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Review

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An overview of structurally diversified anticonvulsant agents

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There are several limited approaches to treat epilepsy in hospitals, for example, using medicines, surgery, electrical stimulation and dietary interventions. Despite the availability of all these new and old approaches, seizure is particularly difficult to manage. The quest for new antiepileptic molecules with more specificity and less CNS toxicity continues for medicinal chemists until a new and ideal drug arrives. This review covers new antiseizure molecules of different chemical classes, the exact mode of action of which is still unidentified. Newer agents include sulfonamides, thiadiazoles, semi- and thiosemicarbazones, pyrrolidine-2,5-diones, imidazoles, benzothiazoles and amino acid derivatives. These new chemical entities can be useful for the design and development of forthcoming antiseizure agents.

Keywords: antiepileptic agents, sulfonamides, imidazoles, thiadiazoles, benzothiazoles and amino acid derivatives

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INTRODUCTION

Epilepsy is a collective term for a group of chronic CNS disorders. All kinds of epilepsies display the occurrence of unprovoked, excessive, sudden, self-regulated neuronal discharge that results in a seizure. Because of excessive neuronal discharge, the finely organized pattern of the integrative activity of the brain is abolished (1).

Prevalence of the disease is observed in every corner of the world, with underdeveloped countries being more vulnerable. It is estimated that almost 50 million people around the world are affected by epilepsy (2). Older people are more prone to epileptic spell (3). The exact etiology of the disease is still unknown. However, factors associated with epilepsy include brain trauma, strokes, brain cancer and drug and alcohol misuse, among others. The multifactorial origin of the disease produces a high degree of disablement to successful discovery of antiepileptic drugs (4). In many cases, there is no direct family relation to the epileptic condition at all. However, some researchers have confirmed that some special types of epilepsy take place more often in some families. It was recently revealed that such

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types of epilepsy were connected with the transfer of specific genes from one generation to another (5–10). There are many mutated genes responsible for various types of inheritable epilepsies, for example, familial nocturnal frontal lobe epilepsy is caused by inheritance of mutated CHRNA2, CHRNA4 and CHRNB2 genes. In the same way, febrile seizures, generalized epilepsy with febrile seizures plus and Dravet syndrome are caused by inheritance of mutated SCN1A, SCN2A, SCN2B and GABRG2 genes. Many studies have confirmed that epigenetically facilitated regulation of Na^+ channel genes (SCN1A, SCN1B, SCN2A and SCN3A) associated with generalized epilepsy with febrile seizures plus (GEFS+) are mediated *via* DNA methylation and methyl-CpG-binding domain 2 (MBD2) binding (11). Some antiepileptic drugs produce epigenetic changes. For example, valproate induces defects of epigenetic transcriptional regulatory mechanisms in glial cells, resulting in reduced cell proliferation, which may in turn lead to cognitive dysfunction or mental illness (12, 13).

Over the past ten years, a large number of new antiepileptic drugs (AEDs) and non-pharmacologic remedies have been added to treat epilepsy. The new drugs are designed to address specific pathophysiologic defects such as seizure generation or spread where the old medicines are not useful any more. Other novel approaches to control epilepsy include electrical stimulation devices, such as vagus nerve stimulator (14–16), deep brain stimulation (DBS) (17, 18) and dietary interventions (ketogenic diet) (19–22). Despite the availability of all new and old AEDs, along with the arrival of new techniques, seizures are particularly challenging to treat. The old generation antiepileptic drugs (AEDs) such as phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepine are potent and extensively used but exhibit considerable adverse effects and also fail to adequately control seizures (23). On the other hand, new AEDs, for example gabapentin, topiramate, lamotrigine, levetiracetam, vigabatrin, and rufinamide are not as potent as the old AEDs and are used as an add-on therapy. They all exhibit significant CNS-related and other side effects (24). This study suggests that only a small number of new AEDs adequately manage major types of epilepsy, the remaining drugs control only one or two types. The undesired side effects and failure to control the major types of epilepsy compel the researchers to find candidates that would meet all the requirements for an ideal drug.

The antiseizure drugs, which are currently prescribed in the clinics, are categorized based on their mode of action as follows (Fig. 1):

(i) drugs that block the sodium channel, for example, phenytoin, carbamazepine, oxcarbazepine, *etc*.,

(ii) drugs that activate GABA-mediated inhibitory action, such as benzodiazepines, barbiturates, vigabatrin, tiagabine,

(iii) drugs that block the Ca^{2+} channel, for example, pregabalin, gabapentine, *etc*.,

(iv) drugs that inhibit glutamate receptors (both NMDA and AMPA), for example, felbamate, topiramate, *etc*.

Some drugs possess a combination of actions, often coupled with additional and unknown mechanisms (25, 26); these include valproic acid, lamotrigine, zonisamide, *etc*.

The newly designed and synthesized antiepileptic agents have been surveyed over the last few years. The diversity of chemical structures and various modes of action of anticonvulsant agents make it hard to attain a universal way of discovering new drugs.

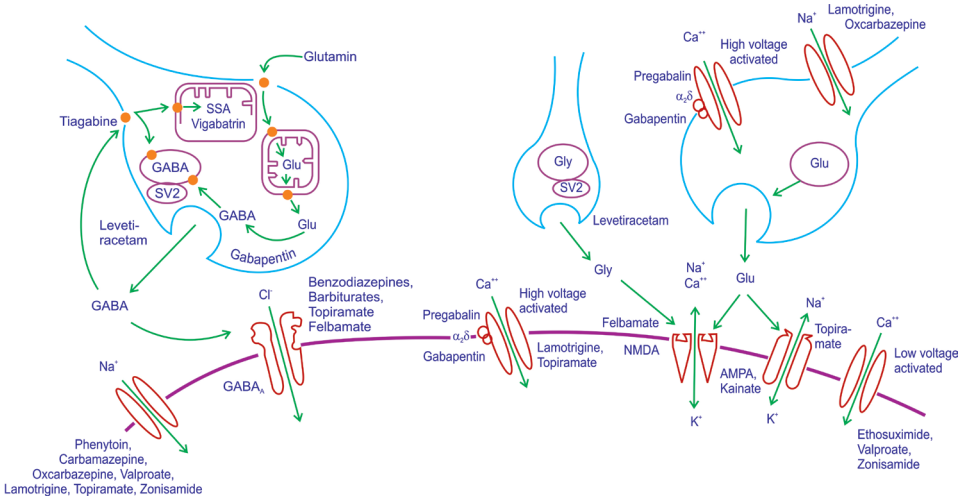


Fig. 1. Mechanism of action of antiepileptic drugs ($\alpha_2\delta$ – auxiliary subunit of voltage dependent Ca^{2+} channels, AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, GABA – γ-aminobutyric acid, Gly – glycine, Glu – glutamate, NMDA – *N*-methyl-*D*-aspartate, SSA – succinate semialdehyde, SV2 – synaptic protein 2).

Novel antiepileptic molecules are discovered *via* screening or modification in the structure of already existing drugs but not by a mechanism-based design.

This review highlights new antiseizure agents containing various chemical structures whose exact mode of action is unknown. These newly synthesized analogues comprise sulfonamides, heterocyclic compounds, functionalized amino acids, and others. These chemical classes of compounds can be useful for the design and development of new antiepileptic drugs in the future.

NEW ANTICONVULSANT AGENTS: A STRUCTURE BASED REVIEW

Sulfonamide derivatives

This class of drugs has displayed a large number of clinical uses. Some of these drugs are used as antimicrobials, also called sulpha drugs. Some are carbonic anhydrase (CA) inhibitors, which are used as diuretics and antiepileptic drugs. In search of newer anticonvulsant agents, researchers discovered acetazolamide and methazolamide (Fig. 2). In general, these drugs are 5-membered heterocycles containing a sulfonamide and an amide as well as a 1,3,4-thiadizole nucleus. They exhibit potent carbonic anhydrase inhibitory activity. Topiramate and zonisamide are recently developed antiepileptic drugs bearing different sulfonamide groups in their structure (Fig. 2). Scozzafava and Supuran (27–32) developed several new carbonic anhydrase inhibitors, which are mainly derivatives of sulfonamide. Recent progress in the development of anticonvulsant agents containing sulfonamide moiety is summarized in Table I.

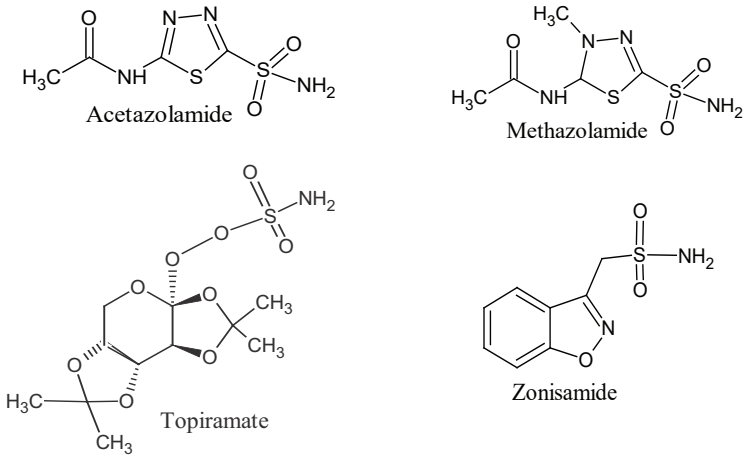


Fig. 2. Antiepileptic drugs containing a sulfonamide group.

Derivatives of thiadiazole

Thiadiazoles are five-membered heterocyclic rings bearing two nitrogen atoms and one sulfur with two nitrogen-carbon double bonds (C=N). These conjugated double bonds between atoms provide the thiadiazole ring aromatic property. Four likely structures can be perceived on the basis of the locations of one sulfur and two nitrogen atoms (Fig. 3). These structures do not interchange and are hence structural isomers (not tautomers). Various isomers of thiadiazole are used as the basic moiety in the process of drug discovery and development (36–38).

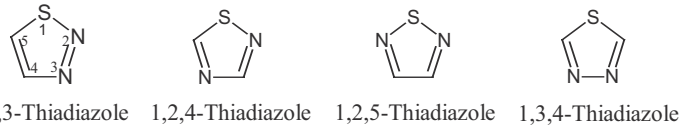


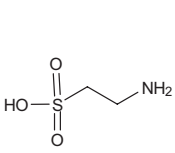
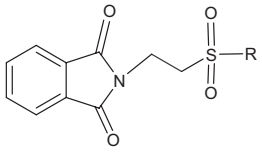
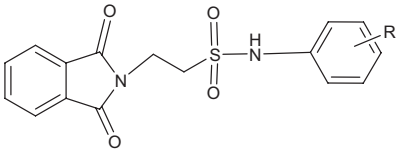
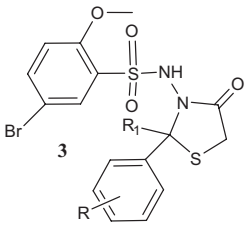
Fig. 3. Four structural isomers of thiadiazoles.

Table II gives an overview of thiadizole-containing new derivatives that display significant antiseizure activity in various animal models.

Semi- and thiosemi-carbazones as anticonvulsant agents

During the last two decades, semicarbazones have been extensively investigated for their anticonvulsant properties (51–54). In the conventional screening process, 4-(4-fluorophenoxy) benzaldehyde semicarbazone was discovered as a lead molecule against the electroshock (MES) seizure test. The protective index of this compound is higher than that of carbamazepine, phenytoin and valproate (55). Later on, a large number of scholars have attempted to find new molecules with significant anticonvulsant activity (Table III).

Table I. Recently designed and significantly active sulfonamide derivatives

Compound	Summary/conclusion	Reference
 Taurine **1**  Phthalimidosulfonamide derivatives of taurine	Two carbon side chains are important for showing anticonvulsant activity. Substitutions in the terminal sulphonamide moiety improve the lipophilic character, giving better CNS activity.	Linden *et al.* (33)
 **2a**; R=3-NO_3, 2-Cl best anti-MES activity at 0.5 h **2b**; R=2-CH_3, 2-$CH(CH_3)_2$, 4-NO_3, 2-Cl best anti-MES activity at 4 h **2c**; R=3-CH_3 and 2-CH_3 highly neurotoxic	Certain substituents, such as Cl, CH_3, and NO_3, in phenyl bound to nitrogen produce highly active analogues in the electroshock seizure test.	Akgul *et al.* (34)
 **3** R=3-OH, 4-Cl, 4-Br R_1=CH_3	These derivatives demonstrated protection in MES and *sc*PTZ seizure models.	Siddiqui *et al.* (35)

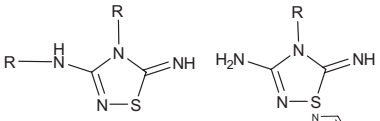
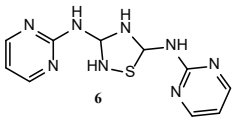
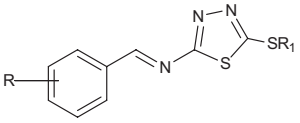
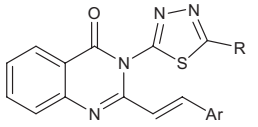
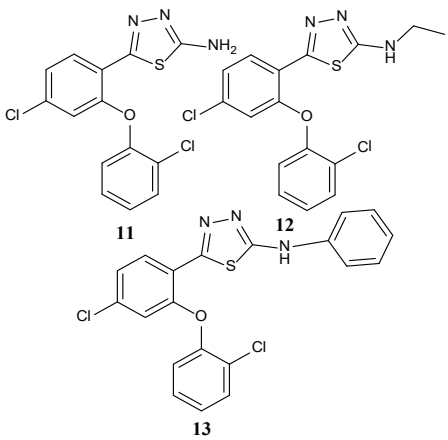
CNS – central nervous system, MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole

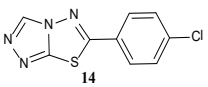
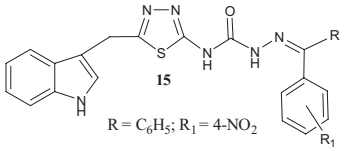
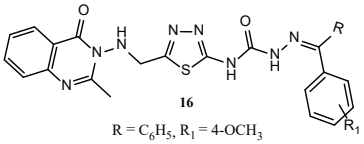
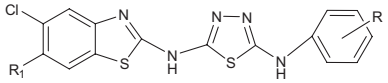
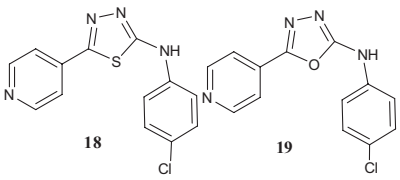
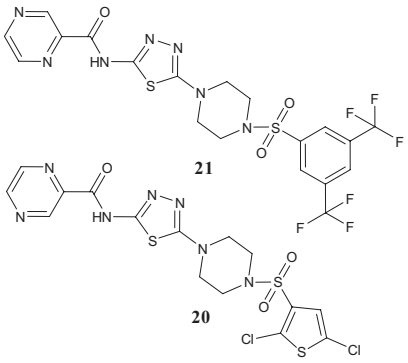
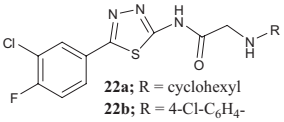
Pyrrolidine-2,5-diones as anticonvulsants

Derivatives of pyrrolidine-2,5-dione, as heterocyclic compounds, have been widely applied in medicinal chemistry. They exhibit abundant biological activities, especially in seizure and tyrosinase inhibitory action. Therefore, progress of new and efficient approaches for the preparation of multi-substituted pyrrolidine-2,5-dione derivatives is a burning issue in organic and medicinal chemistry (61).

Literature survey has revealed that Obniska and Kaminski (62–66), along with other researchers, worked extensively on pyrrolidin-2,5-diones as potential anticonvulsant agents. Some recently developed anticonvulsant agents having pyrrolidin-2,5-dione in their structure are presented in Table IV.

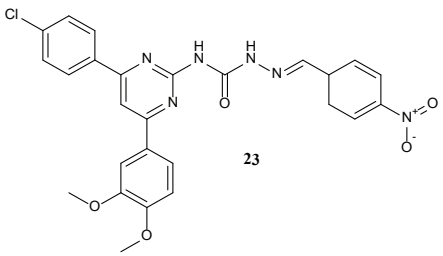
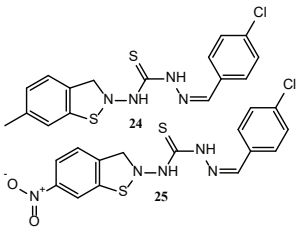
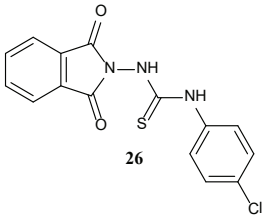
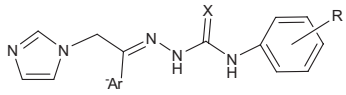
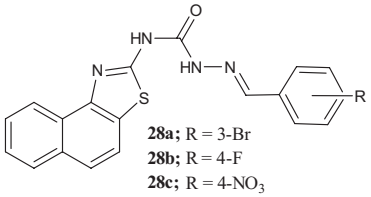
Table II. Some recently developed thiadiazole derivatives as anticonvulsant agents

Compounds	Summary/conclusion	Reference
 **4**; *p*-C_2H_5-O-C_6H_4 **5**; R =	Compounds **4** and **5** showed high activity against the *sc*PTZ model.	Gupta *et al.* (39)
 **6**	Derivative **6** was observed to be highly active in MES and *sc*PTZ test models.	Gupta *et al.* (40)
 **7a**; 2-Cl, R_1 = H **7b**; 4-Cl, R_1 = H **8a**; 2-Cl, R_1 = CH_2-C_6H_5 **8b**; 4-Cl, R_1 = CH_2-C_6H_5 **9a**; 2-Cl, R_1 = CH_2(4-Cl)C_6H_4 **9b**; 4-Cl, R_1 = CH_2(4-Cl)C_6H_4	These compounds displayed moderate to good activity in the MES test.	Ahmed *et al.* (41)
 **10a;** R = C_6H_5, Ar = 4-Cl-C_6H_4 **10b;** R = 3-Cl-C_6H_4, Ar = 4-Cl-C_6H_4 **10c;** R = 4-Cl-C_6H_4, Ar = pyridine	These compounds exhibited excellent anti-MES and anti-*sc*PTZ activity.	Jatav *et al.* (42)
 **11** **12** **13**	Compounds **11**, **12** and **13** were the most active against both electroshock (MES) and chemoshock (PTZ) with an ED_{50} 20.11 to 35.33 mg kg^{-1}.	Foroumadi *et al.* (43)

 **14**	This compound showed anti-seizure activity against MES, *sc*PTZ with a high protective index.	Deng *et al.* (44)
 **15** $R = C_6H_5$; $R_1 = 4\text{-}NO_2$	Compound **15** was observed to be the most protective against both electroshock (MES) and chemoshock (*sc*PTZ).	Rajak *et al.* (45)
 **16** $R = C_6H_5$, $R_1 = 4\text{-}OCH_3$	Analogue **16** showed significant protection in MES and *sc*PTZ seizure models without any neuromotor impairment.	Rajak *et al.* (46)
 **17a;** R = 4-Br, R_1 = Cl **17b;** R = 3-Cl, R_1 = Cl	These two derivatives (**17a**,**b**) exhibited total protection in the electroshock (MES) seizure test.	Siddiqui *et al.* (47)
 **18** **19**	Analogues **18** and **19** were found to be promising antiepileptic agents.	Shahar Yar *et al.* (48)
 **21** **20**	Compounds **20** and **21** confirmed the moderately protective effect against electroshock seizure similar to that of the standard drug phenytoin.	Harish *et al.* (49)
 **22a;** R = cyclohexyl **22b;** R = 4-Cl-C_6H_4- **22c;** R = 4-OCH_3-C_6H_4-	Three analogues **22a**-**c** were found to be protective at a dose of 30 mg kg^{-1} with or without significant neurotoxicity.	Al Rohaimi (50)

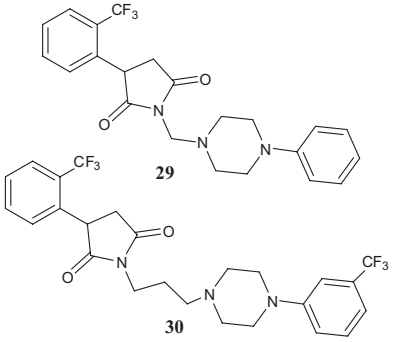
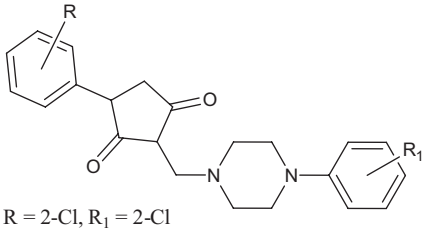
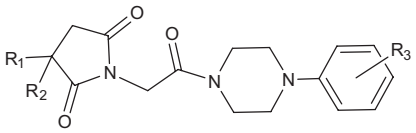
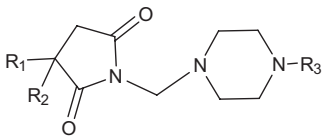
ED_{50} – median effective dose, MES – maximal electroshock seizure, PTZ – pentylenetetrazole, *sc*PTZ – subcutaneous pentylenetetrazole

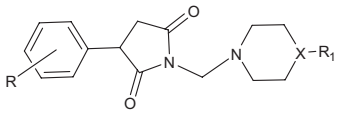
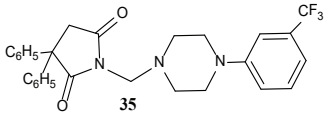
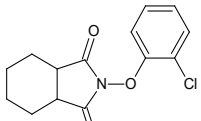
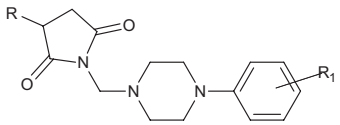
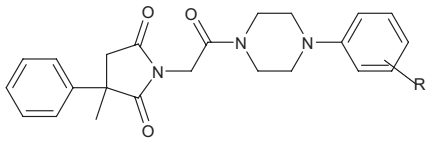
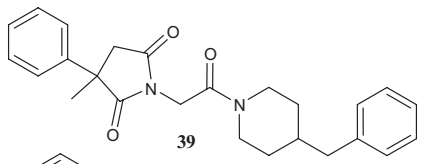
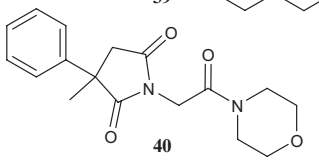
Table III. Some new semi- and thiosemi-carbazones as anticonvulsant agents

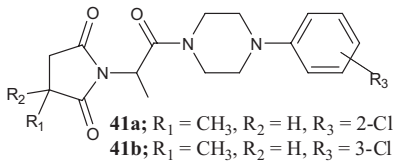
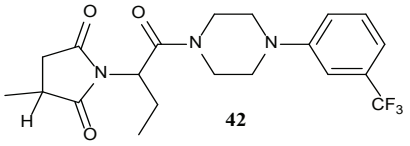
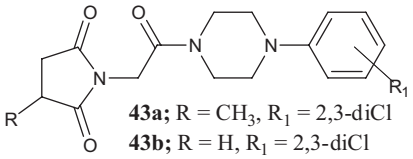
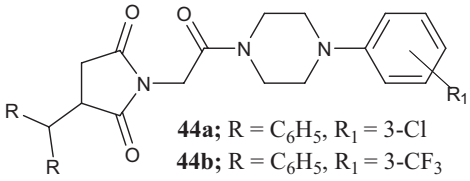
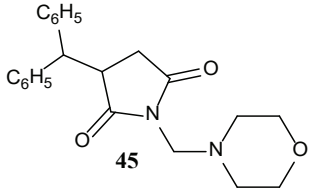
Compound	Summary/conclusion	Reference
 **23**	This compound was found highly active in the MES test without any neuromotor impairment.	Ozair *et al.* (56)
 **24** **25**	Analogues **24** and **25** showed promising outcomes against the MES seizure model with lesser or no neuromotor impairment.	Yogeeswari *et al.* (57)
 **26**	Analogue **26** showed significant activity against MES, *sc*PTZ and *sc*STY seizure tests without any neuromotor impairment	Yogeeswari *et al.* (58)
 **27a;** Ar = naphthyl, X = S, R= 3-Cl **27b;** Ar = biphenyl, X = S, R= 4-F **27c;** Ar = naphthyl, X = S, R= 4-CH_3	All three derivatives were found to be highly active in the MES test.	Çal**l**ş *et al.* (59)
 **28a;** R = 3-Br **28b;** R = 4-F **28c;** R = 4-NO_3	Analogues **28a-c** showed the highest degree of protection in MES and *sc*PTZ seizure models.	Azam *et al.* (60)

MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole, *sc*STY – subcutaneous strychnine

Table IV. Some newer pyrrolidine-2,5-dione as anticonvulsants

Compound	Summary/conclusion	Reference
 **29** **30**	Highly active derivative **29** with ED_{50} 20.78 mg kg^{-1}, when administered orally to rats and **30** with ED_{50} 132.13 mg kg^{-1} after *i.p.* injection to mice in the MES test.	Obniska *et al.* (67)
 **31a;** R = 2-Cl, R_1 = 2-Cl **31b;** R = 3-Cl, R_1 = 2-Cl **31c;** R = 3-Cl, R_1 = 4-Cl **31d;** R = 3-Cl, R_1 = 3-CF_3	In anti-MES and anti-*sc*PTZ tests, compounds **31c** and **31d** were highly active. In psychomotor seizure 6-Hz test, compounds **31a** and **31b** were highly active.	Obniska *et al.* (68)
 **32a;** R_1 = H, R_2 = H, R_3 = 3-CF_3 **32b;** R_1 = CH_3, R_2 = H, R_3 = 4-Cl **32c;** R_1 = CH_3, R_2 = CH_3, R_3 = 4-Cl **32d;** R_1 = CH_3, R_2 =CH_3, R_3 = 3-CF_3	Most anti-MES and anti-*sc*PTZ compounds were **32a-d**. **32a** and **32c** displayed high activity in the 6-Hz psychomotor seizure screening.	Kamiński *et al.* (69)
 **33a;** R_1 = C_6H_5, R_2 = C_6H_5, R_3 = $CH_2CH_2CH_2OH$ **33b;** R_1 = C_6H_5, R_2 = CH_3, R_3 = $CH_2CH_2CH_2OH$ **33c;** R_1 = C_6H_5, R_2 = CH_3, R_3 = CH_3	Compounds **33a-c** showed moderate to good activity in anti-MES and anti-*sc*PTZ tests as well as 6-Hz psychomotor seizure screening.	Obniska *et al.* (70)

 **34a**; R = H, X=N, R_1 = 2-pyrimidinyl **34b**; R = H, X=O **34c**; R = 2-Cl, X = CH, R_1 = benzyl **34d**; R = 2-Cl, X = O	Compound **34a** was Anti-MES and anti-*sc*PTZ active. **34a**, **34b** and **34d** were active in the 6-Hz psychomotor seizure screening. **34b** was found highly effective against status epilepticus.	Kamiński *et al.* (71)
 **35**	Compound **35** was found to be the most active in the MES test, with an ED_{50} equivalent to 30.3 mg kg^{-1} (*per os* in rats).	Obniska *et al.* (72)
 **36**	Compound **36** was the most favorable analogue against the 6-Hz psychomotor seizure model.	Kamiński *et al.* (73)
 **37a;** R_1 = CH_3, R_2 = 3,4-diCl **37b;** R_1 = H, R_2 = 3,4-diCl **37c;** R_1 = CH_3, R_2 = 3-CF_3	All three derivatives **37a-c** were reported highly active in MES and *sc*PTZ tests.	Rybka *et al.* (74)
 **38a**; R = H, **38b**; R = 2-F, **38c**; R=4-F, **38d**; R=3-CF_3, **38e**; R = 2-OCH_3  **39**  **40**	In the MES seizure test, **38b**, **38c** and **38e** were the most active compounds**.** In the *sc*PTZ test, **38a** and **39** were the most active compounds. Some compounds were also found active against the psychomotor seizure 6-Hz test, for example, **38d** and **40.**	Obniska *et al.* (75)

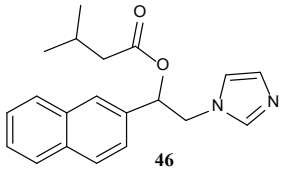
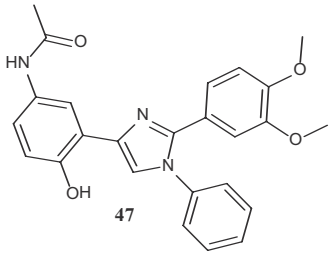
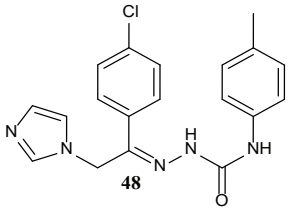
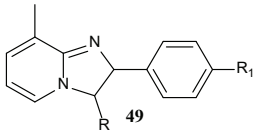
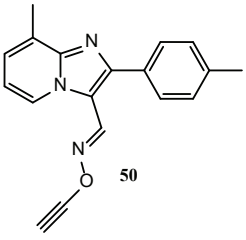
 **41a;** R_1 = CH_3, R_2 = H, R_3 = 2-Cl **41b;** R_1 = CH_3, R_2 = H, R_3 = 3-Cl **41c;** R_1 = CH_3, R_2 = H, R_3 = 3-CF_3  **42**	Broad spectra of activities across the preclinical seizure models were displayed by compounds **41b**, **41c** and **42**. Besides anticonvulsant properties, compound **41a** diminished the pain responses in the formalin model of tonic pain in mice.	Kamiński *et al.* (76)
 **43a;** R = CH_3, R_1 = 2,3-diCl **43b;** R = H, R_1 = 2,3-diCl	Analogues **43a** and **43b** exhibited antiseizure activity in pilocarpine-induced seizure models.	Rapacz *et al.* (77)
 **44a;** R = C_6H_5, R_1 = 3-Cl **44b;** R = C_6H_5, R_1 = 3-CF_3	The most active analogues were **44a** having ED_{50} 42.71 mg kg^{-1} in case of MES and ED_{50} >150 mg kg^{-1} in case *sc*PTZ, and **44b** with ED_{50} 101.46 mg kg^{-1} in case of MES and ED_{50} 72.59 mg kg^{-1} in case *sc*PTZ.	Rybka *et al.* (78)
 **45**	Compound **45** was the most promising compound in all the antiseizure tests.	Rybka *et al.* (79)

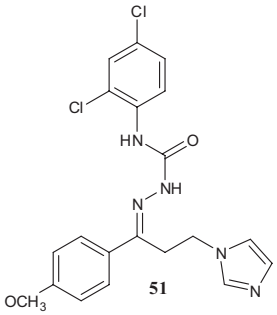
ED_{50} – median effective dose, *i.p.* – intraperitoneally, MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole

Imidazoles as anticonvulsant agents

Imidazole and its analogues are five-membered heterocyclic structures having two nitrogen atoms separated by one carbon atom. Recent studies have revealed that imidazole analogues have attracted a great deal of attention owing to their broad range of biological activities such as analgesic (80), anti-inflammatory (81), *etc*. Literature survey has also shown that imidazole-heterocyclic analogues could be an important class of antiseizure agents; an existing antiseizure drug, phenytoin, contains an imidazole ring (82). Some potent and recently developed imidazole bearing anticonvulsant agents are summarized in Table V.

Table V. Some recently developed imidazoles as anticonvulsant agents

Compound	Summary/conclusion	Reference
 **46**	Compound **46** was highly active with ED_{50} and TD_{50} values of 38.46 mg kg^{-1} and 123.83 mg kg^{-1} in mice, and 20.44 mg kg^{-1} and 56.36 mg kg^{-1} in rats.	Karakurt *et al.* (83)
 **47**	Only compound **47** was found equally active as the standard drugs carbamazepine and phenytoin in the MES test.	Husain *et al.* (84)
 **48**	Compound **48** showed the highest activity among the synthesized analogues in MES and *sc*PTZ without any neuromotor impairment or depressant effects on CNS.	Amir *et al.* (85)
 **49**	Compound **49** was highly active against electroshock (MES) and chemoshock (*sc*PTZ) models.	Ulloora *et al.* (86)
 **50**	Compound **50** was found highly active in MES at both time intervals, *i.e.*, 0.5 and 4 h, suggesting a rapid onset and long duration of action.	Ulloora *et al.* (87)

 **51**	Compound **51** emerged as a highly active candidate showing 100 % protection at a very low dose in the chemoshock (*sc*PTZ) screen without any neuromotor impairment.	Attia *et al.* (88)

CNS – central nervous system, ED_{50} – median effective dose, MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole, TD_{50} – median toxic dose

Benzothiazoles as anticonvulsants

Benzothiazole belongs to the family of bicyclic heterocyclic compounds having the benzene nucleus fused with a five-membered ring comprising nitrogen and sulfur atoms. Benzothiazole is an important scaffold with a wide spectrum of biological activities (89).

Work on benzothiazoles as anticonvulsant agents started recently and now we have a modest number of articles that validate benzothiazoles as potential candidates for controlling seizures (Table VI) (90–100).

Functionalized amino acids (derivatives of amino acids) as anticonvulsants

Kohn and his team (101) revealed a novel class of anticonvulsants which were analogues of amino acids, called functionalized amino acids. Functionalization of the amino and carboxyl terminal of amino acids with different substituents exhibits anticonvulsant activity (102–105).

Heterocyclic amino acid derivatives are based on a proline-like structure having a nitrogen-containing ring in which the nitrogen atom of heterocyclic moiety will serve as amino function and carboxylic group will be attached to the ring. Fig. 4 shows some heterocyclic amino acid derivatives that are used as an add-on therapy for the treatment of epilepsy.

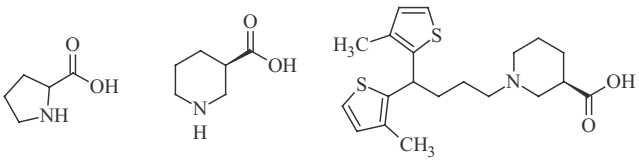
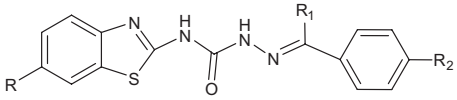
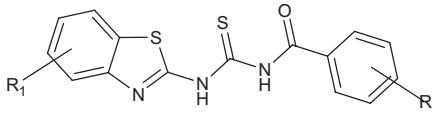
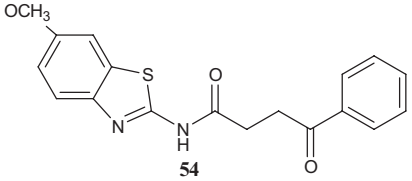
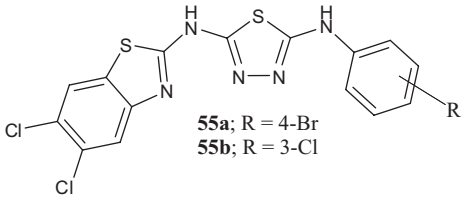
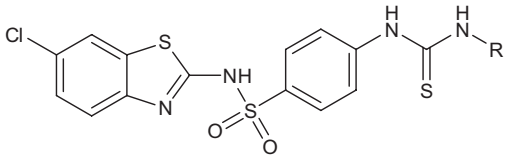
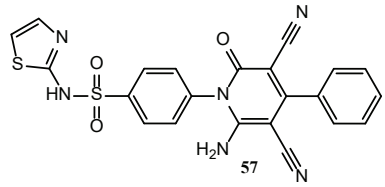
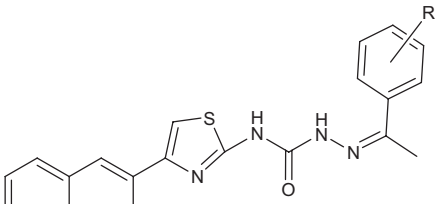
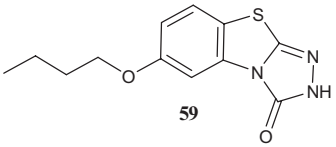
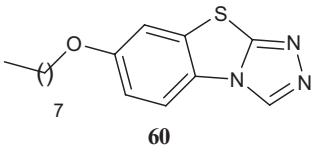
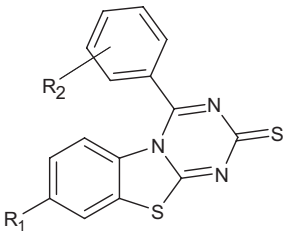
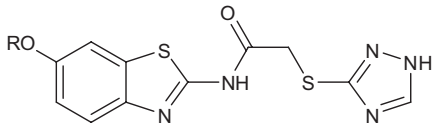


Fig. 4. Amino acid derivatives used as anticonvulsant agents.

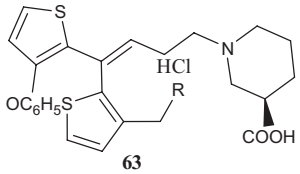
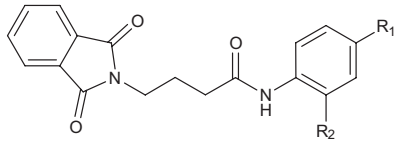
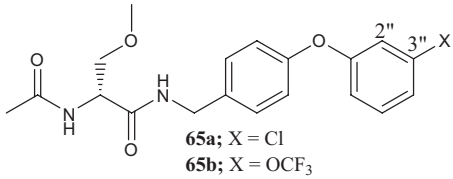
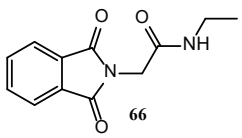
VI. Newly developed benzothiazoles as anticonvulsants

Compound	Summary/conclusion	Reference
 **52a;** R = CH_3, R_1 = CH_3, R_3 = NO_3 **52b;** R = OCH_3, R_1 = CH_3, R_3 = NO_3 **52c;** R = CH_3, R_1 = C_6H_5, R_3 = H	Compounds **52a**-**c** displayed 100 % activity in the MES test at both time intervals, 0.5 and 4 h, without any significant neurotoxicity.	Siddiqui *et al.* (90)
 **53a;** R = H, R_1 = 6-F **53b;** R = 2-Cl, R_1 = 6-CH_3 **53c;** R = 4-OCH_3, R_1 = 6-Br	Compounds **53a**-**c** showed significant activity in MES and *sc*PTZ tests with no sign of neurotoxicity.	Rana *et al.* (91)
 **54**	Compound **54** was highly active, with ED_{50} 40.96 mg kg^{-1} in case of the MES test, 85.16 mg kg^{-1} in case of the *sc*-PTZ test and TD_{50} of 347.6 mg kg^{-1}.	Hassan *et al.* (92)
 **55a**; R = 4-Br **55b**; R = 3-Cl	Derivatives **55a**,**b** displayed complete protection in the MES seizure test.	Siddiqui *et al.* (93)
 **56a**; R = CH_3 **56b**; R = C_6H_5	Both analogues **56a**,**b** showed significant activity in MES and *sc*PTZ tests after 0.5 h of administration, with less or equivalent toxicity compared to carbamazepine.	Siddiqui *et al.* (94)
 **57**	Highly active molecule **57** showing 100 % protection in the MES test.	Farag *et al.* (95)

 **58a**; R = 3,4-diCl **58b**; R = 2-OCH_3 **58c**; R = 4-Br	Compounds **58a**-**c** exhibited significant anticonvulsant activity in the MES test at the dose of 30 mg kg^{-1} comparable to the standard drug phenytoin.	Siddiqui *et al.* (96)
 **59**	Compound **59** was found to be the most active in the MES seizure test with ED_{50} value of 13.6 mg kg^{-1}.	Liu *et al.* (97)
 **60**	Compound **60** was highly active with ED_{50} of 8.0 mg kg^{-1} and PI = 15.0 in the MES test.	Deng *et al.* (98)
 **61a;** R_1 = Cl, R_2 = H **61b;** R_1 = NO_2, R_2 = H **61c;** R_1 = NO_2, R_2 = 4-Cl **61d;** R_1 = Cl, R_2 = 4-Cl	Compounds **61a**-**d** displayed significant protection in the MES test after 0.5 and 4 h.	Siddiqui *et al.* (99)
 **62a;** R = $CH_2C_6H_4$(*m*-F) **62b;** R = $CH_2C_6H_4$(*p*-F)	The two analogues **62a**,**b** were the most potent, having ED_{50} value of 50.8 and 54.8 mg kg^{-1} in the MES test and 76.0 and 52.8 mg kg^{-1} in the *sc*PTZ seizure test, resp.	Liu *et al.* (100)

ED_{50} – median effective dose, MES – maximal electroshock seizure, PI – protective index, *sc*PTZ – subcutaneous pentylenetetrazole, TD_{50} – median toxic dose

Table VII. Recently developed functionalized amino acids as anticonvulsants

Compound	Summary/conclusion	Reference
 **63**	Compound **63** showed highly inhibitory effect of GAT1 comparable to tiagabine.	Zheng *et al.* (107)
 **64a;** R_1 = H, R_2 = H **64b;** R_1 = Br, R_2 = H **64c;** R_1 = C_2H_5, R_2 = H **64d;** R_1 = Cl, R_2 = CH_3	Compound **64a** demonstrated weak seizure protection in the MES seizure screening (300 mg kg^{-1}). Analogues **64b–d** displayed significant protection in *sc*PTZ seizures tests.	Yadav *et al.* (108)
 **65a;** X = Cl **65b;** X = OCF_3	The two analogues (**65a**,**b**) displayed a high protective index in comparison with many antiseizure drugs when tested against MES in mice (intraperitoneally) and rats (intraperitoneally and orally).	Torregrosa *et al.* (109)
 **66**	The ED_{50} of compound **66** in the MES test, upon *i.p.* administration to mice, was 19.1 mg kg^{-1}.	Usifoh *et al.* (110)

ED_{50} – median effective dose, GAT1 – GABA transpoter-1, *i.p.* – intraperitoneally, MES – maximal electroshock seizure, MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole

Tiagabine, a heterocyclic amino acid analogue with nipecotic acid function, is used as a prescription medicine for the treatment of partial seizures (106). A fair number of newly synthesized amino acid derivatives as potential anticonvulsant agents are summarized in Table VII.

CONCLUSIONS

The present review provides an insight into new chemical entities that have shown promising antiepileptic activity and updates the knowledge of currently available AEDs.

Many of the agents shown in this review have been screened by the antiepileptic drug development program. Their antiseizure activity has been assessed through *in vivo* screen-

ings, although the exact mode of action of many agents is still unidentified. Some of the newer anticonvulsant analogues are prepared *via* structural changes of pre-existing drugs, whereas others have been developed with the specific objective of altering targets. Such new synthetic agents generally come from different chemical groups. Some of them represent compounds containing five- or six-membered or other heterocyclic rings in their structure. However, a significant number of literature reports suggest that analogues of amino acids can act as valuable antiseizure agents. Discovery of a large number of active leads may also help in finding alternative drug candidates in the event of drug tolerance. Compounds mentioned in this review can be used in the future as potential drug candidates with more efficacy and lesser toxicity.

Abbreviations, acronyms, symbols. – AEDs – antiepileptic drugs; AMPA – α-amino-3-hydroxy-5--methyl-4-isoxazolepropionic acid; CA – carbonic anhydrase; CHRNA2 – cholinergic receptor nicotinic alpha 2 subunit; CHRNA4 – cholinergic receptor nicotinic alpha 4 subunit; CHRNB2 – cholinergic receptor nicotinic beta 2 subunit; CNS – central nervous system; DBS – deep brain stimulation; ED_{50} – median effective dose; GABA – γ-aminobutyric acid; *i.p.* – intraperitoneal; NMDA – *N*-methyl--*D*-aspartate; GABRG2 – gamma-aminobutyric acid type A receptor gamma 2 subunit; GAT1 – GABA transpoter-1; GEFS+ – generalized epilepsy with febrile seizures plus; MBD2 – methyl cytosine--phosphate-guanine binding domain 2; MES – maximal electroshock seizure; PI – protective index; SCN1A – sodium voltage-gated channel alpha 1 subunit; SCN2A – sodium voltage-gated channel alpha 2 subunit; SCN3A – sodium voltage-gated channel alpha 3 subunit; SCN1B – sodium voltage-gated channel beta 1 subunit; SCN2B – sodium voltage-gated channel beta 2 subunit; *sc*PTZ – subcutaneous pentylenetetrazole; SSA – succinate semi-aldehyde; SV2 – synaptic vesicle protein 2; TD_{50} – median toxic dose

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