenobarbital (**19)** is the most widely used of this group in epileptic episodes. Its action against experimentally induced convulsions and clinical forms of epilepsy closely resembles phenytoin. Phenobarbital and other barbiturates enhance the inhibitory action of $GABA_A$-receptors on chloride ion channels that results in an increased duration of chloride ion channel opening. The action of phenobarbitone can not solely be attributed to interaction with GABA-receptors but it also likely acts by inhibiting excitatory synaptic responses. In addition to its action on sodium channels and GABA-chloride channels, phenobarbital also acts as an antagonist at some glutamate receptors. It is effective against generalized tonic-clonic and partial seizures where the therapeutic levels of phenobarbital range from 10-40 mcg/mL [47, 48].

The 2-deoxyphenobarbitone**,** Primidone (Mysoline®, **20**) [49, 50] appears to act as phenytoin through metabolic oxidation to phenobarbitone and subsequent metabolic cleavage to phenyl ethyl malonyl diamide. The efficacy of this drug is against all types of seizures but it is now rarely used due to hypersensitivity reactions and sedation occurred during its administration. Primidone is most efficacious when plasma levels are in the range of 8-12 mcg/mL. Dosages of 10-20 mg/kg/day are necessary to obtain these levels [51].

Dvornik and Diokic [52] prepared the phenyl methyl barbituric acid, rutonal **(21),** as anticonvulsant, sedative and hypnotic agent, available in tablet form of 0.5 to 3 grains . Reaction of sodium phenobarbitone with chloromethyl-methyl ether afforded the antiepileptic agent Eterobarb **(22)**, which possesses marked anticonvulsant activity against both electrically and chemically induced seizures with ED_{50} of 13.5 and 47.0 mg / kg, respectively. The usual clinical dose is between 120mg to 720 mg. [53].

e. Amides, Monoacylureas and Ureides

The chemical classes, amides, monoacylureas and ureides, comprise compounds having a remarkable anticonvulsant profile.

Beclamide (Nuracene®, **23**) is a propionamide derivative acting as anticonvulsant. Beclamide potentiates the action of other anticonvulsants and neuroleptics. Its mechanism of action may be by inhibiting the release of aspartate and other excitatory amino acids which antagonizes GABA inhibitory effect. It is indicated in generalized epilepsy. Usual dose ranges between 50 to 250 mg/kg (po). On the other hand, plasma level between 10.2-12.4ng/ml is reached with a dose of 7.14-14.28 mg/kg in mice [54].

On the other hand, carbamazepine (Tegretol ®, **24**), which is looked at as a urea surrogate is a very important drug for treating generalized tonic-clonic (grand mal epilepsy) and partial seizures. Its structural pattern can be viewed either as an ethylene bridged 1, 1-diphenylurea or an amido-substituted tricyclic dibenzazepine system. The drug has the potential for haematologic toxicity so it is used with caution. The usual adult dose range for anticonvulsant action is 800-1200mg/day. The therapeutic plasma level between 4-8 mcg/mL [55, 56].

In 2007, Almeida and Soares-da-Silva [57] synthesized and evaluated the S- form of hydroxycarbazepine as its acetate ester, eslicarbazepine **25**. It is a sodium channel blocker; the usual adult dose is 400-1200mg/d with a plasma level around 10 ng/ml. It has proven to be equally potent to carbamazepine **24** and more potent than oxcarbazepine **26.** However the latter has long been considered a drug of choice for both partial and generalized tonic-clonic seizures. Clinical dose of oxcarbazepine in adults needs to be 50% higher than those of carbamazepine (1-2 g) to obtain equivalent seizure control [58].

The cycloheptadiene derivative, cyheptamide **(27),** was found to possess good anticonvulsant activity against maximum electric shock test, ED_{50} =25 ± 1 mg / kg by intrapretoneal route in mice and ED_{50} =33 ± 3.5 mg / kg, orally compared to phenobarbitone sodium, ED_{50} 11.6 ± 1.4 mg / kg and ED_{50} 17.8 ± 2.6 mg / kg intraperitoneally and orally in mice, respectively [59].

Also, the cinnamoylamide, cinromide **(28)**, is a long-acting anticonvulsant similar in action to phenacemid **37** but is less hepatotoxic and with a cumulative dose of 30-

80mg/kg/d. It has been withdrawn due to its CNS and GIT toxicity [60].

Furthermore, Clark *et al.* [61] prepared the 4-amino-benzanilide derivative, ameltolide **(29)**, which displays anticonvulsant profile against maximum electric shock seizures test with an ED_{50} 2.60 mg / kg compared to phenobarbitone (ED_{50} 4.10 mg/kg) and phenytoin (ED_{50} 5.24 mg/kg).

The anticonvulsant amide, ralitoline **(30),** acts by inhibition of voltage-dependent sodium-channels. Daily Dose is from 1-5 mg/kg/d, up to150 mg/kg. its maximum plasma level in healthy subjects is 2-4 hours. Meanwhile plasma level between 300 -1300 ng/ml is reached with dose of 15-240mg/kg in rats subjected to MES test [62].

The antiepileptic triazole carboxamide, rufinamide **(31)** exerts its action by decreasing firing of neurons at sodium-channel. Its total daily dose is 400 - 800mg/d and the serum level is 555ug/ml [63].

Xiao *et al.* [64] disclosed that the simple amide, ilepcimide **(32)**, exhibits antiepileptic effect. Furthermore, the [*R*] -2- acetamido -N- benzyl -3- methoxy propionamide, acetazolamide **(33)** is a diuretic whose main action is in the inhibition of carbonic anhydrase. Mild acidosis in the brain may be the mechanism by which the drug exerts its antiseizures activity. Acetazolamide has been used for all types of seizures but is severely limited by the rapid development of tolerance. The usual dosage is approximately 10 mg/kg/day to a maximum of 1000mg/day [65].

In 2002, Shen *et al.* [66] discussed the anticonvulsant profile of various diverse amino acid amides **34a-c, 35** and **36** using the maximal electric shock seizures test. They showed anticonvulsant profile at ED_{50} ranging from 6.7 to 31.2 mg / kg.

The phenylacetylurea derivative, phenacemide (Phenurone®, **37**), is a broad-spectrum antiepileptic agent and finds some use in complex partial seizures. Phenacemide has been withdrawn from the market because of its severe side effects, which includes personality changes, blood, renal and skin disorders [67].

Also, the α -aminoamide, safinamide **38**, is a novel sodium - and calcium - channel blocker with selective and reversible inhibition of monoamino oxidase type B.The clinical dose is between 50-250mg/d and the plasma level of 300-400ng/ml. In many animal models it has exerted powerful neuroprotectant, anticonvulsant (ED_{50} 26.8 mg/kg i.p. by pentylenetetrazole seizures test) and antiparkinsonian activities with an excellent therapeutic and safety margin [68]. Furthermore, the urea derivative, fluzinamide **(39)** [69], and its demethylated metabolite dezinamide **(40)** [70] are used as potential anticonvulsant amides (10-80mg/kg, MES test).

Umemoto and Hideji [71] synthesized the ureide, acetylpheneturide (Crampol®, **41**), as anticonvulsant with LD_{50} 1.17 g / kg, orally in mice.

In 2008, Rana *et al.* [72] have disclosed a series of 1,3-benzothiazol-2-yl benzamides **(42a-c)** with anticonvulsant potential against seizures at dose of 30 mg/kg. Also, in 2008 Shimoshoni *et al.* [73] reported a series of substituted benzamido-tetramethylcyclopropanes as anticonvulsants. The most potent compound emerging from this study was N-2, 2, 3, 3-tetramethyl-cyclopropane carboxamide)-*p*-phenyl-sulfonamide (**43**) which has an ED_{50} value of 26 mg/kg. This compound possesses a better anticonvulsant and wider safety margin than valproic acid and zonisamide.

Lacosamide (Vimpat®, **44**) is one of the amidic antiepileptic drugs, which protects against psychomotor seizure electroshock test with an ED_{50} of 9.99 mg/kg beside being an analgesic in neuropathic pains [74].

f. Benzodiazepines

Benzodiazepines interact with specific receptors on the $GABA_A$ receptor-chloride ion channel macromolecular complex. In the presence of benzodiazepines, the frequency of chloride ion channel opening is increased. These drugs facilitate the inhibitory effects of GABA.

Benzodiazepines possess anticonvulsant profile besides having anxiolytic, sedative and hypnotic activities [75]. Animal models predict benzodiazepines to be effective against generalized tonic-clonic and partial seizures, also, very highly active against absence seizures. Although this class causes many side effects such as fatigue, abnormal behavior including hallucinations, slow breathing and heart rates, increased or decreased appetite and skin rashes, many benzodiazepine derivatives are of importance in epilepsy therapy [14].

The antiepileptic drug, Diazepam (Valium®, **45**) inhibits excitatory responses from spreading beside its action on $GABA_A$ receptors. It is mainly useful in treating status epileptics, which is an ongoing and potentially fatal generalized tonic-clonic seizure [76]. Its congener, clonazepam (Klonapin®, **46**)**,** is of value in absence seizures and in myoclonic seizures. The maximal tolerated dose is usually in the range of 0.1-0.2 mg/kg and the usual maximum daily dose is 4-40 mg, while the target serum concentration range is 100-1000 ng/mL [77]. The soluble chlorazepate (Tranexene®, **47**) is adjunctively used as anticonvulsant in complex partial seizures in dosages as high as 45 mg/day [78].

Ling *et al.* [79] disclosed that the benzodiazepine derivative, talamapanel **(48)** possesses anticonvulsant property through its antagonizing action on glutamate receptors. The usual dose is 3-100mg and the plasma level is between 173 to 710ug/L [80].

g. Valproic Acid and its Derivatives

Valproic acid (Depakene®, **49**) is a simple α,α disubstituted acetic acid derivative that derivative inhibits most kinds of experimentally induced convulsions and is effective in many kinds of epilepsy, particularly in certain types of infantile epilepsy, where its low toxicity and lack of sedative action are important. Valproic acid exerts its action through causing a significant increase in the γ Aminobutyric acid (GABA) content of the brain. There is some evidence that it enhances the action of GABA by a postsynaptic action besides its action on sodium-channels [81, 82]. In addition to

its action to calcium channel, valproic acid causes neuronal membrane hyper polarization possibly by enhancing potassium channel permeability [21].

The prodrug, valproic acid carboxamide, valpromide (Depamide®, **50**), was synthesized and used as antiepileptic and psychotropic agent through management of behavioral disturbances and acute psychosis, but for a very short plasma half-life 0.84 ± 0.33 hours. Dosages of 25-30 mg/kg/ day may be adequate in some patient, but others may require 60 mg/kg/day or even more. Therapeutic level of valporate ranges from 50-100 mcg/mL [83, 84].

In 2002, Masereel *et al.*[85] prepared the valproic acid derivative, [5-valproyl amido]-1,3,4-thiadiazole-2-sulphonamide (**51**), which exhibited very strong anticonvulsant activity in a maximal electric shock test in mice as compared to the clinically used topiramate.

Furthermore, in 2008, Gravemann *et al.* [86] have developed hydroxamic acid and flourinated derivatives of valproic acid **52** and **53**. All the synthesized compounds exhibited anticonvulsant activity with ED_{50} doses ranging from 0.16mmol/kg to 0.59 mmol/kg as compared to VPA (0.57 mmol/kg).

h. GABA -Analogues

GABA, **54** is considered as a major inhibitory neurotransmitter in the central nervous system. Thus, several designed GABA-analogues were synthesized and used as anticonvulsants [87].

The GABA isostere, amino oxyacetic acid (**55**), was found to have GABA-transaminase inhibitory activity [88]. The 3-hydroxy derivative of GABA, gamibetal **(56)**, as an adjuvant anticonvulsant drug (20-30 mg/ kg) was used in several neurological disorders [89].

Vigabatrin (γ-vinyl GABA, **57**) is the first molecularly designed anticonvulsant as an irreversible inhibitor of the GABA-metabolizing enzyme GABA-transaminase. It has been reported to be effective in a substantial extent in patients resistant to the established orthodox antiepileptic drugs. In adults vigabatrin should be started at an oral dose of 500mg twice daily, a total dose of 2-3 g daily [90, 91]. Interestingly, the hydroflourinated vigabatrin 4-amino-5 -flouro pentanoic acid **(58)**, was also found to evoke anticonvulsant activity [92, 93].

The GABA-analogue, pregabalin **59** (Lyrica®), was proven to exhibit anticonvulsant profile by binding to sodium-channels and modulating without blocking them to prevent irreversible neuronal damage from conditions similar to ischemia. So pregabalin is approved as an adjunct for the treatment of partial seizure with or without secondary generalization and in neuropathic pain. The daily dose of pregabalin range from 150-600 mg/day usually in two or three divided administration [94, 95]. The rigid GABA-congener, 5-amino-1,3-cyclohexadiene carboxylic acid **(60)**, has been found to display anticonvulsant and sedative action [87].

Tiagabine **(61)** was designed as GABA-analogue that is able to penetrate the blood brain barrier due to its high lipophilic character and acts by inhibiting the reuptake of GABA by neurons. It enhances the extra cellular GABA concentration and also potentiates and prolongs GABA-mediated synaptic responses in the brain. Tiagabine is effective in doses ranging from 16-56 mg/day [96].

One of the most interesting designed simple GABA-analogues is gabapentin (Neurontin®, **62**). It was proven to be effective as anticonvulsant in several animal models, but, surprisingly, not by acting on GABA- receptors. Gabapentin is effective as an adjunct against partial and generalized tonic-clonic seizures at doses that reaches up to 2400mg/day in controlled clinical trials and plasma level is between 4-6 mcg/mL [97].

A series of imines of GABA and its decarboxylated metabolite with phenolic benzophenones e.g. tolgabide **(63)** [98], fengabine **(64)** [99] and progabide **(65)** [100] are found to exhibit anticonvulsant activity.

In 2003, a series of aromatic GABA-homologues: 5-amino-3-aryl-pentanoic acid hydrochlorides **66a-c** was synthesized and they exhibited as $GABA_B$ agonist activity with EC_{50} values ranging from 46-170 μM [101].

Ragavendran *et al.* [102] designed and synthesized new GABA analogues which in combination with thiosemicarbazones (**67a-c**) showed anticonvulsant potential at doses of 100 and 300 mg/kg as compared with lamotrigine (30mg/kg).

i. Cycloalkane Derivatives

Aboul-Enein and El-Azzouny synthesized a series of 1, 4-diaza spirodecanediones of which **68** showed a significant anticonvulsant activity in mice against maximal pentylenetetrazole seizures test at dose of 5mg / kg compared with diphenylhydantoin sodium which was used as a reference drug (50mg/kg) [103]. Replacement of the carbonyl group in the 3-position of the above mentioned series by the isosteric imino (=NH) function and the N-methyl group by N-phenyl group led to **69a** and **b**, respectively. They exhibited equipotent anticonvulsant activity at dose of 50mg / kg compared to diphenylhydantoin sodium (50 mg / kg) as reference drug [104]. Aboul-Enein *et al.* disclosed that N-(3, 4, 5-trimethoxybenzyl) -N–(1-piperidin-1-yl-cyclohexylmethyl) benzamide **(70)** exhibited excellent anticonvulsant activity, 10-fold as active as diphenylhydantoin sodium as reference drug. It showed 100% protection at a dose level of 5 mg/kg as compared to 50 mg / kg of the reference drug [105].

The spiro L-camphor hydantoin **(71)** exhibited an anticonvulsant activity, whilst the D- form is less active at a dose level of 100 mg / kg the L-form has 100 % protection while the D- form has 50 % protection against cardiazole induced convulsions .It also displayed remarkable antiarrhythmic properties [106]. Moreover, the camphor surrogate, deramciclane fumarate (**72**), exhibited anxiolytic and anticonvulsant properties against pentylentetrazol induced seizures. It showed a potent non-selective GABA reuptake inhibiting activity at a concentration of 100 μM, while its 2-benzyl analogue (**73**) showed fewer tranquilizing, anticonvulsant and analgesic activities [107, 108].

In 2006, Aboul-Enien *et al*. reported the D- camphor derivative **74**, which showed anticonvulsant activity at dose level of 12.5mg/kg using maximum pentylenetetrazole seizures test as compared to the reference diphenylhydantoin sodium at dose level of 50 mg / kg [109].

j. Semicarbazone Derivatives

Dimmock *et al.* discussed the anticonvulsant activities of various semicarbazones **75a** and **75b, 76a** and **76b** and **77**, which possessed rapid onset of action. They exerted their anticonvulsant effect by interaction with chloride-channels [110-113]. The aryloxy aryl semicarbazones **78a** and **78b**, were prepared and showed anticonvulsant profile after intraperitoneal injection to mice using maximal electric shock test at ED_{50} 5.46 mg / kg and 5.62 mg / kg, respectively, compared to the reference drug phenytoin (ED_{50} = 6.32 mg / kg), and by using pentylenetetrazole seizures test, at ED_{50} = 12.8 mg / kg and 18.7 mg / kg compared to phenytoin (ED_{50} > 50 mg / kg) [114].

Yogeeswari *et al.* reported an array of 3-chloro-2-methylphenyl-substituted semicarbazones **79** which induced moderate anticonvulsant potential against MES dose of 300 mg/kg in comparison to phenytoin at dose of 30 mg/kg [115].

In 2005, Yogeeswari *et al*. reported the synthesis of aryl semicarbazones **80, 81** which were found to possess anticonvulsant profile at doses of 100, 300 mg /kg in the MES test compared with 30 mg/kg for carbamazepine, respectively [116]. Furthermore, in 2009 Azam *et al*. disclosed the anticonvulsant potential of certain N-4-(naphtha [1,2-d]thiazol-2-yl) semicarbazides **82a-c** at doses of 100,100,300 mg/kg, respectively, in the MES test compared to phenytoin at dose of 30 mg/kg [117].

k. γ Butyrolactone Derivatives (GBLs)

The α-substituted GBLs were found to be effective as anticonvulsants by inhibiting pentylenetetrazole seizures in experimental animals. Interestingly, the β substituted GBLs were found to induce seizures and act as convulsant agents [118].

Levine *et al.* disclosed that the α thiolo GBL (**83)** possessed anticonvulsant activity at a dose 250mg / kg by complete protection against tonic-clonic seizures induced by 100mg/kg pentylenetetrazole as well as protection against maximum electric shock seizures test at ED_{50} 230mg / kg compared to valproic acid (ED_{50} 272 mg / kg) [119]. Furthermore, El-Hadri *et al.* found that the N-substituted 4-amino-3,3-propyl substituted GBL **84**, which could be looked at as a rigid cyclized valproic acid, exhibited anticonvulsant potency twice the activity of **83** [120].

l. Imidazoquinazoline Derivatives

Jewery *et al*. claimed that the imidazo[1,2-α] pyrimidine derivatives **(85)** (MED 2mg/kg po) exhibited equipotent activity with chlordiazepoxide[121].

In 1989, Watjen and Hansen claimed that 3- (5-ethyl-1, 2, 4-oxadiazol-3- yl)- 4- methylimidazo [1,5-a] quinazolin-5- (4H)- one **(86)** had potent anticonvulsant activity [122]. The imidazoquinazoline derivatives NNC 14-0185 **(87)** and NNC 14-0189 **(88)** were proved to be more potent as anticonvulsants than diazepam and less likely to produce relaxation at the anticonvulsant dose [123,124]. On the other hand, the imidazoquinazoline derivatives **(89)** [125,126] and **(90)** [127] were found to act as GABA agonists by possessing $GABA_A$- receptor binding affinity.

m. Pyrrolidine Derivatives

Helsley *et al.* synthesized 4-benzoyl-pyrrolidine-1-carboxylic acid amide (ED50= 32-111mg/kg) **(91)**, which exhibited anticonvulsant activity [128].

Bosewell *et al.* reported the 3-phenoxypyrrolidine derivative **92**, as anticonvulsant. It showed 100% protection against electric–shock in a dose of 100 mg / kg i.p. using female mice [129].

Levetiracetam (Keppra®, **93),** was introduced as an adjunctive therapy in the treatment of partial-onset seizures in adults suffering from epilepsy. Levetiracetam binds selectively to a synaptic vesicular protein SV2A. It is likely that levetiracetam modifies the synaptic release of glutamate and GABA through an action on the vesicular function. Dosing can begin with 500mg orally twice daily. (Levetiracetam**, 93),** was introduced as an adjunctive therapy in the treatment of partial-onset seizures in adults suffering from epilepsy [130].

Also, Reddy *et al.* prepared the 2-pyrrolidinone derivatives **94a** and **94b** and evaluated their anticonvulsant activities. They found that **94a** is effective against maximal electric shock seizures test (ED_{50} 41 mg / kg) and **94b** is effective as anticonvulsant by protection against pentylenetetrazole seizures test at ED_{50} 42 mg / kg compared to reference standards phenobarbitone (ED_{50} 22 mg / kg) and valproic acid (ED_{50} 133 mg / kg) [131].

Goodman and Matsun disclosed that (-)-cromakalim **(95)** has anticonvulsant property by acting on potassium-channels and stabilizing cellular hyperexcitability [132].

Aboul-Enein *et al.* reported the anticonvulsant potential of a series of alkyl and aralkyl-4-[(alkyl-amino) methyl]-2-(4-methoxybenzyl) pyrrolidine-3-ols. Compounds **96a**, **96b, 97a** and **97b** showed anticonvulsant activity by giving 100% protection against pentylenetetrazole seizures test at dose level of 30 mg/kg compared to 50 mg / kg of the reference diphenylhydantoin sodium [133].

Moreover, Aboul-Enein *et al.* found that the derivatives of benzoate esters of 1-propyl-2,4-dimethyl-2-(4-methoxy-benzyl)-pyrrolidin-3-ol **(98)** pyrrolidinemethanol (**99**) showed pronounced anticonvulsant properties. They exhibited 100% protection against pentylenetetrazole seizures test at dose level of 15 mg/kg and 3.97mg/kg compared to 50 mg/kg of the reference diphenylhydantoin sodium, respectively [134, 135].

Recently, Rogawiski found that the 4-n-propyl analog of levetiracetam, brivaracetam **(100)** showed anticonvulsant properties by binding to the ubiquitous synaptic vesicle protein SV2A.It is used in treatment of partial epilepsy at dose ranging from 20-100mg/d [136].

Seletracetam **(101),** a new drug in epilepsy-control development, is a pyrrolidone derivative structurally related to levetiracetam (Keppra ®). It displays high binding affinity to the synaptic vesicle 2A (SV2A) protein, which is now known to be the binding site for this family of compounds. Seletracetam shows very potent seizure suppression in models of acquired or genetic epilepsy, as well as high CNS tolerability in various animal models (ED_{50} =0.31mg/kg in mice) [137].

Among the pyrrolidine surrogates are the pyrrolidine carboxylic acids **(102, 103)** that showed anticonvulsant and other pharmacological potential [138]. Furthermore,α-hydroxy-3-pyrrolidine acetic acid **(104)**, which is structurally related to the heterocyclic GABA analogue 3-pyrrolidine acetic acid (homo-β-proline, **105**) is found to be a very potent inhibitor of the presynaptic GABA uptake system responsible for transmission in the central nervous system [139].

Recently, in 2010, Aboul-Enein *et al*. prepared the amino acid 1-*H*-4-hydroxy-5-(4-methoxy-benzyl)-pyrrolidine-3-carboxylic acid hydrochloride (**106**), which was evaluated for its anticonvulsant potential using subcutaneous pentylenetetrazole seizures (scPTZ) test. It was found that it displayed 100% protection against pentylenetetrazole seizures at dose level of 0.0087mmol/kg b.wt., which is about 17.5 - fold more potent than gabapentin (0.14 mmol/kg b.wt.) as a reference drug [140].

n. Miscellaneous Anticonvulsants

This is a group of anticonvulsants that do not belong to any of the previously discussed classes and have diverse chemical structures.

Sulthiame **(107)** is an antiseizures used in combination with other anticonvulsants in the treatment of resistant partial seizures in children. The adult dose is 10mg/kg/d, but not higher than average dose of 600mg, and the plasma level ranges between 5-70 umol/L. Sulphonamide – sensitive patients should not be treated with sulthiame. Also when phenytoin is co- administered with the drug, phenytoin plasma levels are increased because phenytoin has been shown to induce microsomal enzymes responsible for the metabolism of a number of drugs [141].

Felbamate **(108)** is an analogue to the anxiolytic drug meprobamate **(109)**. It is active in many animal seizure models and has a broader clinical spectrum than earlier antiepileptic drugs, but its mechanism of action at the cellular level is uncertain. It has only a weak effect on sodium-channels and little effect on GABA. It is usually used in Lennox-Gastaut Syndrom, which is unresponsive to other antiepileptic drugs usual doses are 2000-4000mg/day in adults and effective plasma level range from 30-100 mcg [142].

Parmar *et al.* discussed the anticonvulsant potential of 1,3,5-trisubstituted pyrazoline derivative **110,** using pentylenetetrazole seizures test in albino mice. It exhibited 90 % protection against at a dose level of 100 mg / kg [143].

Razdan *et al.* disclosed that nabazenil **(111),** which is derived from cannabinoids, is very potent in controlling seizures in mouse in ED_{50} = 1.1 mg / kg [144].

Accidently, during a search for antifungal agents, the imidazole derivative, nafimidone **(112)**, have been discovered to elicit anticonvulsant activity against maximum electric shock seizures test (3-120mg/kg, i.p., in rats). It is also used for gastrointestinal disorders by inhibiting gastric secretion [145]. Furthermore, the benzisoxazole sulfonamide derivative, zonisamide **(113)**, possessed anticonvulsant profile (LD_{50} = 604 mg / kg i.p. in mice) by antagonistic action on calcium-channels [146,147]. The drug is effective against partial and generalized tonic-clonic seizures and doses range from 100-600mg/day in adults.

The triazine derivative, lamotrigine **(114)**, resembles phenytoin and carbamazepine in its pharmacological effects, although it is chemically unrelated to them. It acts on sodium-channels and inhibits the release of excitatory amino acids. Lamotrigine displays a broader therapeutic profile than the earlier drugs. Lamotrigine is effective against partial seizures in adults, with dosage typically between 100 and 300 mg/day and with therapeutic blood level near 3mcg/ml. [148].

Maryanoff *et al.* introduced the O-alkyl sulfamate sugar, topiramate (Topamax®, **115**), with dosage range from 200mg/day to 600mg/day. It exhibits potent antiepileptic activity analogous to that of phenytoin. In the maximal electroshock seizure test, it had an oral ED_{50} of 39 mg / kg and duration of action for more than 8h [149].

Riluzole (Rilutek®, **116**)**,** is an anticonvulsant agent which interferes with glutamergic neurotransmission and acts as glutamate antagonist. It is used in treatment of absence epilepsy at dose level of 50mg/12hours, while the ED_{50} is 27.4mg/kg. Also riluzole is used as anxiolytic and antipsychotic [150]. In 1990, Bowman prepared zoniclezole **(117)**, which was proven to have anticonvulsant profile [151].

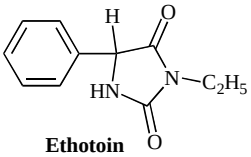
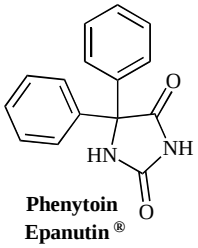
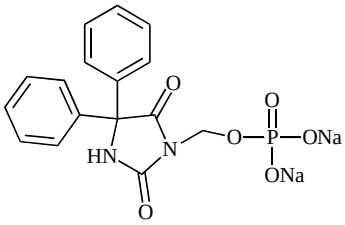
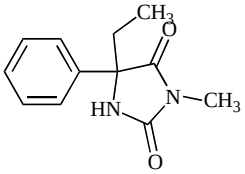
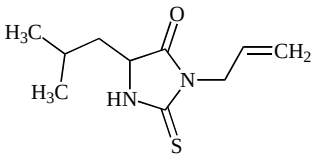
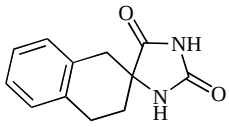
Vaught and Wauquir found that loreclezole **(118)** possesses an anticonvulsant activity by acting on $GABA_A$ receptors [152].The usual adult dose is ranging between 100 to 150mg/d and the plasma level is 1-3 mg/L. The glutamate receptor antagonist, sabeluzole **(119)**, is used as anticonvulsant and antihypoxic agent beside its use in cerebrovascular disorders without major side effects. It acts as glutamate antagonist with dose level of 120-300mg [153].

Goodman and Mattson disclosed that diazoxide **(120)** has anticonvulsant property by acting on potassium-channels and stabilizing cellular hyper excitability. The maximum dose is 150mg/kg (1-3mg/kg, iv.) [132].

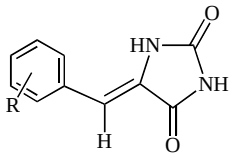
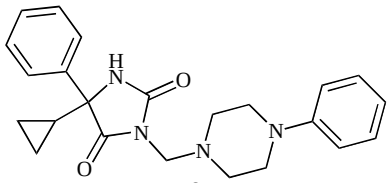
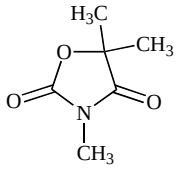
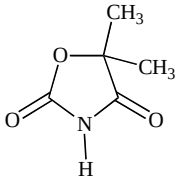
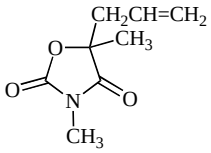
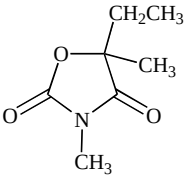
Interestingly, the piperazine derivative, flunarizine **(121)** which is used as vasodilator and is used for migrane prophylaxis, vertigo and for peripheral and cerebra vascular disorders was found to evoke anticonvulsant profile similar to that of phenytoin. It blocks calcium-channels and diminishes the neuronal hyperexcitability. So, it is used for partial and generalized tonic-clonic seizures. Adult dose is ranged from 10 to 25 mg/d, the maintenance dose is 10 mg and the plasma level is 60ng/mL [154].

Recently, Maron *et al*. prepared an array of aminoal-kanolic derivatives of 6-chloroxanthone, among which the

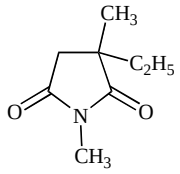
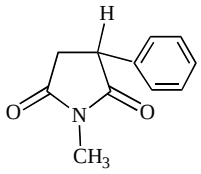
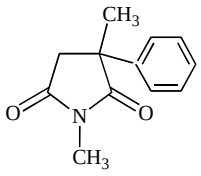
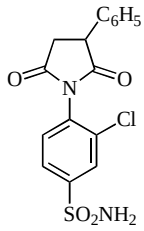
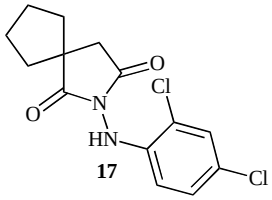
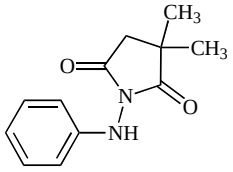
Table 1. Antiepileptic Drugs and Chemical Compounds

Compound Number	Chemical Structure	References
1	 **Ethotoin** **Peganone®** **1**	[15, 25]
2	 **Phenytoin** **Epanutin ®** **2**	[23, 24]
3	 **Fosphenytoin** **Pro-Epanutin ®** **3**	[26, 27]
4	 **Mephenytoin** **(Mesantoin ®)** **4**	[24, 28]
5	 **Albutoin** **5**	[29]
6	 **Tetrantoin** **6**	[30]

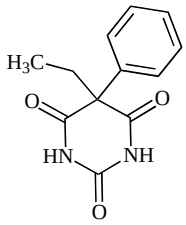
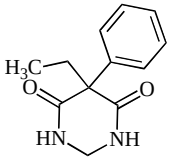
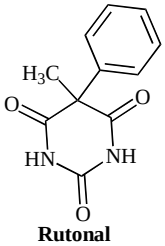
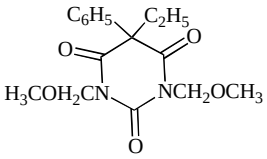
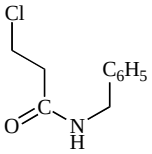
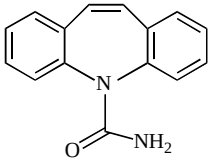
(Table 1). Contd…..

Compound Number	Chemical Structure	References
7	 **7a** R = 2,4-$(CH_3)_2$ **7b** R = 2,4,6-$(CH_3)_3$	[31]
8	 **8**	[32]
9	 **Trimethadione** **Tridion ®** **9**	[33]
10	 **Dimethadione** **10**	[34,35]
11	 **Aloxidone** **11**	[36,37]
12	 **Paramethadione** **Paradione ®** **12**	[38]

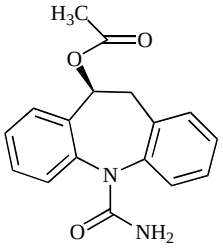
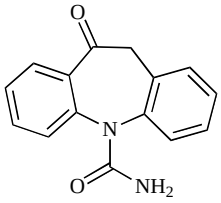
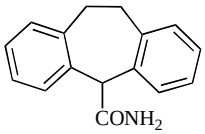
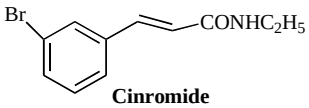
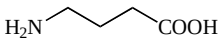
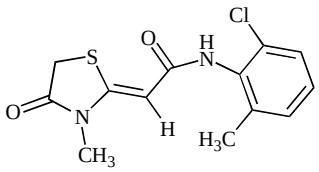
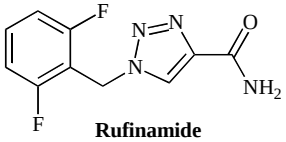
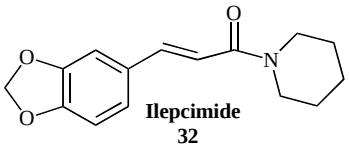
(Table 1). Contd…..

Compound Number	Chemical Structure	References
13	 **Ethosuximide** **Zarontin ®** **13**	[39]
14	 **Phensuximide** **Milontin ®** **14**	[40,41]
15	 **Methsuximide** **Celontin ®** **15**	[40,42]
16	 **Suclophenide** **16**	[43,44]
17	 **17**	[45]
18	 **18**	[46]

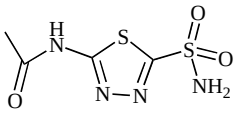
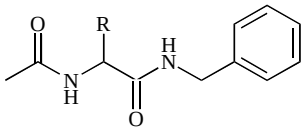
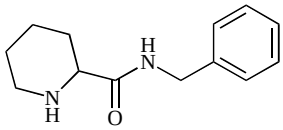
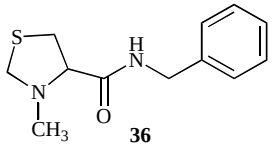
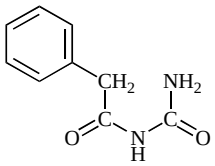
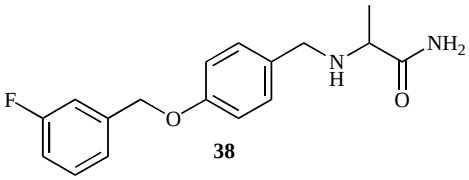
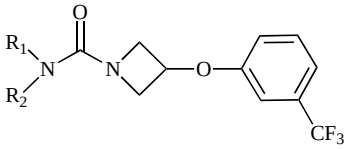
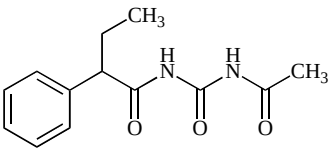
(Table 1). Contd…..

Compound Number	Chemical Structure	References
19	 **Phenobarbitone** **19**	[47,48]
20	 **Primidone** **Mysoline ®** **20**	[49,50]
21	 **Rutonal** **21**	[52]
22	 **Eterobarb** **22**	[53]
23	 **Beclamide** **Nuracene®** **23**	[54]
24	 **Carbamazepine** **Tegretol ®** **24**	[55,56]

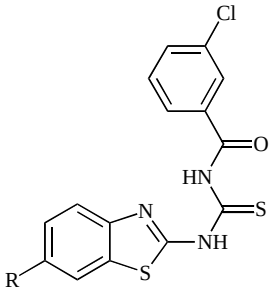
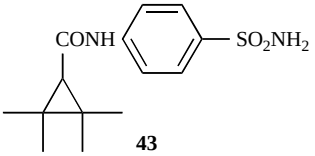
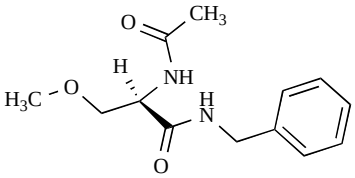
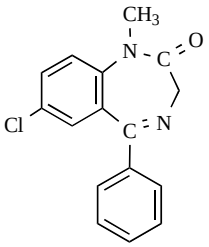
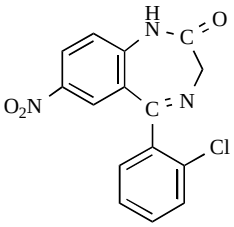
(Table 1). Contd…..

Compound Number	Chemical Structure	References
25	 **Eslicarbazepine acetate** **25**	[57]
26	 **Oxcarbazepine** **26**	[58]
27	 **Cyheptamide** **27**	[59]
28	 **Cinromide** **28**	[60]
29	 **γ-Amino Butyric Acid** **GABA** **29**	[61]
30	 **Ralitoline** **30**	[62]
31	 **Rufinamide** **31**	[63]
32	 **Ilepcimide** **32**	[64]

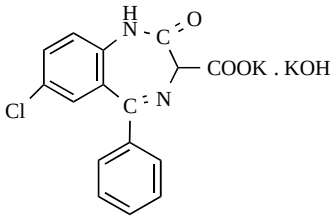
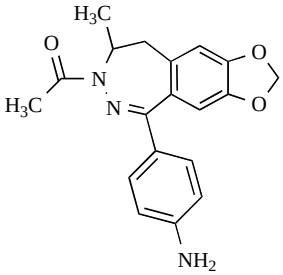
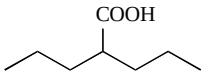
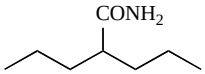
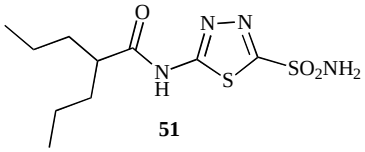
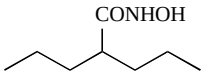
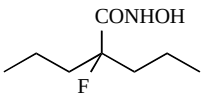
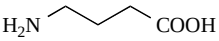
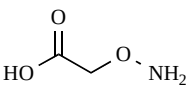
(Table 1). Contd…..

Compound Number	Chemical Structure	References
33	 **Acetazolamide** **33**	[65]
34	 **34a** $R = CH_2OCH_3$ **34b** $R = NH(OCH_3)$ **34c** $R = N(CH_3)OCH_3$	[66]
35	 **35**	[66]
36	 **36**	[66]
37	 **Phenacemide** **Phenurone ®** **37**	[67a,b]
38	 **38**	[68]
39 and 40	 **Fluzinamide 39** $R_1 = H$ $R_2 = CH_3$ **Dezinamide 40** $R_1,R_2 = H$	[69, 70]
41	 **Acetylphenturide** **Crampol®** **41**	[71]

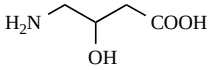
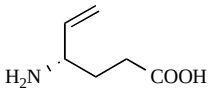
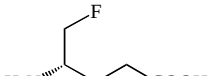
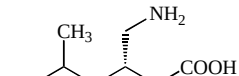
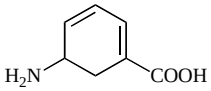
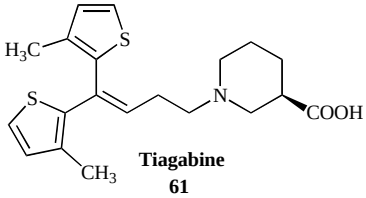
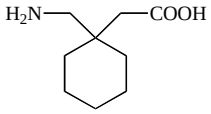
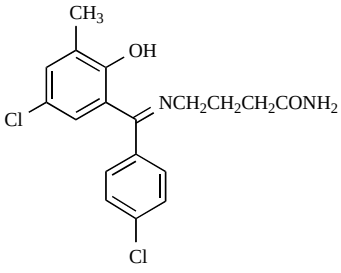
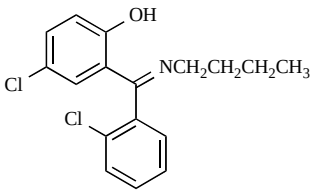
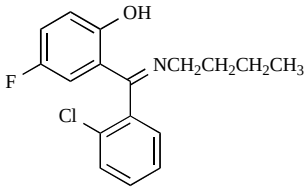
(Table 1). Contd…..

Compound Number	Chemical Structure	References
42	 **42 a-** R = NO_2 **42 b-** R = CH_3 **42 c-** R = CH_3O	[72]
43	 **43**	[73]
44	 **Lacosamide** **Vimpat®** **44**	[74]
45	 **Diazepam** **Valium®** **45**	[76]
46	 **Clonazepam** **Klonapin®** **46**	[77]

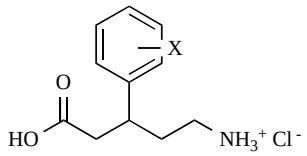
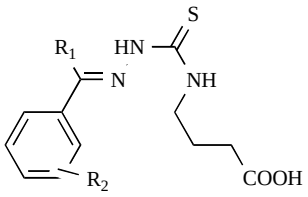
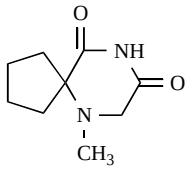
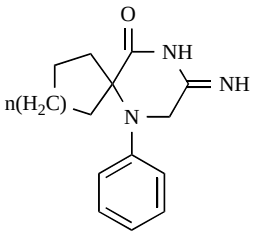
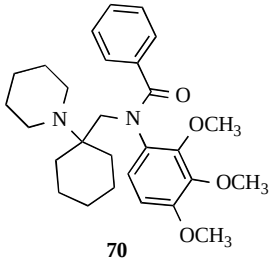
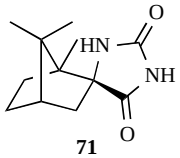
(Table 1). Contd…..

Compound Number	Chemical Structure	References
47	 **Chlorazepate** **Tranxene ®** **47**	[78]
48	 **Talampanel** **48**	[79]
49	 **Valproic acid** **Depakene ®** **49**	[81, 82]
50	 **Valpromide** **Depamide®** **50**	[83,84]
51	 **51**	[85]
52,53	 **Valproic acid Hydroxamicacid** **52**  **Flourinated-Valproic acid Hydroxamicacid** **53**	[86]
54	 **γ-Aminobutyric Acid** **(GABA)** **54**	[87]
55	 **55**	[88]

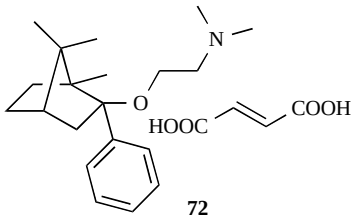
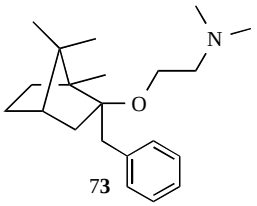
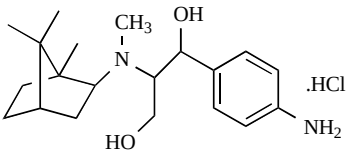
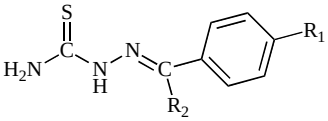
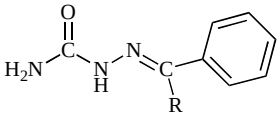
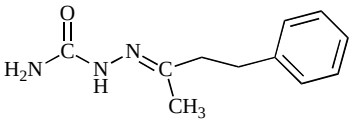
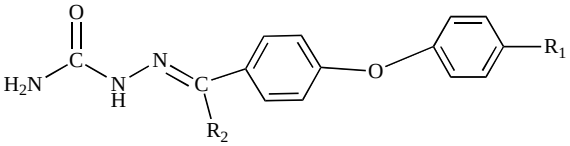
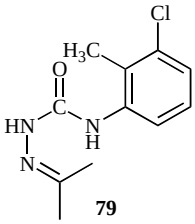
(Table 1). Contd…..

Compound Number	Chemical Structure	References
56	 **Gamibetal** **56**	[89]
57	 **Vigabatrin** **57**	[90, 91]
58	 **58**	[92, 93]
59	 **Pregabalin** **59**	[94,95]
60	 **60**	[87]
61	 **Tiagabine** **61**	[96]
62	 **Gabapentin** **Neurontin®** **62**	[97]
63,64, 65	 **Tolgabide** **63**  **Fengabine** **64**  **Progabide** **65**	[98,99, 100]

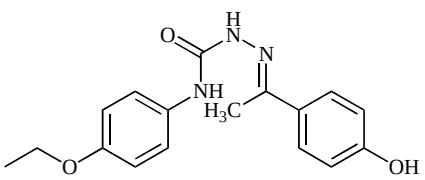
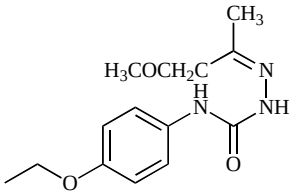
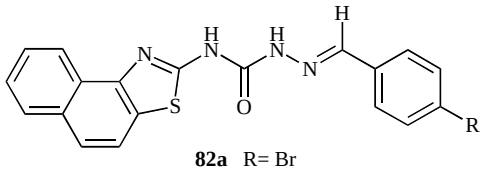
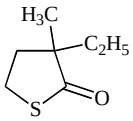
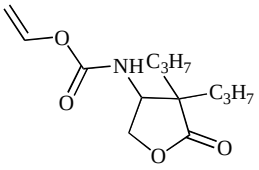
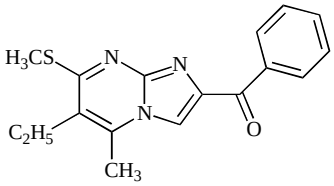
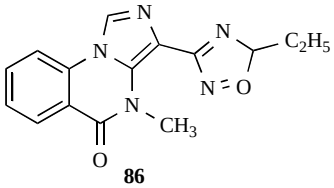
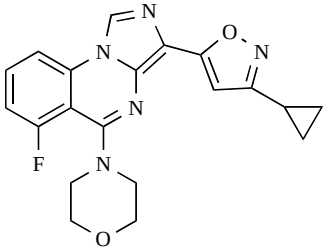
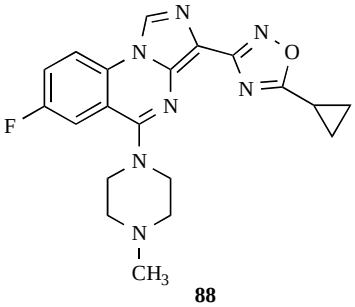
(Table 1). Contd…..

Compound Number	Chemical Structure	References
66	 **66a** X= 4-Cl **66b** X= 3,4-Cl_2 **66c** X= 4-F	[101]
67	 **67a** R_1 =H R_2 = 2-OH **67b** =H = 4-Cl **67c** =CH_3 = H	[102]
68	 **68**	[103]
69	 **69a** n=1 **69b** n=2	[104]
70	 **70**	[105]
71	 **71**	[106]

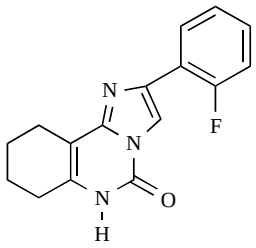
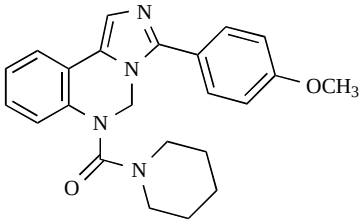
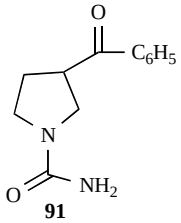
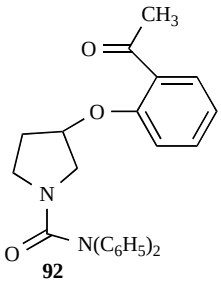
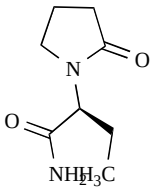
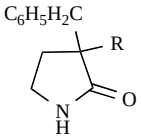
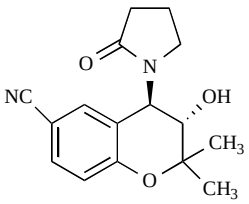
(Table 1). Contd…..

Compound Number	Chemical Structure	References
72	 **72**	[107,108]
73	 7**3**	[107,108]
74	 **74**	[109]
75,76,77	 **75a** $R_1 = H$; $R_2 = CH_3$ **75b** $R_1 = Cl$; $R_2 = CH_3$  **76a** $R = CH_3$ **76b** $R = C_6H_5$  **77**	[110-113]
78	 **78a** $R_1 = F$; $R_2 = C_2H_5$ **78b** $R_1 = R_2 = CH_3$	[114]
79	 **79**	[115]

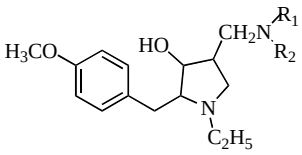
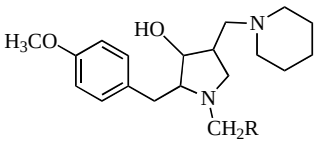
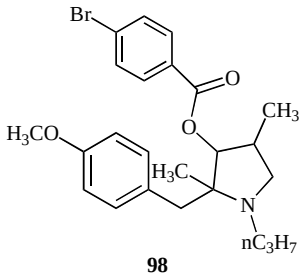
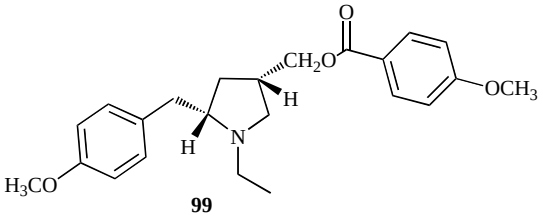
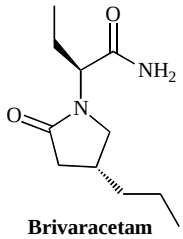
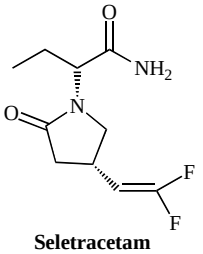
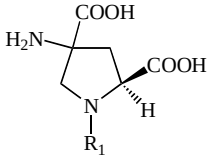
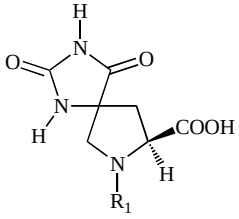
(Table 1). Contd…..

Compound Number	Chemical Structure	References
80, 81	 **80**  **81**	[116]
82	 **82a** R= Br **82b** R=Cl **82c** R=F	[117]
83	 **83**	[119]
84	 **84**	[120]
85	 **85**	[121]
86	 **86**	[122]
87, 88	 **87**  **88**	[123, 124]

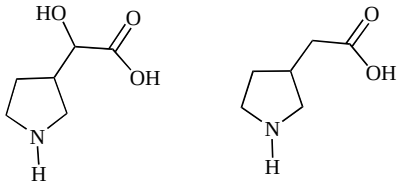
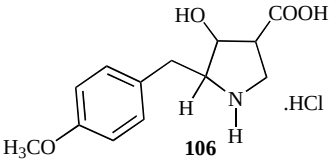
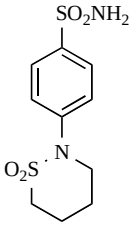
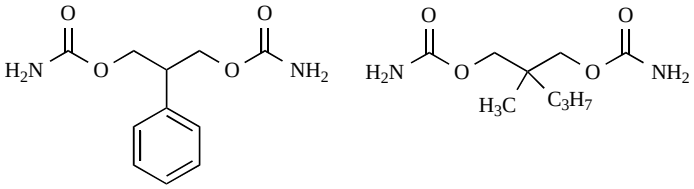
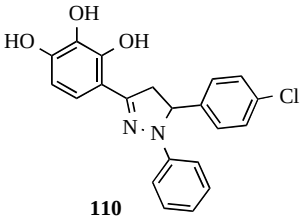
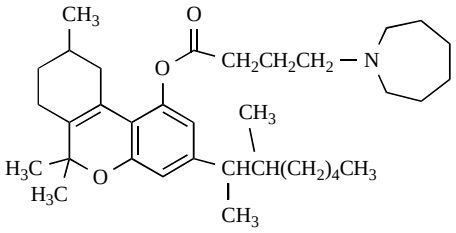
(Table 1). Contd…..

Compound Number	Chemical Structure	References
89, 90	 **89**  **90**	[125-127]
91	 **91**	[128]
92	 **92**	[129]
93	 **Levetiracetam** **Keppra®** **93**	[130]
94	 **94a** R = H **94b** R = C_2H_5	[131]
95	 **(-)-Cromakalim** **95**	[132]

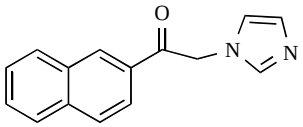
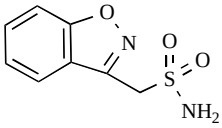
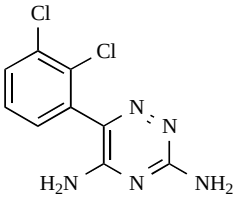
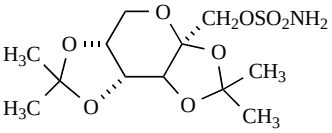
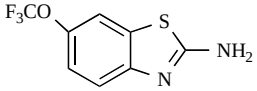
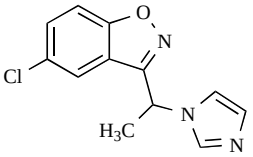
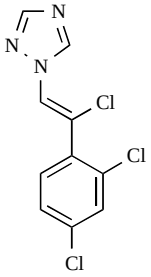
(Table 1). Contd…..

Compound Number	Chemical Structure	References
96, 97	 **96a** R_1R_2= Piperidino **96b** R_1R_2= Morpholino  **97 a** R = C_6H_5 **97 b** R = $CH_2C_6H_5$	[133]
98	 **98**	[134]
99	 **99**	[135]
100	 **Brivaracetam** **100**	[136]
101	 **Seletracetam** **101**	[137]
102, 103	 **102**  **103** Where: R_1 =H, alkyl, aryl, phenylalkyl, carbamoylalkyl, diphenylalkyl	[138]

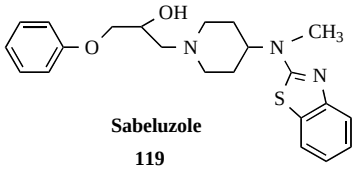
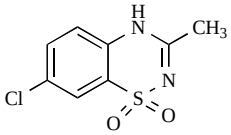
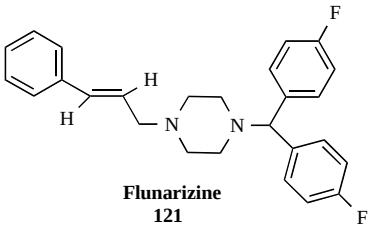
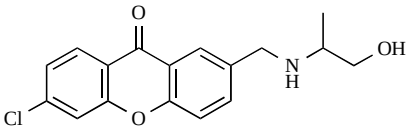
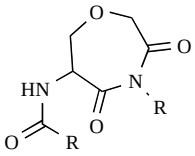
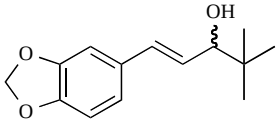
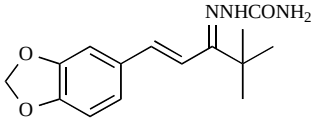
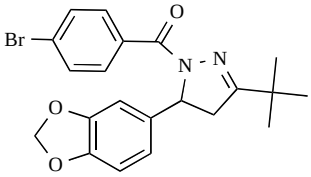
(Table 1). Contd…..

Compound Number	Chemical Structure	References
104, 105	 **104** **105**	[139]
106	 **106**	[140]
107	 **Sulthiame** **107**	[141]
108, 109	 **Felbamate** **108** **Meprobamate** **109**	[142]
110	 **110**	[143]
111	 **Nabazenil** **111**	[144]

(Table 1). Contd…..

Compound Number	Chemical Structure	References
112	 **Nafimidone** **112**	[145]
113	 **Zonisamide** **113**	[146, 147]
114	 **Lamotrigine** **114**	[148]
115	 **Topiramate** **Topamax®** **115**	[149]
116	 **Riluzole** **116**	[150]
117	 **Zoniclezole** **117**	[151]
118	 **Loreclezole** **118**	[152]

(Table 1). Contd…..

Compound Number	Chemical Structure	References
119	 **Sabeluzole** **119**	[153]
120	 **Diazoxide** **120**	[132]
121	 **Flunarizine** **121**	[154]
122	 **122**	[155]
123	 **123a** R= H **123b** R=CH_3	[156]
124	 **Stiripentol** **Diacomit(R)** **124**	[161-163]
125	 **125**	[167]
126	 **126**	[167]

2-amino-1-propanol derivatives of 6-chloro-2-methyl-xanthone (**122**) displayed a protective index in mice (TD_{50}/ED_{50}) of 6.23/6.85 corresponding to that of phenytoin, carbamazepine and valproate [155].

Moreover in 2008, Sharma *et al*. synthesized a series of 6-amino-1,4-oxazepane-3,5-dione derivatives among which (**123a** and **123b**) exhibit a potent anticonvulsant profile at ED_{50} at 55.08mg/kg ,41.02 mg/kg in the PTZ test, respectively [156].

Retigabine [N-(2-amino-4-[fluoro-benzyl amino]-phenyl) carbamic acid; D-23129] is a novel antiepileptic compound with brood spectrum and potent anticonvulsant properties both *in vitro* and *in vivo*. The compound was shown to activate a K+ current, in neuronal cells [157]. Efficacy and safety of retigabine 600, 900 and 1200 mg/day is and can be administered three times daily as adjunctive therapy in patients with partial-onset seizures [158].

The benzopyran carabersat, *trans* (+) 6-acetyl-4S-(4-fluoro-benzoyl amino)-3, 4-dihydro-2,2-dimrethyl-2H-benzo(b)pyran-3R-ol hemihydrate, is a compound that is structurally unrelated to other AEDs [159]. This novel antiepileptic drug undergoes intensive clinical investigation to assess their efficacy and usefulness in the treatment of refractory epilepsy [160].

The anticonvulsant losigamone (LSG) is a racemate of a tetronic acid derivative. It decreases the frequency of spontaneous action potentials and suppresses repetitive firing of neurons. LSG is an effective and safe add-on drug for refractory partial epilepsy in adults at dose of 1200 mg/day and 1500 mg/day [161].

Stiripentol (STP, Diacomit®, **124**) which is *RS*-(1-(benzo[d][1,3]dioxol-5-yl)-4,4-dimethylpent-1-en-3-ol) (is a novel antiepileptic drug belongs to the group of aromatic allylic alcohols [162]. It has been granted orphan drug status in the European Union for the treatment of severe myoclonic epilepsy in infancy (Dravet syndrome) [163]. Although precise mechanism of action of STP remains unknown, it has long been considered to be indirect, as it inhibits the enzymes responsible for metabolism of other antiepileptic drugs. Nevertheless, a recent report suggested that STP might also act at the neuronal level, increasing inhibitory GABAergic neurotransmission through positive allosteric modulation of $GABA_A$ receptors [164]. Stiripentol is a secondary alcohol containing one stereogenic center. So far, it is marketed as a racemic mixture, albeit, there are marked differences in pharmacokinetics and antiepileptic potency between the enantiomers [165]. Yet, *R*-Stiripentol (eutomer) has been separated *via* bio-catalyzed kinetic resolution methodology [166].

In a recent work, Aboul-Enein *et al* [167], have synthesized a series of Stiripentol derivates where compound **125** showed high potency as anticonvulsant particularly in MES screen showing 100% protection at 100 mg/kg (346 μmol/kg).

On the other side, compound **126** was highly effective in *sc*PTZ screen presentation 100% protection at 150 mg/kg (350 μmol/kg) and being two times more active than Stiripentol.

CONCLUSION

In this brief review the most important antiepileptics/anticonvulsants and their mechanism of action are described. They are classified according to the chemical classes they belong together with their reported anticonvulsant potential. The chemical structures and references of these compounds are presented in tabular form (Table **1**). Many of these drugs found route to the market.

It is worth mentioning that the introduction of new antiepileptics and anticonvulsant agents raises hope that epilepsy can be controlled with fewer side effects and improved quality of life, especially for those who experienced failure of traditional therapy.

CONFLICT OF INTEREST

There is no conflict of interest.

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