Acta Pharm. **69** (2019) 321–344 Review
https://doi.org/10.2478/acph-2019-0023

An overview of structurally diversified anticonvulsant agents

FAISAL AL-OTAIBI

Department of Clinical Pharmacy
College of Pharmacy, Shaqra
University, Al-dawadmi
P. O. BOX 33, Saudi Arabia

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

Accepted December 15, 2018
Published online January 7, 2019

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

* Correspondence, e-mail: f.alotaibi@hotmail.com

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.

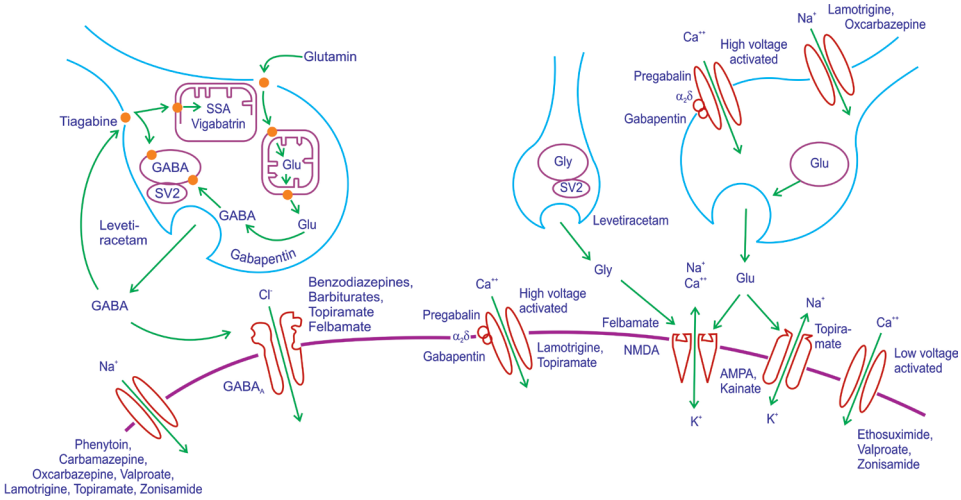


Fig. 1. Mechanism of action of antiepileptic drugs ($\alpha_2\delta$ – auxiliary subunit of voltage dependent Ca^{2+} channels, AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, GABA – γ-aminobutyric acid, Gly – glycine, Glu – glutamate, NMDA – *N*-methyl-*D*-aspartate, SSA – succinate semialdehyde,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

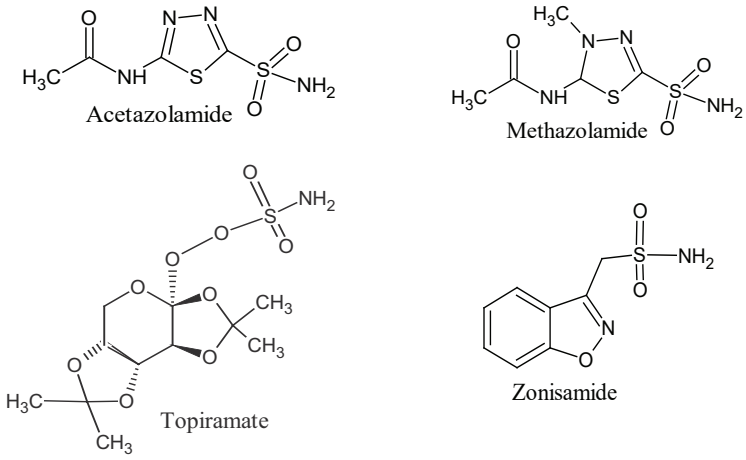


Fig. 2. Antiepileptic drugs containing a sulfonamide group.

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).

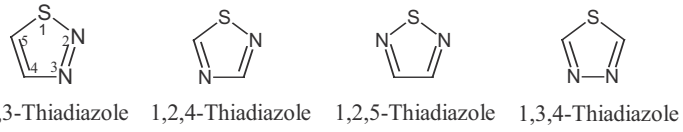


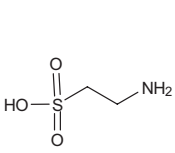
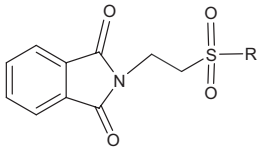
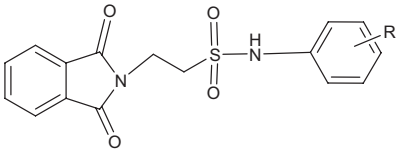
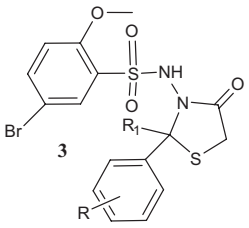
Fig. 3. Four structural isomers of thiadiazoles.

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)

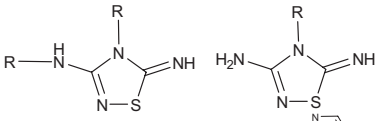
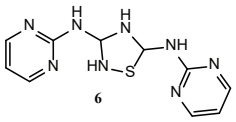
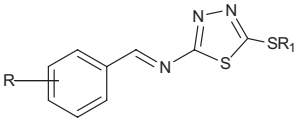
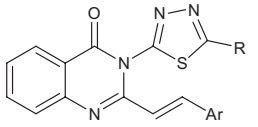
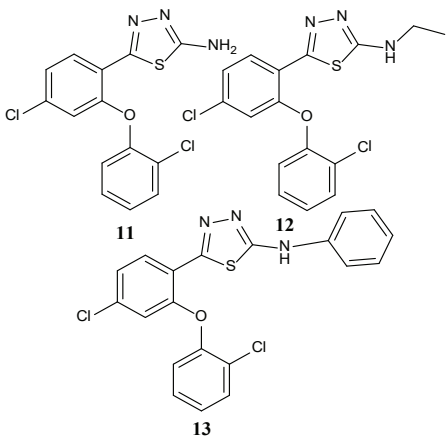
CNS – central nervous system, MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole

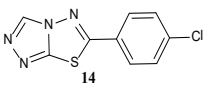
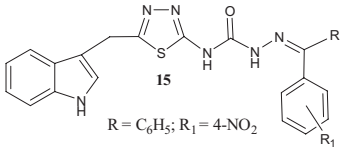
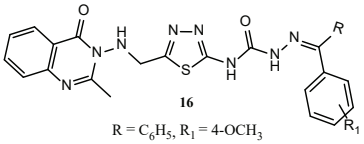
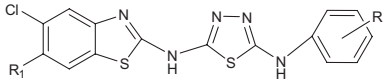
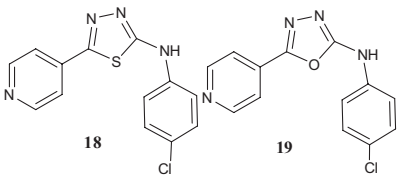
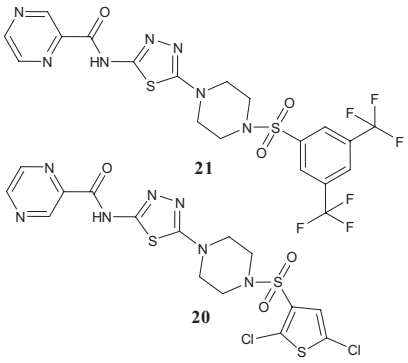
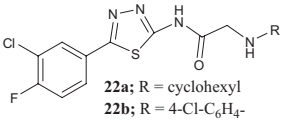
Pyrrolidine-2,5-diones as anticonvulsants

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.

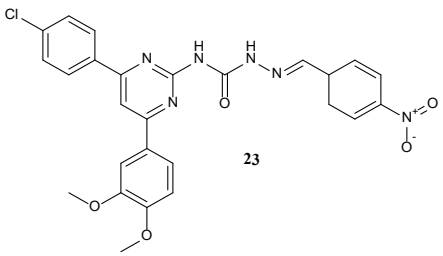
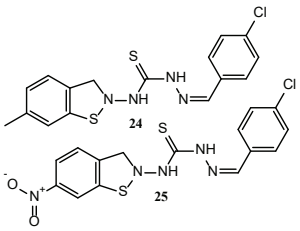
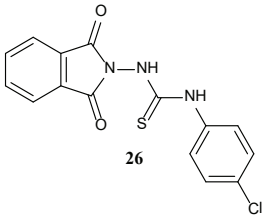
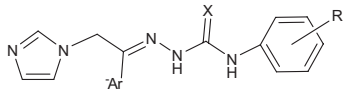
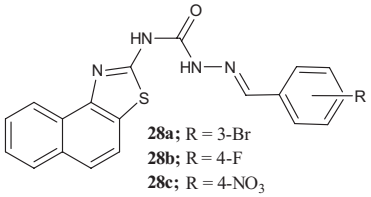
Table II. Some recently developed thiadiazole derivatives as anticonvulsant agents

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)

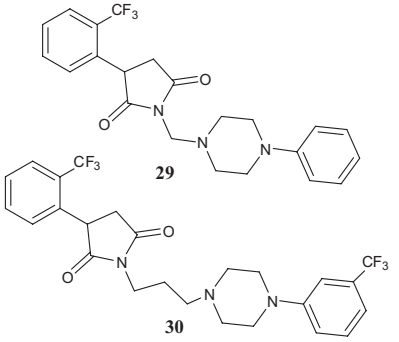
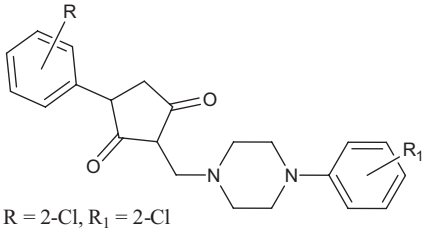
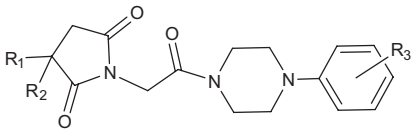
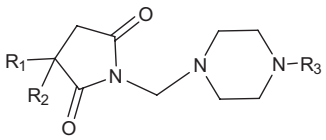
ED_{50} – median effective dose, MES – maximal electroshock seizure, PTZ – pentylenetetrazole, *sc*PTZ – subcutaneous pentylenetetrazole

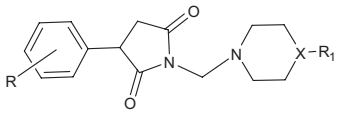
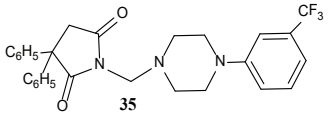
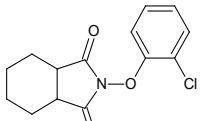
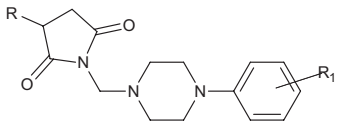
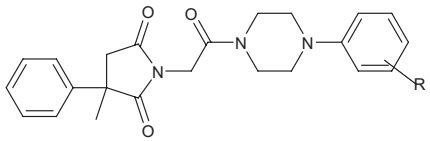
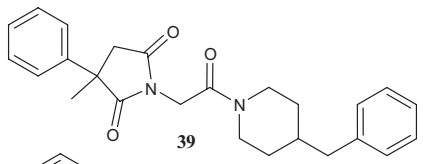
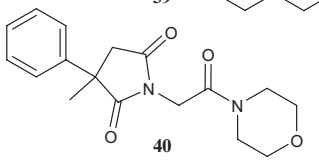
Table III. Some new semi- and thiosemi-carbazones as anticonvulsant agents

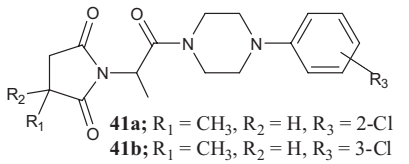
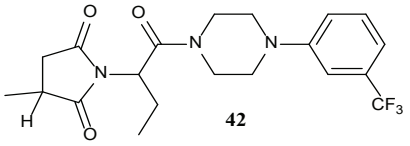
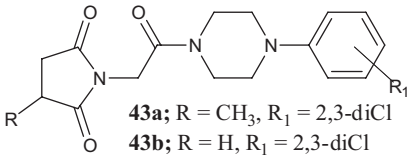
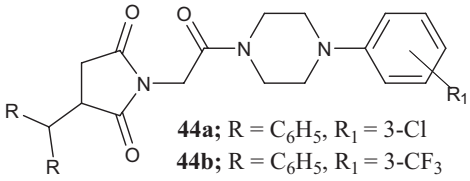
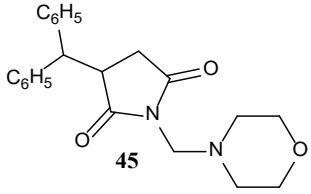
Compound	Summary/conclusion	Reference
 **23**	This compound was found highly active in the MES test without any neuromotor impairment.	Ozair *et al.* (56)
 **24** **25**	Analogues **24** and **25** showed promising outcomes against the MES seizure model with lesser or no neuromotor impairment.	Yogeeswari *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)

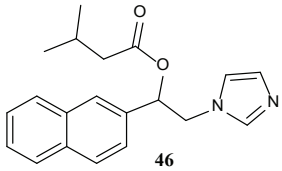
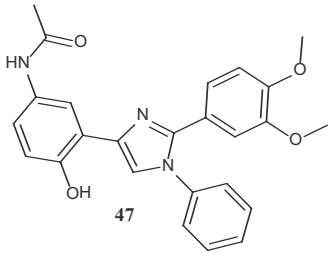
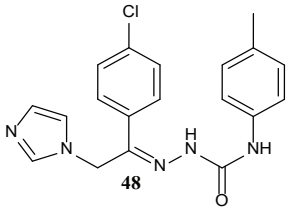
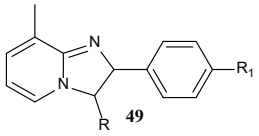
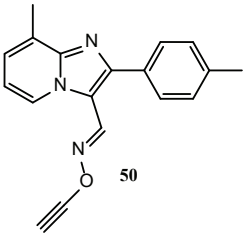
 **41a;** R_1 = CH_3, R_2 = H, R_3 = 2-Cl **41b;** R_1 = CH_3, R_2 = H, R_3 = 3-Cl **41c;** R_1 = CH_3, R_2 = H, R_3 = 3-CF_3  **42**	Broad spectra of activities across the preclinical seizure models were displayed by compounds **41b**, **41c** and **42**. Besides anticonvulsant properties, compound **41a** 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)

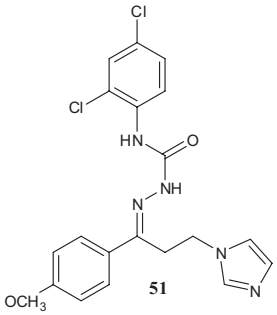
ED_{50} – median effective dose, *i.p.* – intraperitoneally, MES – maximal electroshock seizure, *sc*PTZ – subcutaneous pentylenetetrazole

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.

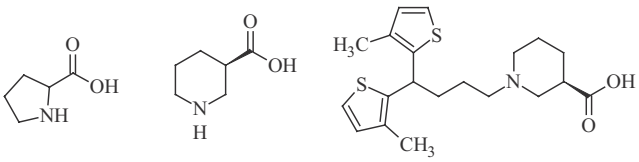
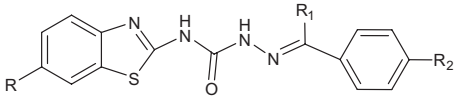
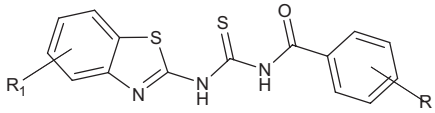
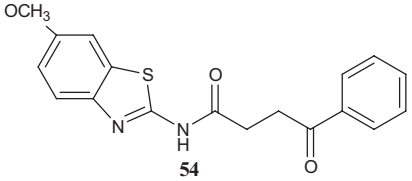
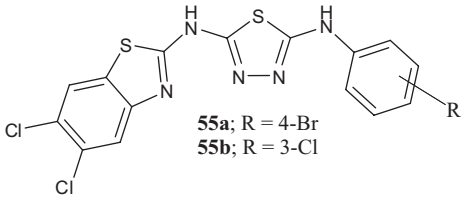
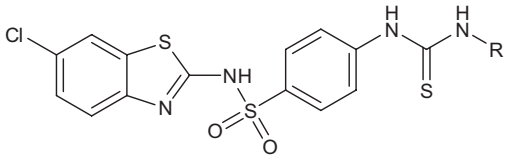
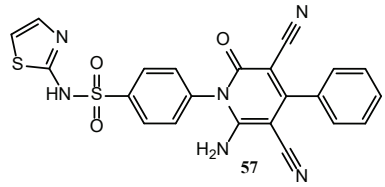
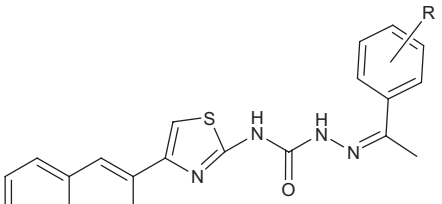
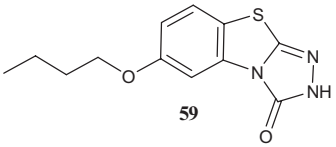
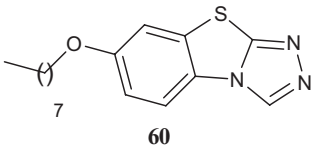
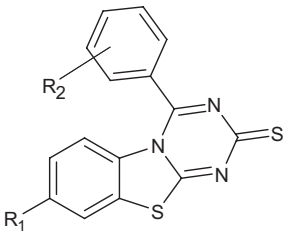
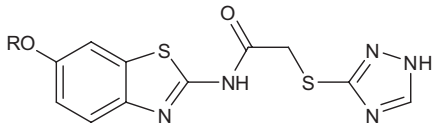


Fig. 4. Amino acid derivatives used as anticonvulsant agents.

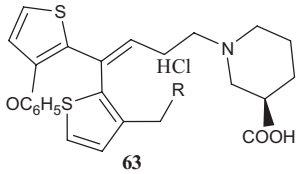
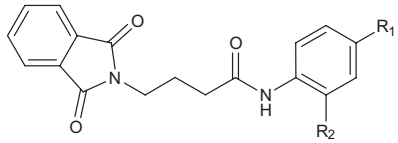
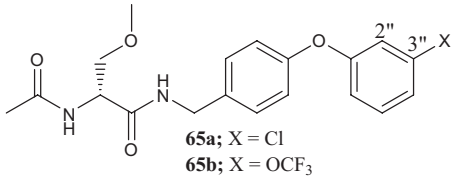
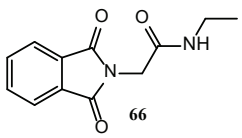
VI. Newly developed benzothiazoles as anticonvulsants

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

REFERENCES

1. R. Fisher, W. Boas, W. Blume, C. Elger, P. Genton, P. Lee and J. Engel, Epileptic seizures and epilepsy: definitions proposed by the international league against epilepsy (ILAE) and the international bureau for epilepsy (IBE), *Epilepsia* **46** (2005) 470–472; https://doi.org/10.1111/j.0013-9580.2005.66104.x
2. P. A. Dekker, *Epilepsy: A Manual for Medical and Clinical Officers in Africa*, WHO, Geneva 2002, pp. 133.
3. M. J. Brodie, A. T. Elder and P. Kwan, Epilepsy in later life, *Lancet Neurol*. **8** (2009) 1019–1030; https://doi.org/10.1016/S1474-4422(09)70240-6
4. E. Proulx, Y. Leshchenko, L. Kokarovtseva, V. Khokhotva, M. El-Beheiry, O. C. Snead and J. L. P. Velazquez, Functional contribution of specific brain areas to absence seizures: role of thalamic gap-junctional coupling, *Eur. J. Neurosci.* **23** (2006) 489–496; https://doi.org/10.1111/j.1460-9568.2005.04558.x
5. S. F. Berkovic, R. A. Howell, D. A. Hay and J. L. Hopper, Epilepsies in twins: Genetics of the major epilepsy syndromes, *Ann. Neurol.* **43** (1998) 435–445; https://doi.org/10.1002/ana.410430405
6. L. A. Corey, J. M. Pellock, M. J. Kjeldsen and K. O. Nakken, Importance of genetic factors in the occurrence of epilepsy syndrome type: A twin study, *Epilepsy Res.* **97** (2011) 103–111; https://doi.org/10.1016/j.eplepsyres.2011.07.018
7. M. J. Kjeldsen, L. A. Corey, M. H. Solaas, M. L. Friis, J. R. Harris, K. O. Kyvik, K. Christensen and J. M. Pellock, Genetic factors in seizures: A population-based study of 47,626 US, Norwegian and Danish twin pairs, *Twin Res. Hum. Genet.* **8** (2005) 138–147; https://doi.org/10.1375/1832427053738836
8. M. Li, X. Heng, R. Tao, J. Liu, L. Zhang, X. Sun, L. Wang, Q. Wu, F. Che and F. Xue, A genetic epidemiological survey of idiopathic epilepsy in the Chinese Han population, *Epilepsy Res.* **98** (2012) 199–205; https://doi.org/10.1016/j.eplepsyres.2011.09.013

9. R. R. Nair and S. V. Thomas, Genetic liability to epilepsy in Kerala State India, *Epilepsy Res.* **62** (2004) 163–170; https://doi.org/10.1016/j.eplepsyres.2004.08.007
10. R. Ottman, *Genetic influences on risk for epilepsy*, in *Pediatric Epilepsy: Diagnosis and Therapy*, Demos Medical Publishing, New York 2007.
11. H. J. Li, R. P. Wan, L. J. Tang, S. J. Liu, Q. H. Zhao, M. M. Gao, Y. H. Yi, W. P. Liao, X. F. Sun and Y. S. Long, Alteration of Scn3a expression is mediated *via* CpG methylation and MBD2 in mouse hippocampus during postnatal development and seizure condition, *Biochim. Biophys. Acta* **1849** (2015) 1–9; https://doi.org/10.1016/j.bbagrm.2014.11.004
12. K. Nagai, T. Natori, T. Nishino and F. Kodaira, Epigenetic dysregulation induces cell growth retardation in primary cultured glial cells, *J. Biosci. Bioeng.* **105** (2008) 470–475; https://doi.org/10.1263/jbb.105.470
13. E. Hessen, M. I. Lossius, I. Reinvang and L. Gjerstad, Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy, *Epilepsia* **47** (2006) 2038–2045; https://doi.org/10.1111/j.1528-1167.2006.00805.x
14. V. C. Terra, R. Amorim, C. Silvado, A. J. de Oliveira, C. L. Jorge, E. Faveret, P. Ragazzo and L. De Paola, Vagus nerve stimulator in patients with epilepsy: indications and recommendations for use, *Arq. Neuro-Psiquiatr.* **71** (2013) 902–906; https://doi.org/10.1590/0004-282X20130116
15. P. Lisowska and B. Daly, Vagus nerve stimulation therapy (VNST) in epilepsy - implications for dental practice, *Br. Dent. J.* **212** (2012) 69–72; https://doi.org/10.1038/sj.bdj.2012.47
16. B. M. Uthman, Vagus nerve stimulation for seizures, *Arch. Med. Res.* **31** (2000) 300–303; https://doi.org/10.1016/S0188-4409(00)00060-6
17. I. S. Cooper and A. R. M. Upton, Use of chronic cerebellar stimulation for disorders of disinhibition, *Lancet* **311** (1978) 595–600; https://doi.org/https://doi.org/10.1016/S0140-6736(78)91038-3
18. I. S. Cooper, A. R. M. Upton and I. Amin, Reversibility of chronic neurologic deficits: Some effects of electrical stimulation of the thalamus and internal capsule in man, *Appl. Neurophysiol.* **43** (1980) 224–258; https://doi.org/10.1159/000102263
19. K. W. Baranano and A. L. Hartman, The ketogenic diet: Uses in epilepsy and other neurologic illnesses, *Curr. Treat. Options Neurol.* **10** (2008) 410–419.
20. A. L. Rogovik and R. D. Goldman, Ketogenic diet for treatment of epilepsy, *Can. Fam. Physician* **56** (2010) 540–542.
21. M. Greener, Food for thought: the ketogenic diet for epilepsy, *Prog. Neurol. Psychiatry* **18** (2014) 6–9; https://doi.org/10.1002/pnp.329
22. M. Ne, L. Ngo, J. I. Sirven and M. R. Sperling, Ketogenic diet in adolescents and adults with epilepsy, *Seizure* **23** (2014) 439–442; https://doi.org/10.1016/j.seizure.2014.02.015
23. R. Hanaya and K. Arita, The new antiepileptic drugs: their neuropharmacology and clinical indications, *Neurol. Med. Chir.* (Tokyo) **56** (2016) 205–220; https://doi.org/10.2176/nmc.ra.2015-0344
24. J. A. French and D. M. Gazzola, New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety? *Ther. Adv. Drug Saf.* **2** (2011) 141–158; https://doi.org/10.1177/2042098611411127
25. G. Gatti, I. Bonomi, G. Jannuzzi and E. Perucca, The new antiepileptic drugs: Pharmacological and clinical aspects, *Curr. Pharm. Design* **6** (2000) 839–860; https://doi.org/10.2174/1381612003400245
26. A. Nicolson and J. P. Leach, Future prospects for the drug treatment of epilepsy, *CNS Drugs* **15** (2001) 955–968; https://doi.org/10.2165/00023210-200115120-00005
27. C. T. Supuran, F. Mincione, A. Scozzafava, F. Briganti, G. Mincione and M. A. Ilies, Carbonic anhydrase inhibitors – Part 52. Metal complexes of heterocyclic sulfonamides: A new class of strong topical

intraocular pressure-lowering agents in rabbits, *Eur. J. Med. Chem.* **33** (1998) 247–254; https://doi.org/10.1016/S0223-5234(98)80059-7

28. M. Ilies, C. T. Supuran, A. Scozzafava, A. Casini, F. Mincione, L. Menabuoni, M. T. Caproiu, M. Maganu and M. D. Banciu, Carbonic anhydrase inhibitors. Sulfonamides incorporating furan-, thiophene- and pyrrole-carboxamido groups possess strong topical intraocular pressure lowering properties as aqueous suspensions, *Bioorg. Med. Chem.* **8** (2000) 2145–2155; https://doi.org/10.1016/S0968-0896(00)00143-7
29. A. Scozzafava, L. Menabuoni, F. Mincone, F. Briganti, G. Mincione and C. T. Supuran, Carbonic anhydrase inhibitors. Perfluoroalkyl/aryl-substituted derivatives of aromatic/heterocyclic sulfonamides as topical intraocular pressure lowering agents with prolonged duration of action, *J. Med. Chem.* **43** (2000) 4542–4551; https://doi.org/10.1021/jm000296j
30. A. Casini, A. Scozzafava, F. Mincione, L. Menabuoni, M. A. Ilies and C. T. Supuran, Carbonic anhydrase inhibitors: Water soluble 4-sulfamoylphenyl-thioureas as topical intraocular pressure-lowering agents with long-lasting effects, *J. Med. Chem.* **43** (2000) 4884–4892; https://doi.org/10.1021/jm001051+
31. B. Masereel, S. Rolin, F. Abbate, A. Scozzafava and C. T. Supuran, Carbonic anhydrase inhibitors: Anticonvulsant sulfonamides incorporating valproyl and other lipophilic moieties, *J. Med. Chem.* **45** (2002) 312–320; https://doi.org/10.1021/jm0109199
32. M. A. Ilies, B. Masereel, S. Rolin, A. Scozzafava, G. Câmpeanu, V. Cîmpeanu and C. T. Supuran, Carbonic anhydrase inhibitors: aromatic and heterocyclic sulfonamides incorporating adamantyl moieties with strong anticonvulsant activity, *Bioorg. Med. Chem.* **12** (2004) 2717–2726; https://doi.org/10.1016/j.bmc.2004.03.008
33. I. B. Linden, G. Gothoni, P. Kontro and S. S. Oja, Anticonvulsant activity of 2-phthalimidoethane sulphonamides: New derivatives of taurine, *Neurochem. Int.* **5** (1983) 319–324; https://doi.org/10.1016/j.bmc.2004.03.008
34. O. Akgul, F. S. Kilic, K. Erol and V. Pabuccuoglu, Synthesis and anticonvulsant activity of some *N*-phenyl-2-phtalimidoethanesulfonamide derivatives, *Arch. Pharm.* (Weinheim) **340** (2007) 656–660; https://doi.org/10.1002/ardp.200700166
35. N. Siddiqui, M. F. Arshad, S. A. Khan and W. Ahsan, Sulfonamide derivatives of thiazolidin-4-ones with anticonvulsant activity against two seizure models: synthesis and pharmacological evaluation, *J. Enzyme Inhib. Med. Chem.* **25** (2010) 485–491; https://doi.org/10.3109/14756360903282833
36. Y. Hu, C. Y. Li, X. M. Wang. Y. H. Yang and H. L. Zhu, 1,3,4-Thiadiazole: Synthesis, reactions, and applications in medicinal, agricultural, and materials chemistry, *Chem. Rev.* **114** (2014) 5572–5610; https://doi.org/10.1021/cr400131u
37. A. K. Jain, S. Sharma, A. Vaidya, V. Ramachandran and R. K. Agrawal, 1,3,4-Thiadiazole and its derivatives: a review on recent progress in biological activities, *Chem. Biol. Drug Des.* **81** (2013) 557–576; https://doi.org/10.1111/cbdd.12125
38. W. Dehaen, V. A. Bakulev, E. C. Taylor and J. A. Ellman, *The Chemistry of 1,2,3-thiadiazoles*, in *The Chemistry of Heterocyclic Compounds* (Ed. E. C. Taylor), 1st ed., John Wiley & Sons, New York 2004, pp. 5–240.
39. A. Gupta, P. Mishra, S. Kashaw, V. Jatav and J. P. Stables, Synthesis and anticonvulsant activity of some novel 3-arylamino/amino-4-aryl-5-imino-Δ2-1,2,4-thiadiazoline, *Eur. J. Med. Chem.* **43** (2008) 749–754; https://doi.org/10.1016/j.ejmech.2007.05.008
40. A. Gupta, P. Mishra, S. N. Pandeya, S. K. Kashaw, V. Kashaw and J. P. Stables, Synthesis and anticonvulsant activity of some substituted 1,2,4-thiadiazoles, *Eur. J. Med. Chem.* **44** (2009) 1100–1105; https://doi.org/10.1016/j.ejmech.2008.06.015
41. B. Ahamad and M. Yusuf, Synthesis of aromatic aldehyde imine derivative of 2-thiobenzyl-1,3,4-thiadiazole and evaluation of their anticonvulsant activity, *Indian J. Chem.* B **49** (2010) 241–246.

42. V. Jatav, P. Mishra, S. Kashaw and J. P. Stables, CNS depressant and anticonvulsant activities of some novel 3-[5-substituted1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones, *Eur. J. Med. Chem.* **43** (2008) 1945–1954; https://doi.org/10.1016/j.ejmech.2007.12.003

43. A. Foroumadi, V. Sheibani, A. Sakhteman, M. Rameshk, M. Abbasi, R. Farazifard, S. A. Tabatabai and A. Shafiee, Synthesis and anticonvulsant activity of novel 2-amino-5-[4-chloro-2- (2- chlorophenoxy) phenyl]-1,3,4-thiadiazole derivatives, *DARU J. Pharm. Sci.* **15** (2007) 89–93.

44. X. Q. Deng, Z. Q. Dong, M. X. Song, B. Shu, S. B. Wang and Z. S. Quan, Synthesis and anticonvulsant activities of some triazolothiadiazole derivatives, *Arch. Pharm.* (Weinheim) **345** (2012) 565–573; https://doi.org/10.1002/ardp.201100326

45. H. Rajak, C. K. Behera, R. S. Pawar, P. K. Singour and M. D. Kharya, Synthesis and anticonvulsant evaluation of some novel 2,5-disubstituted 1,3,4-thiadiazoles: pharmacophore model studies, *Acta Pol. Pharm.* **67** (2010) 503–510.

46. H. Rajak, B. S. Thakur, P. Kumar, P. Parmar, P. C. Sharma, R. Veerasamy and M. D. Kharya, Synthesis and antiepileptic activity of some novel semicarbazones containing 1,3,4-thiadiazole and quinazoline ring, *Acta Pol. Pharm.* **69** (2012) 253–261.

47. N. Siddiqui, A. Rana, S. A. Khan, S. E. Haque, M. F. Arshad, S. Ahmed and W. Ahsan, Synthesis and preliminary screening of benzothiazol-2-yl-thiadiazole derivatives for anticonvulsant activity, *Acta Pharm.* **59** (2009) 441–451; https://doi.org/10.2478/v10007-009-0031-x

48. M. S. Yar and M. W. Akhter, Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives, *Acta Pol. Pharm.* **66** (2009) 393–397.

49. K. P. Harish, K. N. Mohana and L. Mallesha, Synthesis of pyrazine substituted 1,3,4-thiadiazole derivatives and their anticonvulsant activity, *Org. Chem. Int.* **2013** (2013) Article ID 631723 (8 pages); https://doi.org/10.1155/2013/631723

50. A. H. Al Rohaimi, Neuropharmacological and toxicity study of newly prepared *N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]- 2-substituted acetamides, *Acta Pol. Pharm.* **72** (2015) 1315–1320.

51. J. R. Dimmock, S. C. Vashistha and J. P. Stable, Anticonvulsant properties of various acetylhydrazones, oxymoylhydrazones, and semicarbazones derived from aromatic and unsaturated carbonyl compounds, *Eur. J. Med. Chem.* **35** (2000) 241–248; https://doi.org/10.1016/S0223-5234(00)00123-9

52. J. R. Dimmock, S. C. Vashistha and J. P. Stable, Ureylene anticonvulsants and related compounds, *Pharmazie* **55** (2000) 490–494.

53. S. N. Pandeya, H. Manjula and J. P. Stables, Design of semicarbazones and their bio-isosteric analogues as potential anticonvulsants, *Pharmazie* **56** (2001) 121–124.

54. S. N. Pandeya, I. Ponnilavarasan, A. Pandey, R. Lakhan and J. P. Stables, Evaluation of p-nitrophenyl substituted semicarbazones for anticonvulsant properties, *Pharmazie* **54** (1999) 923–925.

55. J. R. Dimmock, R. N. Puthucode, J. Tuchek, J. B. Baker, C. N. Hinko, C. L. Steinmiller and J. P. Stable, Anticonvulsant activity of 4-(4′-fluorophenoxy)benzaldehyde semicabazone, *Drug. Dev. Res.* **46** (1999) 112–125; https://doi.org/10.1002/(SICI)1098-2299(199902)46:2<112::AID-DDR4>3.0.CO;2-N

56. O. Alam, P. Mallick, S. P. Verma, S. J. Gilani, S. A. Khan, N. Siddiqui and W. Ahsan, Synthesis, anticonvulsant and toxicity screening of newer pyrimidine semicarbazone derivatives, *Eur. J. Med. Chem.* **45** (2010) 2467–2472; https://doi.org/10.1016/j.ejmech.2010.02.031

57. P. Yogeeswari, D. Sriram, S. Mehta, D. Nigam, M. M. Kumar, S. Murugesan and J. P. Stables, Anticonvulsant and neurotoxicity evaluation of some 6-substituted benzothiazolyl-2-thiosemicarbazones, *I. L. Farmaco* **60** (2005) 1–5; https://doi.org/10.1016/j.farmac.2004.09.001

58. P. Yogeeswari, D. Sriram, V. Saraswat, J. V. Ragavendran, M. M. Kumar, S. Murugesan, R. Thirumurugan and J. P. Stables, Synthesis and anticonvulsant and neurotoxicity evaluation of N4-phthalimido phenyl (thio) semicarbazides, *Eur. J. Pharm. Sci.* **20** (2003) 341–346; https://doi.org/10.1016/j.ejps.2003.08.002

59. U. Çalış, E. Septioğlu and M. D. Aytemir, Synthesis and anticonvulsant evaluation of some novel (thio) semicarbazone derivatives of arylalkylimidazole, *Arzneimittelforschung* **61** (2011) 327–334; https://doi.org/10.1055/s-0031-1296206

60. F. Azam, I. A. Alkskas, S. L. Khokra and O. Prakash, Synthesis of some novel N4-(naphtha[1,2-d]thiazol-2-yl)semicarbazone as potential anticonvulsants, *Eur. J. Med. Chem.* **44** (2009) 203–209; https://doi.org/10.1016/j.ejmech.2008.02.007

61. E. D. Ilieva, N. I. Petkova and R. D. Nikolova, A new and efficient method for the synthesis of 3,4-disubstituted pyrrolidine-2,5-diones, *Molecules* **17** (2012) 4936–4949; https://doi.org/10.3390/molecules17054936

62. J. Obniska and K. Kamiński, Synthesis and anticonvulsant properties of new *N*-phenylamino derivatives of 2-azaspiro[4.4]nonane, 2-azaspiro[4.5]decane-1,3-dione and 3 cyclohexyl-pyrrolidine-2,5-dione. Part IV, *Acta Pol. Pharm.* **63** (2006) 101–108.

63. J. Obniska and K. Kamiński, Lipophilicity characterization of new N-phenylamino-azaspiranes as potential anticonvulsant agents, *Biomed. Chromatogr.* **20** (2006) 1185–1191; https://doi.org/10.1002/bmc.682

64. J. Obniska, R. Lesyk, D. Atamanyuk and K. Kamiński, Synthesis and anticonvulsant activity of a series of N-substituted bicyclo[2,2,1]hept-5-ene-2,3-dicarboximides, *Acta Pol. Pharm.* **62** (2005) 213–219.

65. J. Obniska, S. Jurczyk, A. Zejc, K. Kamiński, E. Tatarczynska and K. Stachowicz, Anticonvulsant properties of *N*-(4-methylpiperazin-1-yl)- and *N*-[3-(4-methyl-piperazin-1-yl)propyl] derivatives of 3-aryl and 3-spirocycloalkyl-pyrrolidine-2,5-dione, *Pharmacol. Rep.* **57** (2005) 170–175.

66. K. Kamiński and J. Obniska, Design, synthesis, and anticonvulsant activity of N-phenylamino derivatives of 3,3-dialkyl-pyrrolidine-2,5-diones and hexahydro-isoindole-1,3-diones, *Bioorg. Med. Chem.* **16** (2008) 4921–4931; https://doi.org/10.1016/j.bmc.2008.03.037

67. J. Obniska, K. Kamiński, D. Skrzynska and J. Pichor, Synthesis and anticonvulsant activity of new N-[(4-arylpiperazin-1-yl)- alkyl] derivatives of 3-phenyl-pyrrolidine-2,5-dione, *Eur. J. Med. Chem.* **44** (2009) 2224–2233; https://doi.org/10.1016/j.ejmech.2008.05.020

68. J. Obniska, M. Kopytko, A. Zagórska, I. Chlebek and K. Kamiński, Synthesis and anticonvulsant properties of new Mannich bases derived from 3-aryl-pyrrolidine-2,5-diones. Part 1, *Arch. Pharm.* (Weinheim) **343** (2010) 333–341; https://doi.org/10.1002/ardp.200900250

69. K. Kamiński, S. Rzepka and J. Obniska, Synthesis and anticonvulsant activity of new 1-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]pyrrolidine-2,5-diones, *Bioorg. Med. Chem. Lett.* **21** (2011) 5800–803; https://doi.org/10.1016/j.bmcl.2011.07.118

70. J. Obniska, I. Chlebek and K. Kamiński, Synthesis and anticonvulsant properties of new Mannich bases derived from 3,3-disubstituted pyrrolidine-2,5-diones, Part IV, *Arch. Pharm.* (Weinheim) **345** (2012) 713–722; https://doi.org/10.1002/ardp.201200092

71. K. Kamiński, J. Obniska, I. Chlebek, B. Wiklik and S. Rzepka, Design, synthesis and anticonvulsant properties of new N-Mannich bases derived from 3-phenylpyrrolidine-2,5-diones, *Bioorg. Med. Chem. Lett.* **21** (2013) 6821–6830; https://doi.org/10.1016/j.bmc.2013.07.029

72. J. Obniska, I. Chlebek, K. Kamiński and J. Karolak-Wojciechowska, Synthesis and anticonvulsant properties of new N-Mannich bases derived from 3, 3-diphenyl- and 3-ethyl-3-methyl-pyrrolidine-2,5-diones, Part III, *Arch. Pharm.* (Weinheim) **346** (2013) 71–82; https://doi.org/10.1002/ardp.201200265

73. K. Kamiński, B. Wiklik and J. Obniska, Synthesis, anticonvulsant properties, and SAR analysis of differently substituted pyrrolidine-2,5-diones and piperidine-2,6-diones, *Arch. Pharm.* (Weinheim) **347** (2014) 840–852; https://doi.org/10.1002/ardp.201400179

74. S. Rybka, J. Obniska, A. Rapacz, B. Filipek and K. Kamiński, Synthesis, physicochemical, and anticonvulsant properties of new N-Mannich bases derived from pyrrolidine-2,5-dione and its 3-methyl analog, *Arch. Pharm.* (Weinheim) **347** (2014) 768–776; https://doi.org/10.1002/ardp.201400152

75. J. Obniska, A. Rapacz, S. Rybka, B. Powroznik, E. Pekala, B. Filipek, P. Zmudzki and K. Kamiński, Design, synthesis and biological activity of new amides derived from 3-methyl-3-phenyl-2, 5-dioxo-pyrrolidin-1-yl-acetic acid, *Eur. J. Med. Chem.* **102** (2015) 14–25; https://doi.org/10.1016/j.ejmech.2015.07.017

76. K. Kamiński, M. Zagaja, A. Rapacz, J. J. Tuszczki, M. Andres-Mach, M. Abram and J. Obniska, New hybrid molecules with anticonvulsant and antinociceptive activity derived from 3-methyl- or 3,3-dimethyl-1-[1-oxo-1-(4-phenylpiperazin-1-yl) propan-2-yl]pyrrolidine-2,5-diones, *Bioorg. Med. Chem.* **24** (2016) 606–618; https://doi.org/10.1016/j.bmc.2015.12.027

77. A. Rapacz, S. Rybka, J. Obniska, K. Sałat, B. Powroźnik, E. Pękala and B. Filipek, Evaluation of anticonvulsant and antinociceptive properties of new N-Mannich bases derived from pyrrolidine-2,5-dione and 3-methylpyrrolidine-2,5-dione, *Naunyn-Schmiedeberg Arch. Pharmacol.* **389** (2016) 339–348; https://doi.org/10.1007/s00210-015-1194-2

78. S. Rybka, J. Obniska, A. Rapacz, B. Filipek and P. Zmudzki, Synthesis and anticonvulsant activity of new N-Mannich bases derived from benzhydryl- and isopropyl-pyrrolidine-2,5-dione, *J. Enzyme Inhib. Med. Chem.* **31** (2016) 1038–1047; https://doi.org/10.3109/14756366.2015.1088842

79. S. Rybka, J. Obniska, A. Rapacz, B. Filipek and P. Zmudzki, Synthesis and evaluation of anticonvulsant properties of new N-Mannich bases derived from pyrrolidine-2,5-dione and its 3- methyl-, 3-isopropyl, and 3-benzhydryl analogs, *Bioorg. Med. Chem. Lett.* **27** (2017) 1412–1415; https://doi.org/10.1016/j.bmcl.2017.02.002

80. F. Schiaffella, A. Macchiarulo, L. Milanese, A. Vecchiarelli and R. Fringuelli, Novel ketoconazole analogues based on the replacement of 2,4-dichlorophenyl group with 1,4-benzothiazine moiety: Design, synthesis, and microbiological evaluation, *Bioorg. Med. Chem.* **14** (2006) 5196–5203; https://doi.org/10.1016/j.bmc.2006.04.004

81. L. Navidpour, H. Shadnia, H. Shafaroodi, M. Amini, A. R. Dehpour and A. Shafiee, Design, synthesis, and biological evaluation of substituted 2-alkylthio-1,5-diarylimidazoles as selective COX-2 inhibitors, *Bioorg. Med. Chem.* **15** (2007) 1976–1982; https://doi.org/10.1016/j.bmc.2006.12.041

82. J. C. Thenmozhiyal, P. T. Wong and W. K. Chui, Anticonvulsant activity of phenylmethyl-enehydantoins: A structure-activity relationship study, *J. Med. Chem.* **47** (2004) 1527–1535; https://doi.org/10.1021/jm030450c

83. A. Karakurt, M. Ozalp, S. Isik, J. P. Stables and S. Dalkara, Synthesis, anticonvulsant and antimicrobial activities of some new 2-acetylnaphthalene derivatives, *Bioorg. Med. Chem.* **18** (2010) 2902–2911; https://doi.org/10.1016/j.bmc.2010.03.010

84. A. Husain, N. Siddiqui, M. Sarafroz, Y. Khatoon, M. Rasid and N. Ahmad, Synthesis, anticonvulsant and neurotoxicity screening of some novel 1,2,4-trisubstituted-1H-imidazole derivatives, *Acta Pol. Pharm.* **68** (2011) 657–663.

85. M. Amir, I. Ali and M. Z. Hassan, Imidazole incorporated semicarbazone derivatives as a new class of anticonvulsants: Design, synthesis and in vivo screening, *Med. Chem.* **9** (2013) 571–580; https://doi.org/10.2174/1573406411309040011

86. S. Ulloora, R. Shabaraya, S. Aamir and A. V. Adhikari, New imidazo[1,2-a]pyridines carrying active pharmacophores: Synthesis and anticonvulsant studies, *Bioorg. Med. Chem. Lett.* **23** (2013) 1502–1506; https://doi.org/10.1016/j.bmcl.2012.12.035

87. S. Ulloora, R. Shabaraya and A. V. Adhikari, Facile synthesis of new imidazo[1,2-*a*] pyridines carrying 1,2,3-triazoles *via* click chemistry and their antiepileptic studies, *Bioorg. Med. Chem. Lett.* **23** (2013) 3368–3372; https://doi.org/10.1016/j.bmcl.2013.03.086

88. M. I. Attia, M. N. Aboul-Enein, A. A. El-Azzouny, Y. A. Maklad and H. A. Ghabbour, Anticonvulsant potential of certain new (2*E*)-2-[1-aryl-3-(1*H*-imidazol-1-yl)propylidene]-*N*-(aryl/*H*) hydrazinecarboxamides, *Sci. World J.* **2014** (2014) Article ID 357403 (9 pages); https://doi.org/10.1155/2014/357403

89. R. K. Gill, R. K. Rawal and J. Bariwal, Recent advances in the chemistry and biology of benzothiazoles, *Arch. Pharm.* (Weinheim) **348** (2015) 155–178; https://doi.org/10.1002/ardp.201400340

90. N. Siddiqui, A. Rana, S. A. Khan, M. A. Bhat and S. E. Haque, Synthesis of benzothiazole semicarbazones as novel anticonvulsants - the role of hydrophobic domain, *Bioorg. Med. Chem. Lett.* **17** (2007) 4178–4182; https://doi.org/10.1016/j.bmcl.2007.05.048

91. A. Rana, N. Siddiqui, S. A. Khan, S. E. Haque and M. A. Bhat, *N*-{[(6-substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides: Synthesis and pharmacological evaluation, *Eur. J. Med. Chem.* **43** (2008) 1114–1122; https://doi.org/10.1016/j.ejmech.2007.07.008

92. M. Z. Hassan, S. A. Khan and M. Amir, Design, synthesis and evaluation of N-(substituted benzothiazol-2-yl) amides as anticonvulsant and neuroprotective, *Eur. J. Med. Chem.* **58** (2012) 206–213; https://doi.org/10.1016/j.ejmech.2012.10.002

93. N. Siddiqui, A. Rana, S. A. Khan, S. E. Haque, M. F. Arshad, S. Ahmed and W. Ahsan, Synthesis and preliminary screening of benzothiazol-2-yl thiadiazole derivatives for anticonvulsant activity, *Acta Pharm.* **59** (2009) 441–451; https://doi.org/10.2478/v10007-009-0031-x

94. N. Siddiqui, S. N. Pandeya, S. A. Khan, J. Stables, A. Rana, M. Alam, M. F. Arshad and M. A. Bhat, Synthesis and anticonvulsant activity of sulfonamide derivatives-hydrophobic domain, *Bioorg. Med. Chem. Lett.* **17** (2007) 255–259; https://doi.org/10.1016/j.bmcl.2006.09.053

95. A. A. Farag, S. N. Abd-Alrahman, G. F. Ahmed, R. M. Ammar, Y. A. Ammar and S. Y. Abbas, Synthesis of some azoles incorporating a sulfonamide moiety as anticonvulsant agents, *Arch. Pharm.* (Weinheim) **345** (2012) 703–712; https://doi.org/10.1002/ardp.201200014

96. N. Siddiqui, M. F. Arshad and S. A. Khan, Synthesis of some new coumarin incorporated thiazolyl semicarbazones as anticonvulsants, *Acta Pol. Pharm.* **66** (2009) 161–167.

97.D. C. Liu, X. Q. Deng, S. B. Wang and Z. S. Quan, Synthesis and anticonvulsant activity evaluation of 7-alkoxy[1,2,4]triazolo[3,4-b]benzothiazol-3(2H)-ones, *Arch. Pharm*. (Weinheim) **347** (2014) 268–275; https://doi.org/10.1002/ardp.201300277

98. X. Q. Deng, M. X. Song, C. X. Wei, F. N. Li and Z. S. Quan, Synthesis and anticonvulsant activity of 7-alkoxy-triazolo-[3,4-*b*]benzo[*d*]thiazoles, *Med. Chem.* **6** (2010) 313–320; https://doi.org/10.2174/157340610793358855

99. N. Siddiqui, A. Rana, S. A. Khan, S. E. Haque, M. S. Alam, W. Ahsan and S. Ahmed, Synthesis of 8-substituted-4-(2/4-substituted phenyl)-2*H*-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole-2-thiones and their anticonvulsant, anti-nociceptive, and toxicity evaluation in mice, *J. Enzyme Inhib. Med. Chem.* **24** (2009) 1344–1350; https://doi.org/10.3109/14756360902888176

100. D. Liu, H. Zhang, C. Jin and Z. Quan, Synthesis and biological evaluation of novel benzothiazole derivatives as potential anticonvulsant agents, *Molecules* **21** (2016) Article ID 164 (13 pages); https://doi.org/10.3390/molecules21030164

101. J. D. Conley and H. Kohn, Functionalized DL-amino acid derivatives. Potent new agents for the treatment of epilepsy, *J. Med. Chem.* **30** (1987) 567–574; https://doi.org/10.1021/jm00386a021

102. H. Kohn, J. D. Conley and J. D. Leander, Marked stereospecificity in a new class of anticonvulsants, *Brain Res.* **457** (1988) 371–375; https://doi.org/10.1016/0006-8993(88)90709-3

103. H. Kohn, K. N. Sawhney, P. LeGall, J. D. Conley, D. W. Robertson and J. D. Leander, Preparation and anticonvulsant activity of a series of functionalized α-aromatic and α-heteroaromatic amino acids, *J. Med. Chem.* **33** (1990) 919–926; https://doi.org/10.1021/jm00165a006

104. H. Kohn, K. N. Sawhney, P. LeGall, D. W. Robertson and J. D. Leander, Preparation and anticonvulsant activity of a series of functionalized α-heteroatom-substituted amino acids, *J. Med. Chem.* **34** (1991) 2444–2452; https://doi.org/10.1021/jm00112a020

105. H. Kohn, K. N. Sawhney, P. Bardel, D. W. Robertson and J. D. Leander, Synthesis and anticonvulsant activities of α-heterocyclic α-acetamido-N-benzylacetamide derivatives, *J. Med. Chem.* **36** (1993) 3350–3360; https://doi.org/10.1021/jm00074a016

106. K. E. Andersen, C. Braestrup, F. C. Groenwald, A. S. Joergensen, E. B. Nielsen, U. Sonnewald, P. O. Soerensen, P. D. Suzdak and L. J. S. Knutsen, The synthesis of novel GABA uptake inhibitors. 1.

Elucidation of the structure-activity studies leading to the choice of (*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid (Tiagabine) as an anticonvulsant drug candidate, *J. Med. Chem.* **36** (1993) 1716–1725; https://doi.org/10.1021/jm00064a005

107. J. Zheng, R. Wen, X. Luo, G. Lin, J. Zhang, L. Xu, L. Guo and H. Jiang, Design, synthesis, and biological evaluation of the N-diarylalkenyl-piperidinecarboxylic acid derivatives as GABA uptake inhibitors (I), *Bioorg. Med. Chem. Lett.* **16** (2006) 225–227; https://doi.org/10.1016/j.bmcl.2005.09.004
108. N. Yadav, M. Malhotra, V. Monga, S. Sharma, J. Jain, Abdul Samad and A. Deep, Synthesis, characterization, and pharmacological evaluation of new GABA analogs as potent anticonvulsant agents, *Med. Chem. Res.* **21** (2012) 2208–2216; https://doi.org/10.1007/s00044-011-9743-9
109. R. Torregrosa, X. F. Yang, E. T. Dustrude, T. R. Cummins, R. Khanna and H. Kohn, Chimeric derivatives of functionalized amino acids and α-aminoamides: Compounds with anticonvulsant activity in seizure models and inhibitory actions on central, peripheral, and cardiac isoforms of voltage-gated sodium channels, *Bioorg. Med. Chem.* **23** (2015) 3655–3666; https://doi.org/10.1016/j.bmc.2015.04.014
110. C. O. Usifoh, D. M. Lambert, J. Wouters and G. K. E. Scriba, Synthesis and anticonvulsant activity of N,N-phthaloyl derivatives of central nervous system inhibitory amino acids, *Arch. Pharm.* (Weinheim) **334** (2001) 323–331; https://doi.org/10.1002/1521-4184(200110)334:10<323::AID-ARDP323>3.0.CO;2-O