



## Recent developments and advances on medicinal chemistry of Anti-convulsants drugs

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### Abstract

Epilepsy is not a disease, but a syndrome of different cerebral disorders of the CNS. This syndrome is characterized by paroxysmal, excessive, and hyper synchronous discharges of large numbers of neurons. The first major division of epilepsy is localization-related (i.e., focal, local, partial) epilepsies, which account for about 60% of all epilepsies. The remainder, about 40%, is composed of generalized epilepsies. The most common, and most difficult to treat, seizures in Adult patients are complex partial seizures, whereas primary generalized tonic-clonic (formerly, "Grand mal" epilepsy) seizures respond in most patients to treatment with anticonvulsants. Thus a need for new drugs with a greater benefit as related to side effects and tolerability, even at the expense of efficacy, when compared to the existing antiepileptic agents.

**Keywords:** epilepsy, seizures, anticonvulsants, EEG.

### 1. Introduction

The central nervous system constitutes the cerebral cortex, the limbic system, the midbrain, the brainstem, the cerebellum, and the spinal cord [1]. Epilepsy is one of the most common disorders of the brain, affecting about 50 million individuals worldwide. Epilepsy is a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures that are caused by abnormal discharge of cerebral neurons [2]. These seizures may be identified on the basis of their clinical characteristics. These clinical attributes, along with their electroencephalographic pattern, can be used to categorize seizures [3]. Seizures are basically divided into two major groups: partial and generalized. Partial (focal, local) seizures are those in which clinical or EEG evidence exists to indicate that the disorder originates from a localized origin, usually in a portion of one hemisphere in the brain [4]. Partial seizures may be further subdivided into simple partial, complex partial and partial seizures evolving into secondarily generalized seizures. In generalized seizures, the evidence for a local origin is lacking. Generalized seizures may be further subdivided into absence (no convulsive), myoclonic, clonic, tonic, tonic-clonic, and atonic seizures. More than 40 distinct epileptic syndromes have been identified, making epilepsy an extremely diverse collection of disorders. An epilepsy, or epileptic syndrome, is idiopathic, virtually synonymous with genetic epilepsy; or symptomatic, which is attributed to a structural modification or major identifiable metabolic derangements [5, 6]. Both types of seizure patterns and epilepsy determine the choice and prognosis of therapy. However, for many seizure types and epilepsy syndromes, there is little information about the pathophysiological basis. However, on the other hand, and most fortuitously, insight into how partial seizures, generalized tonic-clonic seizures, and generalized absence seizures arise is substantial, given that these seizure types constitute about 90% of seizures [7].

### 2. Clinical Applications

In the absence of a specific etiologic understanding in any of the epilepsies or epileptic syndromes, approaches to drug therapy of epilepsy must of necessity be directed at the control of symptoms, that is, the suppression of seizures. Currently, all available drugs are anticonvulsant (i.e., antiseizure) rather than antiepileptic [8]. The latter term should be used only for drugs that prevent or treat epilepsy and not solely its symptoms. The goal of therapy with an anticonvulsant agent is to have the patient seizure free without interfering with normal brain function. Thus, the selection of an anticonvulsant agent is based primarily on its efficacy for specific types of seizures and epilepsy [9, 10]. Although seizure control is generally good in most patients, a significant proportion of patients with epilepsy suffer from intractable or drug-resistant epilepsy, despite early treatment and an optimum daily dosage of an adequate anticonvulsant agent [11, 13]. There is thus a need of how new drugs with a greater benefit as related to side effects and tolerability, even at the expense of efficacy, when compared to the existing antiepileptic agents [14, 15].

### 3. Recent Developments and Chemistry

The following drugs are in various stages of developments as anti-convulsants.

#### ▪ AWD 131-138

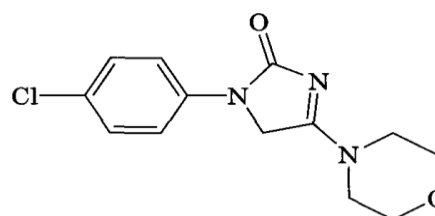


Fig 1

Chemically, AWD 131-138 is 1-(chlorophenyl)-4-morpholino imidazolin-2-one. This compound is currently in Phase I clinical development [16]. It possesses a broad spectrum of anticonvulsant activity as well as anxiolytic action. Its mechanism of action is by blockade of the voltage-activated  $\text{Ca}^{2+}$  channel in a dose-dependent manner. The  $\text{Ca}^{2+}$  channel subtype is currently unclear. AWD 131-138 is rapidly absorbed in rats and dogs and displays a high metabolic stability under in vitro human liver slices [17, 19].

#### 4. Harkoseride

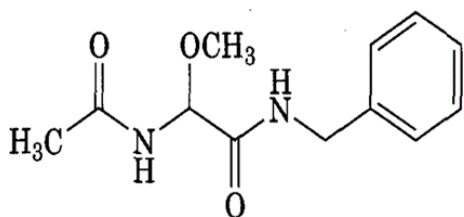


Fig 2

Chemically, harkoseride is (R)-2-acetamido-N-benzyl-3-methoxypropionamide, part of a class of functionalized amino acid derivatives developed by Kohn and coworkers and Paruszewski [20, 21]. Harkoseride shows excellent anticonvulsant activity in several animal models, including two models of status epilepticus. It also provides neuroprotective effects in rat models of focal ischemia [22]. It is currently undergoing phase II clinical evaluation. It was found to be rapidly and completely absorbed. The drug is eliminated primarily by renal excretion and the metabolites have not been identified. Preliminary data indicate that harkoseride does not affect the blood levels of carbamazepine, phenytoin, or valproate [23].

#### ▪ NPS 1776

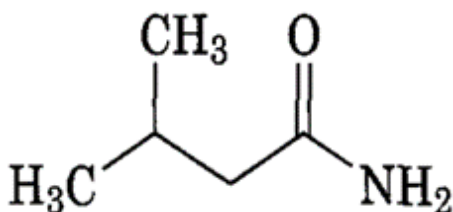


Fig 3

Chemically, NPS 1776 is 3-methylbutanamide, or isovaleramide, a branched chained aliphatic amide that contains a broad spectrum of activity similar to that of valproate (240). The mechanism of action is unknown; it was inactive in in vitro neurotransmitter binding or uptake assays [24]. This suggests that its mechanism does not involve a direct receptor-mediated action. Being a small, neutral molecule, it is easily soluble in aqueous media and readily diffuses through biological membranes. It is thus rapidly absorbed and extensively distributed throughout body water. It is not bound to plasma proteins, but is extensively metabolized, with about 50% excreted in the urine of rats as the w (i.e., 4-hydroxy), and w-1 (i.e., 3-hydroxy) oxidation products. The drug has successfully completed Phase I clinical trials [25].

#### ▪ NW-1015

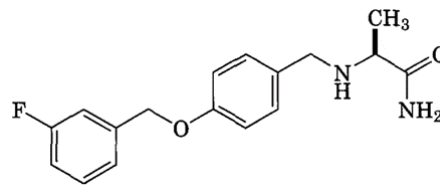


Fig 4

Chemically, NW-1015 is (S) (+)-2-[4-(3-fluorobenzoyloxy)benzylamino]propanamide. The compound combines frequency and use-dependent blockade of  $\text{Na}^{+}$  channels,  $\text{Ca}^{2+}$  channel modulation, inhibition of glutamate release, and monoamine oxidase B inhibition. A study in human volunteers was successfully completed. The findings of MAO-B inhibition at the dosages tested indicate the possibility of the potential use in Parkinson's disease [26].

#### ▪ Remacemide

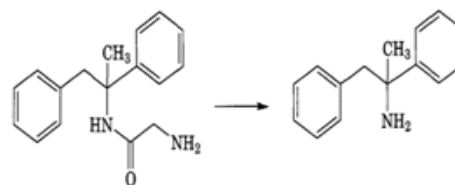


Fig 5

Remacemide, which chemically is 2-amino-N-(1-methyl-1,2-diphenylethyl)acetamide, and its principal active desglycyl metabolite, are low-affinity, noncompetitive NMDA receptor blockers and  $\text{Na}^{+}$  fast channel blockers. Remacemide is rapidly absorbed on oral administration and achieves a peak plasma level in 1 h, whereas the active metabolite takes 2-3 h. The parent has a half-life of 3-4 h, compared to 12-15 h for the active metabolite [27]. Comedication with enzyme-inducing anticonvulsants (i.e., phenytoin, carbamazepine, and Phenobarbital) induces the metabolism of remacemide, thus reducing their plasma concentration. The agent has been studied for its anticonvulsant effect, and because of its neuroprotective potential, trials have also been conducted for other indications, including Parkinson's disease and Huntington's disease. A phase-III study in a monotherapy trial with carbamazepine, however, indicated that the efficacy of remacemide was inferior to that of carbamazepine [28].

#### ▪ Retigabine (D-23129)

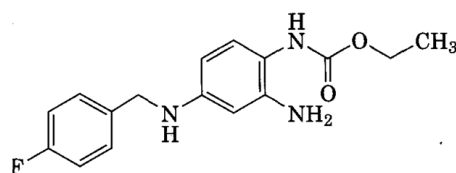


Fig 6

Chemically, retigabine (D-23129) is ethyl N-(2-amino-4-(4-fluorobenzylamino)phenyl)carbamate and is structurally unrelated

to currently marketed anticonvulsant agents. It shows a unique mode of action by increasing K<sup>+</sup> conductance in neuronal cells (198). Phase- I and II studies have shown good tolerability and efficacy trials are ongoing [29].

▪ **Rufinamide (CGP 331 01)**

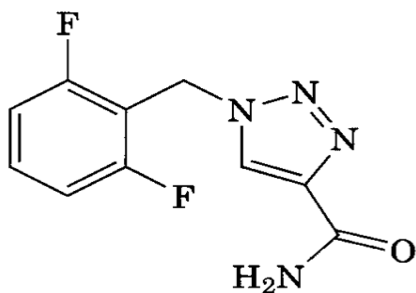


Fig 7

Chemically, rufinamide (CGP 33101) is 1-(2, 6-difluorobenzyl)-1H-1,2,3-triazolo-4-carboxamide, which interacts with the inactivated state of the Na<sup>+</sup> channel, limiting high frequency firing of action potentials in neurons. It does not significantly interact with the following neurotransmitter systems: GABA, adenosine; NMDA; monoaminergic; cholinergic binding sites; and other excitatory amino acid binding sites [30]. Based on the broad-spectrum preclinical profile, favorable clinical pharmacological characteristics, and efficacy and safety results from early clinical trials, phase-I development procedures are being undertaken [31].

▪ **Losigamone (AO-33)**

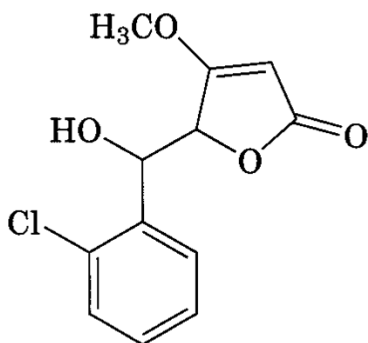


Fig 8

Chemically, losigamone (AO-33) is (+)-5(R, S), α-(S&)-5-[(2-chlorophenyl) hydroxymethyl]-4-methoxy (5H)-furanone, and belongs to the group of p-methoxy-butenolides, which is found in a large number of natural products [e.g., the piperolides obtained from *Piper sanctum*. Losigamone exists as a racemic mixture of two enantiomers. There is evidence that the two isomers differ in anticonvulsant activity; the (+)- isomer (AO-242) is more potent than the (-)-isomer (AO-294), but the reverse may be true depending on the animal model (226). The toxicity profiles, however, are identical. The mechanism of action of losigamone is unclear at present. The agent is rapidly absorbed, with peak plasma concentrations occurring 2-3 h after an oral dose. It is bound to plasma proteins to the extent of 60%, and has a half-life of 4 hrs. Although the preceding data refer to the

racemate, there are data that an enantioselective difference exists in the pharmacokinetics of the drug [32]. When the individual isomers are given separately, the apparent oral clearance of the (-)-enantiomer is >10 times that of the (+)-enantiomer. Losigamone is eliminated primarily by oxidation. Biotransformation is stereoselective, with the (-)-enantiomer undergoing greater first-pass metabolism compared to that of the other isomer. It has undergone one clinical trial with no serious adverse events reported [33].

▪ **Stiripentol**

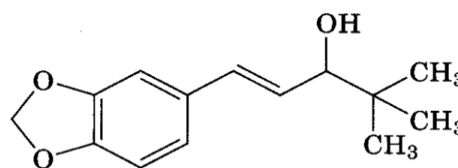


Fig 9

Chemically, stiripentol is 4, 4-dimethyl-1-[(3, 4-methylenedioxy) phenyl]-1-penten-3-ol. This agent is limited by its extensive metabolism. Phase-II trials in Europe have demonstrated its efficacy in hard-to-treat epilepsies. Its effectiveness in partial seizures, however, is lower than that of the currently available agents [34].

▪ **Canaxolone (CCD 1042)**

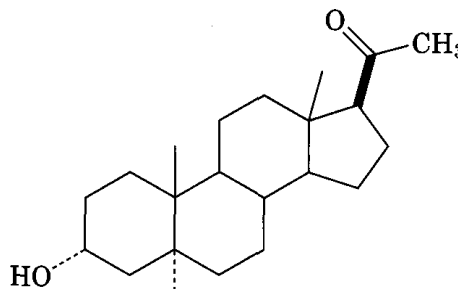


Fig 10

This steroid is a member of a novel class of neuroactive steroids, termed epalons that allosterically modulate the GABA<sub>A</sub> receptor complex through a unique recognition site [35]. This compound was developed after observations that endogenously occurring metabolites of progesterone had significant anticonvulsant effects in animals. Although chemically related to progesterone, ganaxolone possesses no hormonal activity. The agent was successful in phase I and phase-II studies in refractory infantile spasms. The safety and Tolerability was generally good. Because of extensive first- pass metabolism, the development of a suppository dosage form is underway [36].

▪ **Soretolide (D 2916)**

Chemically, soretolide (D 2916) is N45-methyl-3- isoxazolyl)-2, 6-dimethylbenzamide (641, a compound similar to carbamazepine in its activity profile. It was noted that the active hydroxymethyl metabolite, (64a), was formed preferentially in female rats; however, it is uncertain whether this species-specific offered is noted in humans. It is currently undergoing a multicenter study in refractory partial epilepsy [37].

#### 4. Things to Come

##### ▪ (Aryloxy) Aryl Semicarbazones

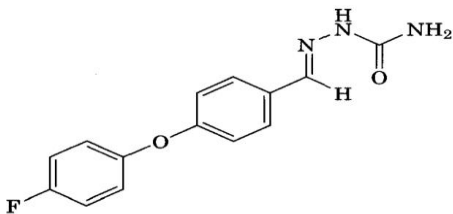


Fig 11

Dim mock *et al.* has prepared an extensive series of semicarbazones. The lead compound among the (aryloxy) aryl Semicarbazones is 4-(4'-fluorophenoxy) benzaldehyde semicarbazone. Preclinical evaluations have been completed. The compound is a potent sodium channel blocker and it is planned to be developed for the treatment of neuropathic pain. Phase- I clinical trials are scheduled in the near future. Of further interest was the model Dim mock employed in determining the structure activity relationship among the compounds in this series [38].

##### ▪ AMP397A

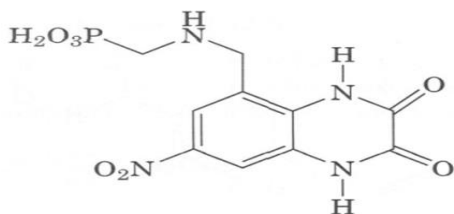


Fig 12

Evolved from a series of N-phosphonoalkyl-5-aminomethylquinoxaline-2, 3-diones, AMP397A has emerged. This compound is an orally active, potent competitive AMPA receptor antagonist active in a broad spectrum of anticonvulsant tests. AMP397A combines a high affinity for native human AMPA receptors (IC<sub>50</sub> = 11 nM) with moderate affinity for the competitive site of NMDA receptors (IC<sub>50</sub> = 420 nM). The NMDA component does not contribute significantly to its antiepileptic properties [39]. In addition to its broad anticonvulsant spectrum (MES, pentylenetetrazol, strychnine, and picrotoxin), it strongly decreases burst activities in genetically epilepsyprone rats with absence-type seizures, suppresses kindling development, and decreases the severity of behavioral syndromes in kindled rats. As a result of preclinical results, it is expected to be active in patients with partial, generalized tonic-clonic, and myoclonic/absence type seizures [40].

##### ▪ U-594494A

U-594494A, cis-3, 4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-Benzamide, is a potent, long-acting anticonvulsant without sedative or analgesic effects. It is not only effective in antagonism of electroshock seizures, but also effective against excitatory amino acids and Ca<sup>2+</sup>-induced seizures. The drug is structurally related to a K-opioid agonist, although it shows no binding affinity to this receptor. Its primary effect is with sodium

channels; it blocks NIE-115 mouse neuroblastoma cells in a voltage- and use-dependent manner. The compound was found to be a long acting anticonvulsant, but its brain levels could not account for its extended time course [41]. The individual enantiomers were recently evaluated and the (-)-isomer was metabolized to a lesser extent than the (+)-isomer, which had a lower oral bioavailability as well. Fischer *et al.* independently evaluated U-54494A. It observed in this study that there was considerable evidence to suggest that the stimulation of K-receptors reduces the entry of Ca<sup>2+</sup> into neurons or nerve terminals, which may be related to the closure of N-type Ca<sup>2+</sup> channels. This action can result in a decrease of neuronal excitability and a reduction of transmitter release. Fischer concluded that it was thus difficult to draw definitive conclusions regarding the involvement of central K-opioid receptor mechanisms in the anticonvulsant actions of U- 54494A [42].

##### ▪ SB-204269

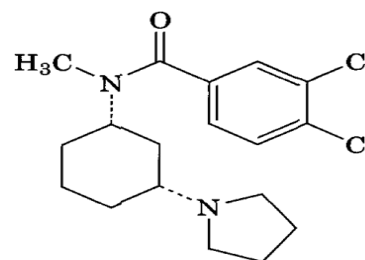


Fig 13

SB-204269 showed good anticonvulsant activity in the MES evaluation and is currently undergoing clinical evaluation of epilepsy and has progressed to Phase II of clinical development [43]. The stereochemistry was found to be necessary with the trans4S configuration essential for activity. As with levetiracetam, this series were discovered with a unique [3HISB-204269 binding site assay. In a subsequent study, a series of alternative structural classes were prepared by high throughput screening of the SB compound library in the [3HISB-204269 binding assay and led to the following series of active 1, 2, 3, 4-tetrahydroisoquinolinyl benzamide. As seen from the data, the structure-activity studies have led to a refinement of the original pharmacophore model. It should also be noted that these structures bear a close structural resemblance to (-)-levcromakalim, an antihypertensive ATP-sensitive potassium channel opener; however, the 3S, 4R stereochemistry abolished anticonvulsant activity [44, 46].

#### 5. Conclusion

A recent report indicated that cryptogenic epilepsy, the group of epilepsy syndromes for which an etiology is unknown, consisting of about 20% of all epilepsy syndromes, may be caused by *Toxoplasma gondii* [47]. A statistically significant elevation of *T. gondii* antibodies was found compared to that of controls, suggesting that *T. gondii* infection with brain cysts may be a cause of the disease.

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