American Journal of Current Organic Chemistry

American Journal of Clinical Anesthesiology
http://www.ivyunion.org/index.php/ajcoc
Vol 1, Article ID 201400586, 23 pages

Review

Anticonvulsant Activities of Various Series of Heterocyclic Compounds Containing Triazole, Thiadiazine, Benzo-triazole, Benzothiazole, Oxadiazole Ring Systems

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Abstract

In searching for better anticonvulsant drug and the importance of 2,5-disubstituted 1,3,4-oxadiazoles, 2-amino-5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazole **(1),** 1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-urea **(2)** and N-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)-hydrazine carbox-amide (3) and N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-(4-substituted benzaldehyde) -semicarbazones (4a-f) and N1-(5-{2-[(2,6-dichloro phenyl) amino] benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-substituted phenyl) ethanone]-semicarbazone (5a-d) and N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl) -N4-[1-(4-substituted henyl) (phenyl) methanone]-semicarbazones (6a-d) were evaluated for their anticonvulsant activity. Among all the compounds, 6b emerged out as the most potent compound. The anticonvulsant activity of 7-alkoxy-triazolo-[3,4-b]benzo[d]thiazoles (7a-u). Most compounds showed good anticonvulsant activity. Compound (7g) was found to be the most potent compound. A series of 2-(1H-Benzotriazol-1-yl)-N'-[substituted]acetohydrazides (8a-j) were tested for anticonvulsant activity and the most active compound was (8i). Various 6-phenyl-7H-[1,2,4]triazolo [3,4-b] [1,3,4] thiadiazines (9a-n) fused with 1,2,4-triazoles. Most compounds showed some degree of anticonvulsant activity. Compound (9h) was the most promising compound. A series of benzothiazole sulfonamides, 2-Amino-1,3-benzothiazoles (**10a-c**), 6-Sulfamido-1,3-benzothiazo-2-yl-thiosemicarbazides (**11a-c**) and N-[(1,3-benzothiazole-2-ylamino) (imino)methyl]-nitro-benzene sulfonamides **12a-b** were tested for the anticonvulsant activity. The significant results were found with compounds (**11c**) and (**10c**). Compound (**10c**), (**11c**) and compound (**10b**) were found to be raised in the onset of convulsion and other test drugs showed moderate protection.

Keywords: Anticonvulsant; triazole; thiadiazine; Benzotriazole; benzothiazole; oxadiazoles

Academic Editor: Taihong Shi, PhD, PhD, Sun Yat-sen University, China

Received: December 13, 2014; **Accepted**: January 6, 2015; P**ublished**: April 8, 2015

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Epilepsy is recognized as a neurological disorder, affecting a large section of people both male and female across the world. Every year about 2,50,000 new cases are added to this figure. Epilepsy also poses a considerable economic burden on the society. The direct costs of epilepsy vary significantly depending on the severity of the disease and the response to the treatment. The known potential causes of epilepsy include brain tumors, infections, traumatic head injuries, perinatal insults, developmental malformations, cerebrovascular diseases, febrile seizures and status epilepticus (Loscher. 2002). Many patients have seizures that are resistant to the available antiepileptic drugs (AEDs). Although 70–80% of epileptics are currently controlled by a variety of drugs, seizure protection is often accompanied by numerous side effects including drowsiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsutism, and megaloblastic anemia. The older 'first generation' AEDs are phenobarbitol, carbamazepine, valproic acid and newer 'second generation' AEDs are lamotrigine, topiramate, vigabatrin, tiagabine, gabapentin and levetiracetam (Brazil and Pedly. 1998; McCabe. 2000). The selection of an AEDs for the treatment is predicated on its efficacy for the specific type of seizures, tolerability and safety (Regesta and Tanganelli. 1999; Kwan and Brodie. 2000). Therefore, it is essential to search for newer chemical entities for the therapy of epilepsy (Cosford et al., 1998). The 3-piperidinecarboxylic acid (nipecotic acid) has become an emerging new class of potent anticonvulsants.

Epilepsy results from a temporary electrical disturbance of the brain due to an imbalance between excitatory and inhibitory neurotransmitters. The mechanisms of action of the AEDs consist in the blockade of voltage-dependent Na^+ channels or T-type Ca^{2+} channels, inhibition of glutamatergic transmission and facilitation of γ-aminobutyric acid (GABA) inhibitory neurotransmission (Strine, et al., 2005; Mc Namara et al., 2006; Thiry et al., 2008; Kaindl et al., 2006). However, 30% of epileptic patients continue to have seizures despite optimized treatment with classical AEDs. Moreover, many serious side effects are reported in many patients treated with presently available AEDs. There is a growing interest for new AEDs acting on novel therapeutic targets with a pharmacological profile characterized by enhanced efficacy and minimal side effects. This needs to be coupled with a better understanding of generation of seizures (Willams and Lamke. 2002; Fisher et al., 2005). Epilepsy also affects about 4% of individuals over their lifetime. Despite the development of several new AEDs, over 30% of people with epilepsy do not have seizure control and others do so only at the expense of significant dose-related toxicity and peculiar adverse effects that range in harshness from minimal brain impairment to death from aplastic anemia or hepatic failure (Brown and Holmes. 2001). Thus, have there is an immense need for the development of more effective and safer AEDs. Several investigations have also revealed the anticonvulsant potential of 1,3,4-oxadiazole analogs (Zarghi et al., 2005; Almasirad et al., 2004). A pharmacophoric model has been proposed for anticonvulsant activity as a result of conformational studies on existing AEDs, such as Phenytoin, Carbamazepine, Rufinamide and Phenobarbitone (Pandeya et al., 1999).

Benzotriazole derivatives constitute an important class of heterocyclic compounds and present a wide range of bioactivities. Among the most important are: anticonvulsant (Dawood et al., 2006; Rajasekaran et al., 2006; Srivastava and Rawat. 1999), CNS depressant, antimicrobial (Nanjunda et

al., 2006; Omran et al., 2009), anticancer (Zhang et al., 2008), analgesic and anti-inflammatory activity (Purohit and Srivastava. 1992). Several derivatives of benzotriazole are reported as agonists of peroxisome proliferator activated receptors (Sparatore et al., 2006). The 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance. For example, a triazolothiadiazine system may be viewed as a cyclic analog of thiosemicarbazide, the latter often displays antimicrobial (Plech et al., 2011), anticancer (Vrdoljak et al., 2010), and anticonvulsant activities (Jain et al., 2010; Gülerman et al., 1997; Gürsoy and Karali. 1995). For this reason and in continuation to efforts directed toward the synthesis of new heterocyclic compounds with anticonvulsant biological activities. A series of condensed system, which combine two biolabile components (1,2,4-triazole and [1,3,4]thiadiazine) in a ring together to give a compact and moderate rigid structure, and evaluated them for their anticonvulsant profile after subtle structural modification. The carbonic anhydrase (CA) inhibitor acetazolamide (AZA) is used as an AED in the treatment of epilepsy having sulfonamide group. Despite the development of a rapid tolerance consisting in diminished therapeutic efficacy after the initial response of the patients, AZA is still used in combination therapy with other AEDs or in refractory epilepsies (Garrison et al., 1991). Zonisamide another sulfonamide with CA inhibitory properties is also used as adjunctive therapy for refractory partial seizures in adult (Supuran. 2007; Supuran. 2008). Its sulfamoyl group was expected to suppress seizures in a similar way to AZA through the inhibition of carbonic anhydrase (Supuran and Scozzafava. 2007; Simone et al., 2005; Joo et al., 2010; Basaran et al., 2008). However, this does not appear to be the only primary mechanism of action. The sulfamate, topiramate is a recent antiepileptic drug which has been shown to be clinically effective against different types of seizures (Casini et al., 2003; Chegwidden et al., 2000; Herrero et al., 2002; Supuran et al., 2003). Basic ring having the sulfonamide group of benzothiazole ring system have various pharmacological activity. Various 2-amino-1,3-benzothiazoles were tested for neurotoxicity and anticonvulsant study. In this respect, we prompted to prepare a new class of heterocyclic sulphonamides and study their anticonvulsant activity. In order to obtain some information about the activity of synthesized compounds, anticonvulsant activity was tested by Maximal electroshock (MES) seizure model and their neurotoxic effects were determined by rotorod test.

Antiepileptic activities of various heterocyclic compounds

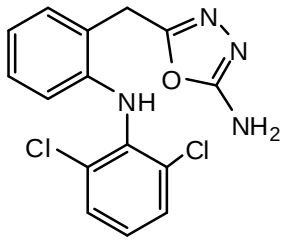
In searching for better anticonvulsant drug and the importance of semicarbazones and 2,5-disubstituted 1,3,4-oxadiazoles such as 2-amino-5-{2-[(2,6-dichlorophenyl)amino] benzyl}-1,3,4-oxadiazole **(1),** 1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4- oxadiazol-2-yl)-urea **(2)** and N-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl) -hydrazine carboxamide **(3)** and N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4- oxadiazol- 2-yl)-N4-(4-substituted benzaldehyde)-semicarbazone **(4a-f),** N1-(5-{2-[(2,6-dichloro phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-(benzaldehyde) -semicarbazone **(4a),** N1-(5-{2-[(2,6-dichloro phenyl)amino] benzyl}-1,3,4-oxadiazol-2-yl)-N4-(4-nitro-benzaldehyde)-semicarbazone **(4b),** N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-(4-hydroxy benzaldehyde)-semi-carbazone **(4c),** N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-

(4-methyl- benzaldehyde)-semicarbazone **(4d),** N1-(5-{2-[(2,6- dichlorophenyl) amino]benzyl} -1,3,4-oxadiazol-2-yl)-N4-(4-methoxybenzaldehyde)- semi- carbazone **(4e)**, and N1-(5-{2-[(2,6-dichloro-phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-(4-chlorobenzaldehyde)- semi-carbazone **(4f)** and N1-(5-{2-[(2,6-dichloro phenyl)amino] benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-substituted phenyl) ethanone]-semicarbazone **(5a-d)** namely N1-(5-{2-[(2,6-dichloro phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-hydroxy phenyl)-ethanone]-semicarbazone **(5a),** N1-(5-{2-[(2,6-dichlorophenyl) amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-methoxy phenyl)-ethanone]-semicarbazone **(5b),** N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-nitrophenyl)-ethanone]-semicarbazone (**3c)** and N1-(5-{2-[(2,6-dichloro-phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-chlorophenyl)-ethanone]-semicarbazone **(5d)** and N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-substituted phenyl) (phenyl) methanone]-semicarbazone **(6a-d)** namely N1-(5-{2-[(2,6-dichlorophenyl)amino] benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(diphenyl) methanone]-semicarbazone **(6a),** N1-(5-{2-[(2,6-dichloro-phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-hydroxyphenyl) (phenyl) methanone]-semicarbazone **(6b),** N1-(5-{2-[(2,6-dichloro phenyl)amino]benzyl}-1,3,4-oxadiazol -2-yl)-N4-[1-(4-nitrophenyl) (phenyl) methanone]-semicarbazone **(6c)** and N1-(5-{2-[(2,6 -dichloro-phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-methoxyphenyl) (phenyl) methanone]-semicarbazone (**6d)** were evaluated for their anticonvulsant activity. Among all the compounds, N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-hydroxyl-phenyl)(phenyl) methanone]-semicarbazone **6b** emerged out as the most potent compound, showing considerable activity in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0 h) and subcutaneous pentylenetrtrazole model (at 300 mg/kg after 4.0 h) without any neurotoxicity (up to 300 mg/kg after 4.0 h). The results of the present study validated that the pharmacophore model with four binding sites is essential for anticonvulsant activity.

Anticonvulsant Activity

The anticonvulsant screening was performed using male albino mice (swiss, 18-25 g) and rat (wistar 100-150 g). The anticonvulsant potential of the test compounds was assessed by two models namely, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) models. Acute neurological toxicity in mice was evaluated by rotorod test [16]. All the synthesized compounds were screened for their anticonvulsant potential through MES and scPTZ models in doses of 30, 100, 300 mg/kg by intraperitoneal (*i.p.)* injection. The data indicates that 64% of the compounds *i.e.*, **4a, 4c, 4f, 5a, 5c, 6a, 6b, 6c,** and **6d** were active in the MES screening as compared to 35% of the compounds *i.e.*, **4e, 5a, 5d,** and **6b** in the ScPTZ test. Thus, the compounds displayed some MES selectivity. The majority of the compounds *i.e.*, **4a, 4c, 4e to 5a,** and **5c to 6d** showed activity in either of the MES or ScPTZ models after 4 h, indicating that the test compounds are slow acting anticonvulsants (Tables **1** and **2**). On critical overview of synthesized compounds, it has been found that compounds bearing the groups like hydroxy, nitro on distant phenyl ring possess high potency in MES and scPTZ tests. Whereas, replacement of these groups with methoxy and methyl groups on the distant phenyl ring has resulted in compounds with decrease in anticonvulsant activity. Replacement of the proton on the carbimino carbon atom by methyl group *i.e.*, **5a-d** or

phenyl ring *i.e.*, **6a** to **6d** has demonstrated variation in activity due to increase in the dimension of the group at this position of the molecule. Compounds with phenyl ring exhibited considerable anticonvulsant activity in comparison to methyl group. The amplified anticonvulsant activity of compounds **6a-d** may be endorsed to the presence of phenyl substitution, which might be accountable for additional van der Waals bonding to the binding site. The designed and synthesized the compounds with keeping a fact in mind that a number of clinically active anticonvulsants possess a nitrogen hetero atomic system with one or two phenyl rings and at least one carbonyl group in their structure. The structure of the title compounds **4a-f 5a-d** and **6a-d** fulfilled all the pharmacophoric structural requirements *i.e.*, presence of 5-{2-[(2,6-dichlorophenyl) amino] benzyl}-1,3,4-oxadiazol-2-yl moiety as hydrophobic portion, N as electron donor system and another hydrophobic distal aryl ring responsible for metabolism. Thus, the results confirmed the four binding site hypothesis for semicarbazones. In the present study, N1-(5-{2-[(2,6-dichloro-phenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-hydroxy phenyl) (phenyl) methanone]-semicarbazone emerged out as the most active compound, showing abroad spectrum of activity without any neurotoxicity (Rajak et al., 2009).



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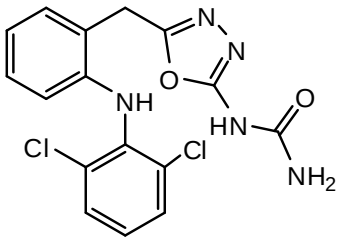

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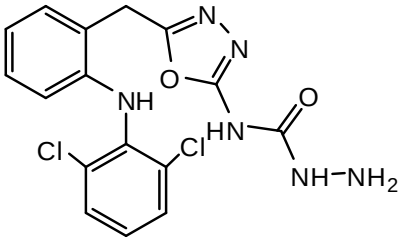

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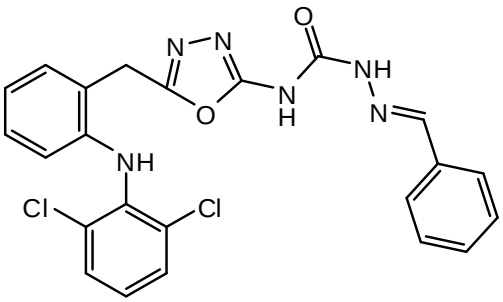

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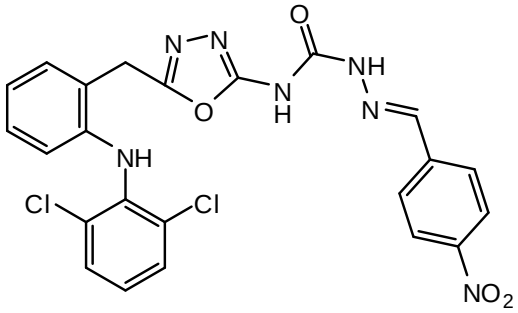

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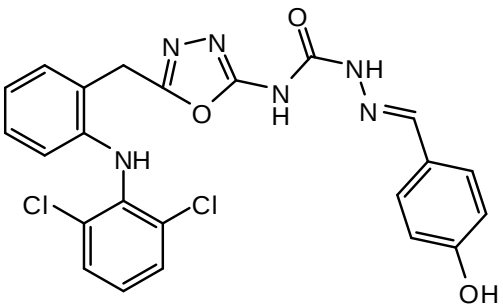

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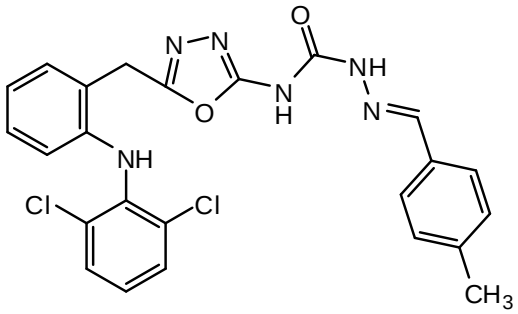

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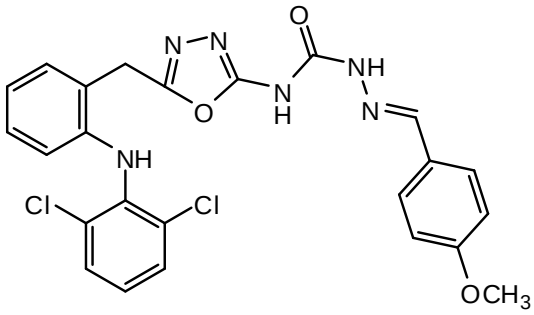

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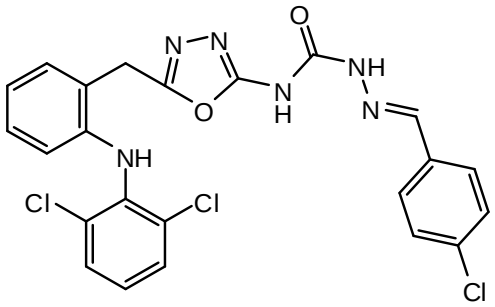

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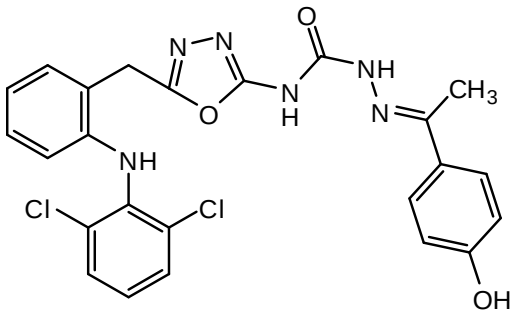

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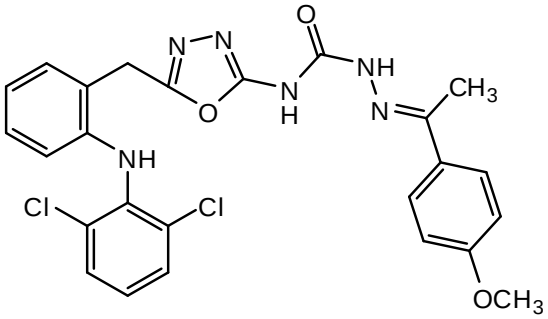

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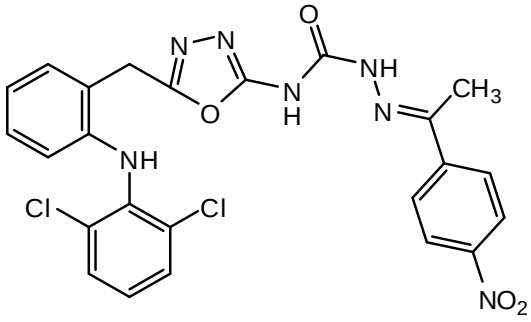

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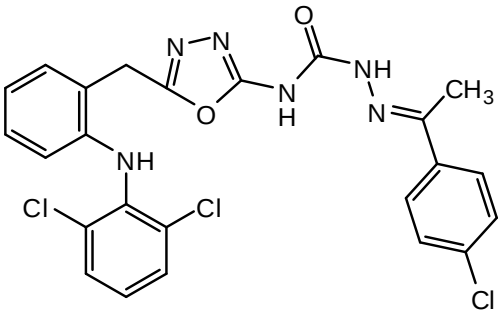

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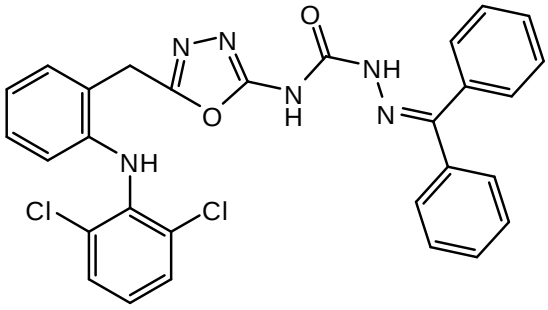
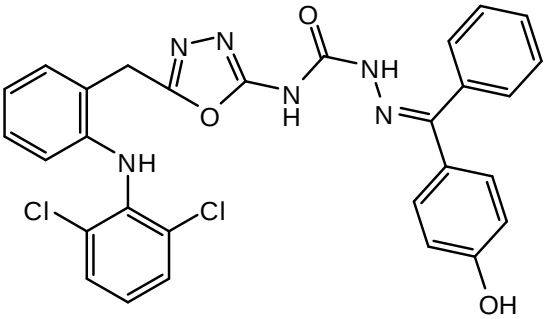
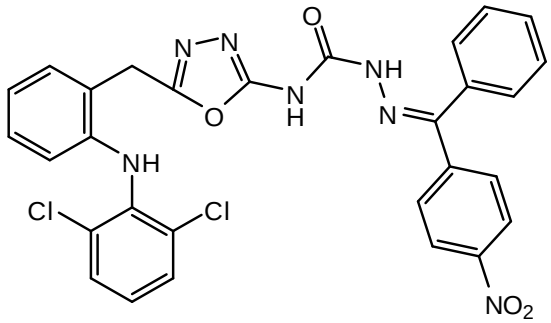


6a



6b



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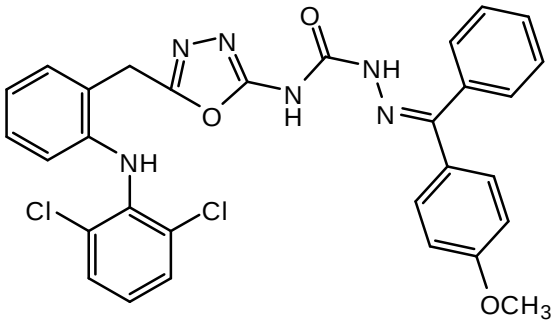
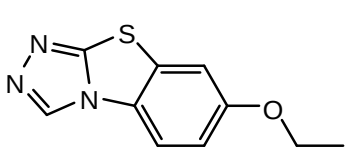


6d

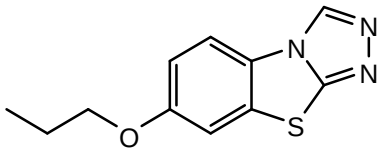
A series of novel N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-(4-substitutedbenzaldehyde)-semicarbazone **4a-f**, N1-(5-{2-[(2,6-dichlorophenyl) amino] benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-substitutedphenyl)ethanone]-semicarbazone **5a-d** and N1-(5-{2-[(2,6-dichlorophenyl)amino]benzyl}-1,3,4-oxadiazol-2-yl)-N4-[1-(4-substituted pshenyl) (phenyl)methanone]-semicarbazone **4a-f, 5a-d** and **6a-d** were synthesized to meet structural requirements necessary for anticonvulsant activity. Our results validated that the pharmacophore model with four binding sites is vital for anticonvulsant activity. These new facts might be expedient in the future research and development of semicarbazones as novel anticonvulsants.

The anticonvulsant activity evaluation of a series of 7-alkoxy-triazolo-[3,4-b]benzo[d]thiazoles (**7a-u**) viz 7-Ethoxyl-Triazolo-[3,4-b] Benzo[d]Thiazole **(7a),** 7-Propoxy-Triazolo-[3,4-b] Benzo [d]Thiazole **(7b),** 7-Butoxy-Triazolo-[3,4-b]Benzo[d]Thiazole **(7c),** 7-Pentyloxy-Triazolo-[3,4-b] Benzo[d]Thiazole **(7d),** 7-Hexyloxy-Triazolo-[3,4-b]Benzo[d] Thiazole **(7e),** 7-Heptyloxy-Triazolo-[3,4-b]Benzo[d]Thiazole **(7f),** 7-Octyloxy-Triazolo-[3,4-b] Benzo[d] Thiazole **(7g),** 7-Decyloxy-Triazolo-[3,4-b]Benzo[d]Thiazole **(7h),** 7-Dodecyloxy-triazolo-[3,4-b]benzo [d] thiazole **(7i),** 7-Benzyloxy-triazolo-[3,4-b]benzo[d]thiazole **(7j),** 7-(2-Fluoro benzyloxy)-triazolo-[3,4-b]benzo[d]thiazole **(7k),** 7-(3-Fluorobenzyloxy)-triazolo-[3,4-b]benzo [d]thiazole **(7l),** 7-(4-Fluorobenzyloxy)-triazolo-[3,4-b]benzo[d]thiazole **(7m),** 7-(2-Chloro-benzyloxy)-triazolo-[3, 4-b]benzo[d]thiazole **(7n),** 7-(3-Chlorobenzyloxy)-Triazolo-[3, 4-b] Benzo[d]Thiazole **(7o),** 7-(4-Chlorobenzyloxy)-Triazolo-[3,4-b]Benzo[d]Thiazole **(7p),** 7-(2-Bromobenzyloxy)-Triazolo-[3,4-b]Benzo[d]Thiazole **(7q),** 7-(3-Bromobenzyloxy)-Triazolo-[3, 4-b]Benzo[d]Thiazole **(7r),** 7-(4-Bromobenzyloxy)-Triazolo-[3,4-b]Benzo[d]Thiazole **(7s),** 7-(4-Methylbenzyloxy) -Triazolo-[3,4-b]Benzo[d]Thiazole **(5t)** and 7-(4-Methoxybenzyloxy)-Triazolo-[3,4-b]Benzo[d]Thiazole **(7u)**. Most compounds exhibited good anticonvulsant activity in the Maximal electroshock (MES) test. And the structure-activity relationships (SAR) were analyzed. Among the compounds studied, compound (**7g**) was found to be the most potent compound with a median effective dose (ED50) value of 8.0 mg/kg and a protective index (PI) value of 15.0, possessing better anticonvulsant activity and higher safety than marketed drugs carbamazepine and phenytoin. The mechanism study of compound **7g** showed that it displayed broad spectrum activity in several models, and it is likely to have several mechanisms of action (including inhibiting voltage-gated ion channels and GABA-ergic activity). The anticonvulsant activity of 7-alkoxyl-4H-[1,2,4]triazolo [4,3-d]benzo [b][1,4]thiazines (Zhang et al., 2010), Among these compounds, 7-(2-fluorobenzyloxy)-4H-[1,2,4]triazolo[4,3-d]benzo[b][1,4]thiazine was the most active compound with an ED50 of 17.0

mg/kg and a protective index (PI; TD50/ED50) of 14.3 in the MES. With the intent to discover effective compounds with lower neurotoxicity, a series of 7-alkoxy-triazolo-[3,4-b] benzo[d] thiazoles, the ring contraction analogues of 7-alkoxyl-4H-[1,2,4]triazolo [4,3-d]benzo[b] [1,4]thiazines through removal of a CH2, were anticipated to possess a better anticonvulsant activity. Their anticonvulsant activity was evaluated using the MES test in mice and their neurotoxicity was evaluated with the rotarod test. For explaining the possible mechanism of action, the most active compound (7**g)** was tested in Pentylenetetrazole (PTZ), Isoniazid (ISO), and Bicuculline (BIC) induced seizure tests.



7a



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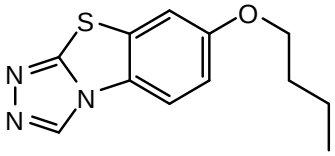

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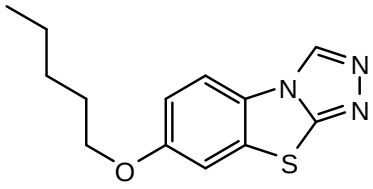

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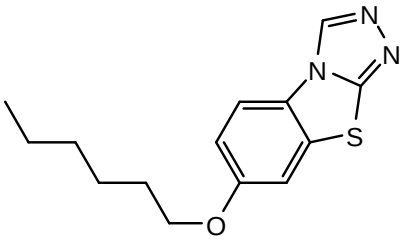

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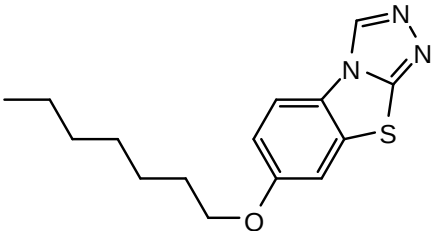

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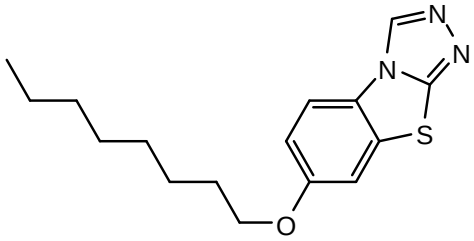
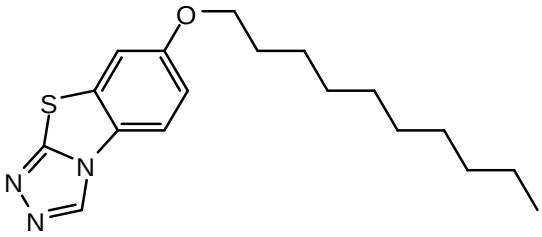


7g



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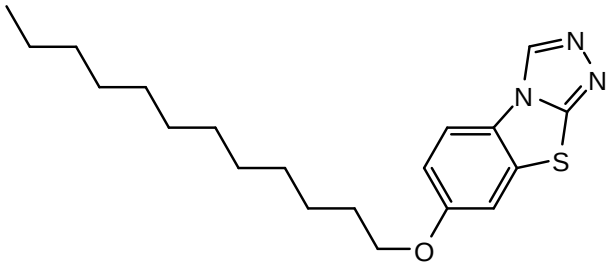

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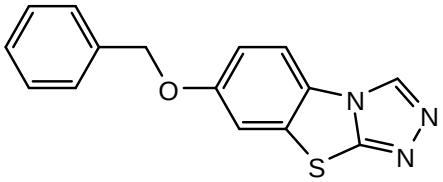

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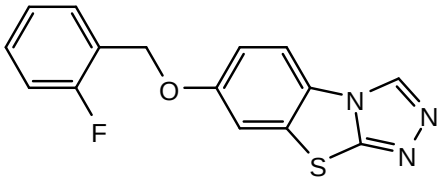

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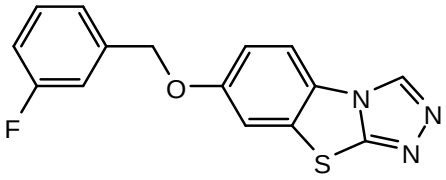

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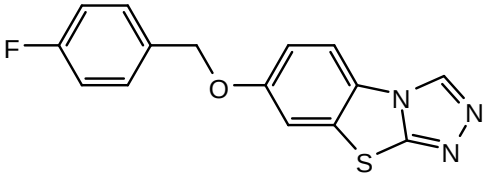

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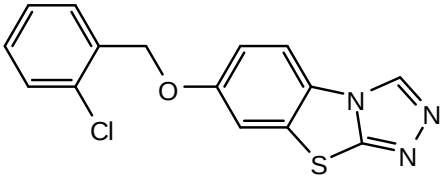

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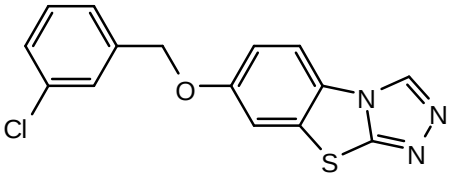

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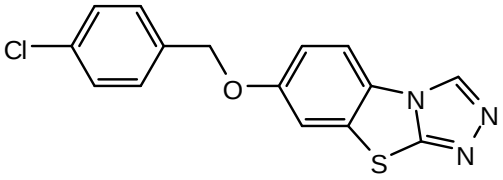

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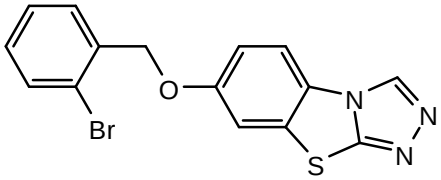

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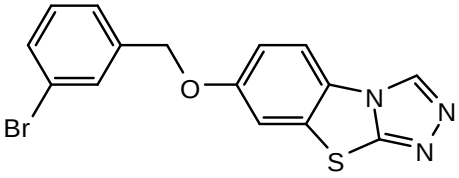

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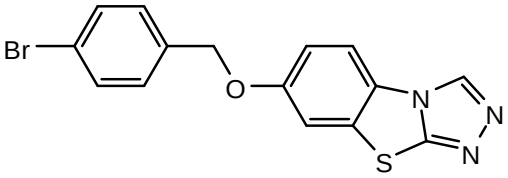

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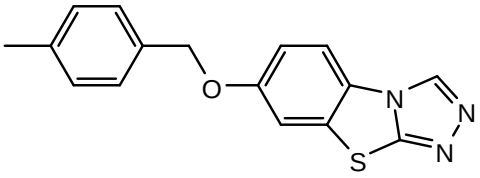
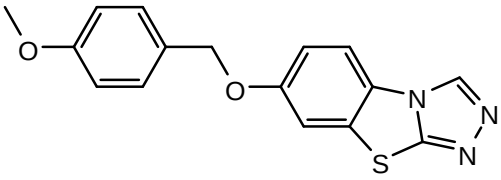


7t



7u

As with any other class of drugs, the preclinical discovery and development of a new chemical entity for the treatment of epilepsy rely heavily on the use of predictable animal models. At the present time, there are three *in vivo* models that are routinely used by most AED discovery programs. They include the maximal electroshock seizure (MES), the subcutaneous

pentylenetetrazol (scPTZ), and the kindling model. Of these, the MES and scPTZ seizure models represent the two animal seizure models, which are most widely used in the search for new AEDs (White. 2003; Levy et al., 1995). In this study, the MES seizure model was used for preliminary (phase **I**) screening of compounds 7**a-7s.** All of the compounds except were active in the MES test, indicative of their ability to prevent seizure spread. Among those compounds, four compounds **7d-7g** showed prominent anticonvulsant activity exhibiting protection against MES-induced seizure at the dose of 10 mg/kg. At the dose of 30 mg/kg, compounds **7b-7g, 7j**, and **7k** showed protection. At the dose of 100 mg/kg, most compounds showed protection except **7i, 7o-7p,** and **7s**. Compounds **7i, 7o-7p,** and 7**s** exhibited comparatively lower anticonvulsant activity at the dose of 300 mg/kg. None of the compounds showed protection in the 4 h period. As a result of preliminary screening, compounds **7a–g, 7j-7k, 7r,** and 7**t** were subjected to the next phase of trials concerning quantification of their anticonvulsant activity (indicated by ED50) and neurotoxicity (indicated by TD50) in mice. Results of the quantitative test for the selected compounds, along with the data on the standard drug carbamazepine and phenytoin. Among the tested compounds, 7-octyloxy-triazolo-[3, 4-b]benzo[d] thiazole (7**g**), which gave an ED50 value of 8.0 mg/kg and a TD50 value of 120.0 mg/kg resulting in a higher protective index (PI) value-that is TD50/ED50 = 15.0, was the most active and promising compound in this study. With an ED50 value of 11.6 and PI value of 11.3, compound **7f** was equipotent to carbamazepine in activity and safer than carbamazepine. Though Compounds 7**j** and **7k** showed the lower activity compared to carbamazepine or phenytoin, they exhibited higher PI value than carbamazepine and phenytoin. Analyzing the activity of the synthesized compounds, the following structure–activity relationships (SAR) were obtained.

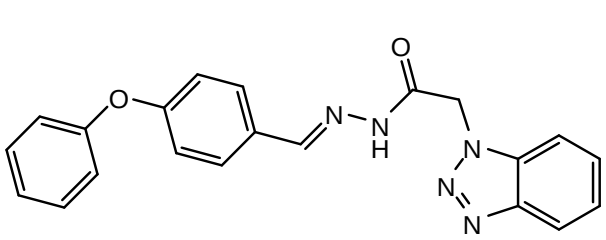
Compounds 7**a-7i** were triazolo-[3, 4-b]benzo[d]thiazole molecules substituted by alkoxyl chains. The length of the alkyl chain appeared to have a direct impact on anticonvulsant activity of these derivatives. From compounds 7**a-g**, as the alkyl chain length increased, ED50 gradually increased, with the compound **7g** (with the noctyloxy substituted group) being the most active. The trend reversed, however, when the alkyl chain had more than eight carbon atoms. Obviously, in this study the activity curve of the alkyl chain substituted derivatives is bell-shaped with a maximum activity peak. Compound **7g,** with the maximum activity peak, probably reflected the optimal partition coefficient associated with the easiest crossing of the biological membranes. Compounds **7j-u** were triazolo-[3, 4-b]benzo[d]thiazole molecules substituted by benzyloxy groups. The activity of them was comparatively weaker than that of the compounds mentioned above. With the exception of compounds **7j, 7k, 7r,** and **7t,** which exhibited the anticonvulsant activity with ED50<100mg/kg, the rest showed weak activity at the dose of 100 or 300mg/kg. Among **7j-u**, compound **7g** was the most promising compound with an ED50 of 21.9 mg/kg, TD50 of 262.9 mg/kg and PI of 12.0. Comparing the derivatives with different F-substitution positions on the benzyl ring, their activity order was o-F > p -F > m -F. Activity order of the Cl and Br substituted derivatives were o-Cl > m -Cl > p-Cl and m-Br > o-Br > p-Br, respectively. Two electron-donor containing derivatives **7t** and 7**u** were also designed and prepared, containing p-CH_3 and p-OCH_3. The ED50 value of **7t** was 65.5mg/kg. And **7u** showed weak activity at the dose of 100mg/kg. They both decreased the activity compared to 7**j**, having non-substituted in the ring of benzyl group (Deng et al., 2010).

Most compounds are highly potent in the MES test, and the MES test is known to be sensitive to

sodium channel inhibitors (e.g. phenytoin, carbamazepine), which suggested that they may inhibit voltage-gated ion channels (particularly sodium channels). To further investigate the effects of the anticonvulsant activity in several different models and speculate about the possible else mechanism of anticonvulsant action, compound **7g** was tested against convulsions induced by chemical substances, including PTZ, ISO, and BIC. Compound **7g** was administered into mice i.p. at the dose of 30 mg/kg, which was higher than its ED50 value and far below its TD50 value. The reference drug carbamazepine was also administered i.p. at the dose of 30 mg/kg. In the sc-PTZ model, compound **7g** thoroughly inhibited the clonic seizures, tonic seizures and lethality induced by sc-PTZ, while the reference drug carbamazepine did not inhibit the clonic seizures induced by sc-PTZ. Compound **7g,** exhibiting high anticonvulsant activity in the MES and sc-PTZ model which are most widely used in the search for new AEDs, suggested that it really possessed a good anticonvulsant profile. In the isoniazid model, carbamazepine inhibited the clonic seizures, tonic seizures and death induced by isoniazid at the rates of 40%, 100% and 100%, respectively; and compound 7**g** showed inhibition of the clonic seizures, tonic seizures and death induced by isoniazid at the rates of 40%, 80% and 100%, respectively. Carbamazepine and **7g** both exhibited protection activity in the isoniazid model. PTZ and ISO have been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission. GABA is the main inhibitory neurotransmitter in the brain, and is widely implicated in epilepsy. Inhibition of GABAergic neurotransmission or activity has been shown to promote and facilitate seizures (Gale. 1992), while enhancement of GABAergic neurotransmission is known to inhibit or attenuate seizures. The findings of the present study suggest that the newly synthesized compound **7g** might inhibite or attenuate PTZ-induced seizures and isoniazid-induced seizures in mice by enhancing GABAergic neurotransmission. Bicuculline (BIC) induced seizure model was also used to evaluate the anticonvulsant profile of compound **7g**. In the BIC induced seizure model, both carbamazepine and **7g** inhibited the tonic seizures and death, but did not inhibit clonic seizures. Carbamazepine showed inhibition at the rate of 0%, 100% and 80% of the clonic seizures, tonic seizures and death, respectively. And **7g** showed inhibition at the rates of 0%, 80% and 50%, respectively. In this test, compound **7g** showed a positive inhibition to the tonic seizures induced by BIC, and half protection against animal death induced by BIC. BIC is a competitive antagonist of GABAA receptor. BIC produces convulsions through its antagonism of GABAA receptor. Compound **7g** can inhibit the seizures induced by BIC, which suggested that it exerts anticonvulsant activity partially through GABAA-mediated mechanisms. The 7-alkoxy-triazolo-[3,4-b]benzo[d]thiazoles have potent anticonvulsant activity in the MES test. Especially, compound **7g** showed better anticonvulsant activity and higher safety than marketed drugs carbamazepine and phenytoin. In addition, compound **7g** demonstrated antagonistic activity against seizures induced by PTZ, Isoniazid, and Bicuculline. Compound **7g** are likely to have several mechanisms of action (including inhibit voltage-gated ion channels and GABA-ergic activity).

A series of 2-(1*H*-Benzotriazol-1-yl)-*N*'-[substituted]acetohydrazides (**8a-j**) viz 2-(1H-Benzo-triazol-1-yl)-N'-(4-phenoxybenzylidene)acetohydrazide (**8a**), 2-(1H-Benzo-triazol-1-yl)-N'-[4-(4-nitrophenoxy)benzylidene]acetohydrazide (**8b**), 2-(1H-Benzotriazol-1-yl)-N'-[4-(4 methyl-phenoxy)benzylidene]acetohydrazide (**8c**), 2-(1H-Benzotriazol-1-yl)-N'-[4-(4-chloro phenoxy) benzylidene]acetohydrazide (**8d**), 2-(1H-Benzotriazol-1-yl)-N'-[4-(4-bromo-phenoxy)

benzylidene]acetohydrazide (**8e**), 2-(1H-Benzotriazol-1-yl)-N'-[4-(4-fluoro-phenoxy) benzylidene] acetohydrazide (**8f**), 2-(1H-Benzotriazol-1-yl)-N'-[4-(4-chloro-3-methyl-phenoxy) benzylidene] aceto- hydrazide (**8g**), 2-(1H-Benzotriazol-1-yl)-N'-[4-(naphthalen-2-yloxy) benzylidene] acetohydrazide **(8h),** N'-[4-(1,3-Benzodioxol-5-yloxy) benzylidene]-2-(1Hbenzotriazol-1-yl) acetohydrazide **(8i)** and 2-(1H-Benzotriazol-1-yl)-N'-[(3Z)-2-oxo-1,2-dihydro-3H-indol -3-ylidene]acetohydrazide (**8j**), were synthesized keeping in view the structural requirement of pharmacophore and evaluated for anticonvulsant activity and neurotoxicity. The anticonvulsant activity of the compounds was assessed using the 6 Hz psychomotor seizure test. The neurotoxicity was assessed using the rotarod method. The most active compound of the series was **(8i)**, which showed good activity with 75 % protection (3/4, 0.5 h) at a dose of 100 mg/kg in mice. None of the compounds exhibited neurotoxicity. Synthesis and biological activity of 1*H*-benzotriazole analogs as inhibitors of the NTpase/helicase and some related Flavivirade have been extensively investigated (Bretner et al., 2005). In the twenties, 1*H*-benzotriazole moiety containing compounds such as benzotriazole and benzofuran-based heterocycles (Dawood et al., 2006), 1-(2-Amino phenyl)-2-[5-(2-benzotriazol-2-yl-ethyl)-tetrazol-2-yl]-ethanone and 1-(4-Amino phenyl)-2-[5-(2-benzotriazol-2-yl-ethyl)-tetrazol-2-yl]-ethanone (Rajasekaran et al., 2006) were reported as potential anticonvulsants. In fact, these evidences suggest that the 1*H*-benzotriazole moiety, possesses a pharmacophoric character for anticonvulsant activity. In addition, the 4-(2-phenoxyphenyl)semicarbazones were reported as potential anticonvulsants (Shafiee et al., 2009). Continuing our studies on benzfused derivatives that are attractive candidates as anticonvulsant agents (Kumar et al., 2011), we designed a series of functionalized 2-(1*H*-Benzotriazol-1-yl)-*N*'-[substituted] acetohydrazides compounds **8a-j,** exploring 1*H*-benzotriazole, as starting material. The rational design of these new derivatives **8a-j,** was planned by molecular hybridization of substituted 1*H*-benzotriazole **8g**, and 4-(aryloxy) phenyl semicarbazones **8f**. Based on the literature review, we are the first to report the synthesis and anticonvulsant activities of 2-(1*H*-Benzotriazol-1-yl)-*N*'-[substituted] acetohydrazides. All the synthesized compounds comprised of the essential pharmacophoric elements that are necessary for good anticonvulsant activity (Unverferth et al., 1998). In addition, their anticonvulsant activity was evaluated by using 6 Hz psychomotor seizure test in mice. The rotorod assay was performed in mice to evaluate the neurotoxicity of the compounds.



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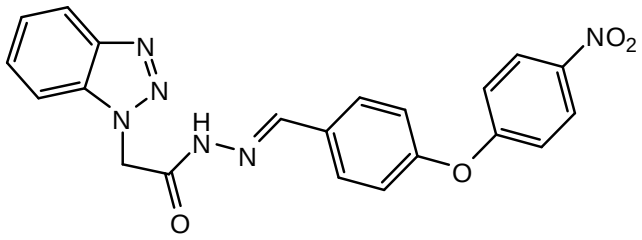

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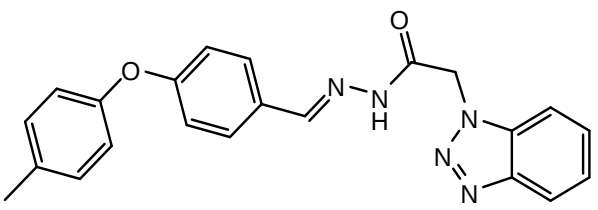

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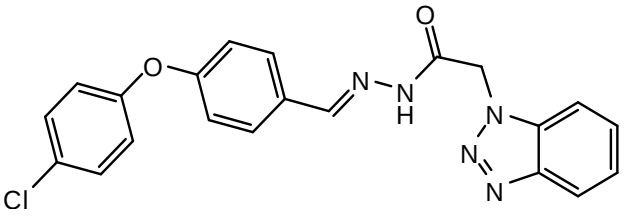

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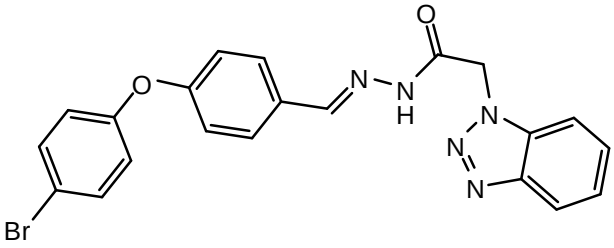

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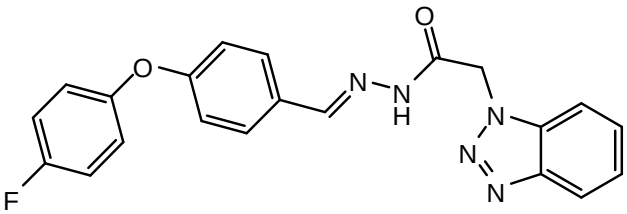
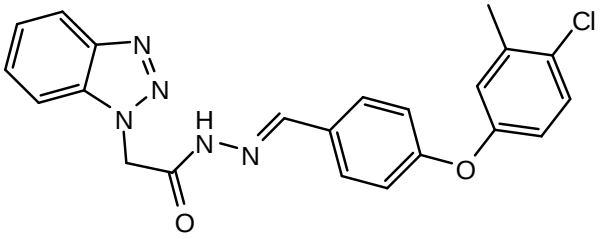
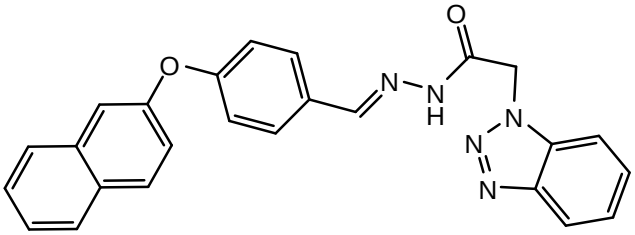


8f



8g



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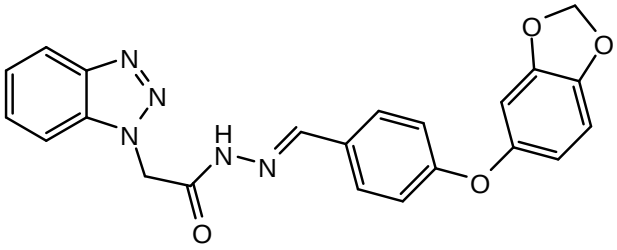
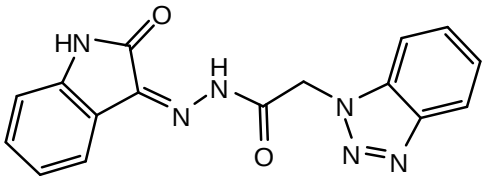


8i



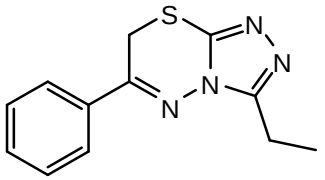
8j

The synthesized 2-(1*H*-Benzotriazol-1-yl)-*N*'-[substituted] acetohydrazides **8a-j** were subjected to anticonvulsant screening by 6 Hz psychomotor seizure or minimal clonic seizure test to identify their anticonvulsant activity at five different time points, i.e., 0.25 h, 0.5 h, 1.0 h, 2.0 h and 4.0 h after i.p. administration in mice at a dose of 100 mg/kg. As observed from the results of various tested 2-(1*H*-Benzotriazol-1-yl)-*N*'-[substituted] acetohydrazides, compound **8i** was the most active one in this series with 75 % protection (3/4, 0.5 h) at a dose of 100 mg/kg. At a dose of 100 mg/kg, compounds **8d, 8e** and **8h** showed 50% protection (2/4) at a time point of 1.0 h, 0.5 h and 0.5 h respectively. Other compounds showed mild to moderate activity. These active compounds contain 1,3-benzodioxol-5-yl,4-chlorophenyl,4-bromophenyl and naphthalen-2-yl substitution attached to basic molecular structure. None of the compounds showed neurotoxicity in the highest administered dose (Kumar and Tripathi. 2012). A series of 2-(1*H*-Benzotriazol-1-yl)-*N*'-[substituted] acetohydrazide was

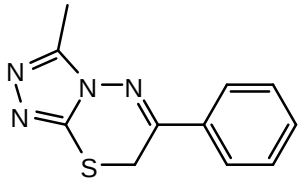
designed, synthesized, and their anticonvulsant activity was evaluated after intraperitoneal administration in 6 Hz psychomotor seizure test. The compound **8i** displayed significant protection and emerged as a lead in this series. Further, compounds **8d, 8e** and **8h** came out as a potential candidate for further investigation. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these molecules (Kumar and Tripathi. 2012).

Various 6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives (**9a-n**) were designed keeping in view the wide bioactivities of 1,2,4-triazoles and their fused heterocyclic derivatives. All 6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **(9a-n)**namely 3-ethyl-6-phenyl-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazine **(9a),** 3-methyl-6-phenyl-7H-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazine **(9b),** 6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(9c),** 6-(2-fluorophenyl)-7H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazine **(9d),** 6-(4-fluorophenyl)-7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazine **(9e),** 6-(2-chlorophenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine **(9f),** 6-(3-chlorophenyl)-7H-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazine **(9g),** 6-(4-chloro-phenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(9h),** 6-(2,4-dichlorophenyl)-7H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazine **(9i),** 6-(2-bromophenyl)-7H-[1,2,4]triazolo[3,4-b] [1,3,4] thiadiazine **(9j),** 6-(3-bromophenyl)-7H-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazine **(9k),** 6-(4-bromo-phenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(9l),** 6-(4-methyl-phenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(9m)** and 6-(4-methoxyphenyl)-7H-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazine**(9n)**have been evaluated for their anticonvulsant activity against MES-induced seizures. The results showed that most of the compounds displayed some degree of anticonvulsant activity. Among them, compound (**9h**) was the most promising compound with an ED50 value of 40.9 mg/kg and a PI value of 6.5. The ambient nucleophilic centers presented in 3-substituted-4-amino-5 -mercapto-1,2,4-triazoles render them as useful synthons for the synthesis of various N-bridged heterocycles **(Smicius et al., 2007).** The 6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives (**9a-9n**) were evaluated for their anticonvulsant activities. In the phase **I** preliminary anticonvulsant screening, Al most all the compounds (except **9a**) showed some degree of protection in MES screen which was the indicative of the good ability of these compounds to prevent the seizure spread. Majority of the compounds were active at a dose of 100 mg/kg after 0.5 h. These include compounds **9c-h, 9j** and **9k**. Compounds **9b, 9i, 9m-n** were showed protection from seizure at the dose 300 mg/kg after 0.5 h. None of the compounds showed protection at 4 h which indicated the nature of these compounds having quick onset and short duration of action. In the neurotoxicity screening, compounds that were devoid of minimal motor impairment at any dose were **9a, 9b, 9j,** and **9l**. Rest of the compounds showed some degree of neurotoxicity. On the basis of the considerable anticonvulsant promise suggested in phase I testing, compounds **9c-h, 9j** and **9k** were subjected to phase **II** trials for quantification of their anticonvulsant activity (indicated by ED50) and neurotoxicity (indicated by TD50) in mice. Results of the quantitative test for selected compounds, along with the data on the standard drug carbamazepine and valproate, are reported. All the compounds showed weaker anticonvulsant activity compared to currently used antiepileptic drugs carbamazepine but better than valproate. 6-(4-Chlorophenyl) -7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**9h**) possessed nice anti-MES activity with ED50 of 40.9 mg/kg, and a protective index of 6.5, which was equal to carbamazepine and better than that of valproate. The design of compounds was in following way. Compounds **9a-9c** were first prepared to confirm our presumption that the exposure of triazole is very important for the anticonvulsant activity. The triazole exposed (no substitute in 5th position), and the phenyl ring attached to the thiadiazine moiety was

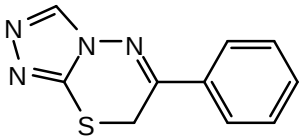
substituted with different electron withdrawing groups and electron releasing groups at different positions expecting to find some compounds with better anticonvulsant activity. The derivatives with chloro group attached to the phenyl ring were the most active of the series. The effect of electron withdrawing groups was found to be uncertain on the anticonvulsant activity. Compounds with electron releasing groups in phenyl ring decreased anticonvulsant activity (Song et al., 2011).



9a



9b



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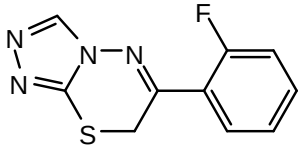
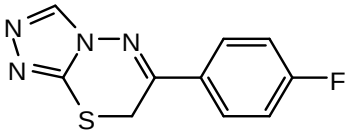
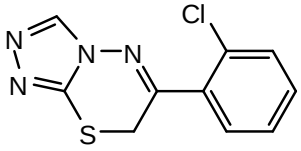


9d



9e



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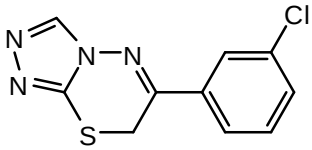
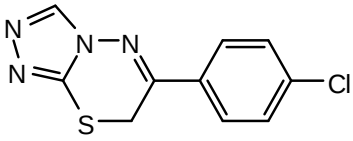
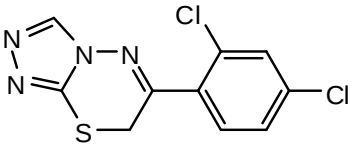


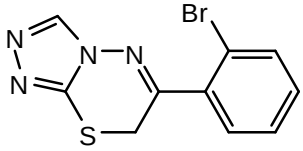
9g



9h



9i



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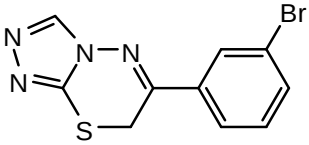

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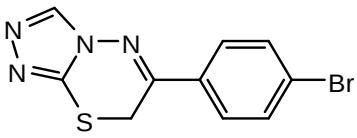
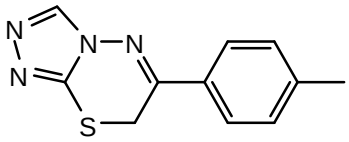
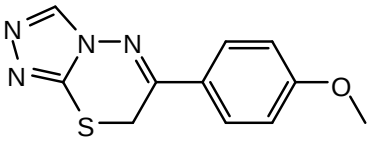


9l



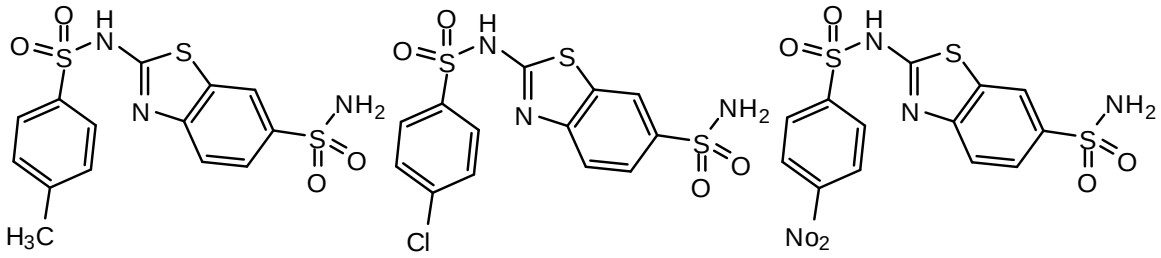
9m



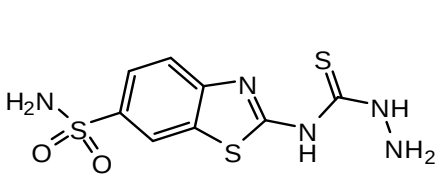
9n

A series of benzothiazole sulfonamides, thiosemicarbazones and guanidine derivatives were synthesized 2-Amino-1, 3-benzothiazole derivatives (**10a-c**, 6-Sulfamido 1,3 benzothiazo 2-yl thiosemicarbazide derivatives **11a-c** and N-[(1, 3-benzothiazole-2-ylamino)(imino) methyl] -nitro benzene sulfonamide **12a-b** by different pathways and tested for the neurotoxicity studies by the Rotarod method. The minimal motor impairment, the significant results were found with compounds (**11c**) and (**10c**). Some of these compounds also showed anticonvulsant activity by decreasing the duration of convulsions in albino mice. Compound (**10c**), (**11c**) and also compound (**10b**) were found to be increased in the onset of convulsion and other test drugs showed moderate

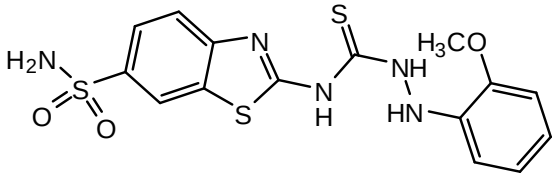
protection and animals were recovered in these groups. Various 2-Amino-1, 3-benzothiazole derivatives (Gunakkunru and Verma. 2007; Jiminet et al., 1994; Maleki and Salehabadi. 2010; Fukuyama et al., 1997). Some compounds were showing positive results in this test. In the minimal motor impairment by rotarod, the significant results were found with (**11c**) and (**10c**). When these test drugs were compared to standard drug diazepam (80.15%), % decrease in fall off time was 49.66%, and 24.96%. The compounds were further screened for anticonvulsant activity by PTZ evoked convulsion. Anticonvulsant studies on some of the compounds were carried out by PTZ animal model (Wagle et al., 2009; Stables and Kupferberg. 1995; Abraham. 2003). In the anticonvulsant screening of test drugs, onset of action and duration of convulsion were observed to show the protection by test drugs. Compound (**10c**) and compound (**11c**) were increasing the onset of convulsion and other test drugs were showing moderate protection, animals were recovered in these groups. Compound (**10b**) was also showing a decrease in duration of convulsion. These compounds are weak inhibitors; they may constitute leads for developing tighter binding compounds and may create a novel interest, in addition to the sulfonamide and sulfamate. The new applications of sulfonamides range from antiglaucoma agents with topical activity, to anticonvulsants, antipain, antiobesity, and antitumor agents/diagnostic tools for cancer. This idea is not widely accepted, there is potential to develop anti-infectives (antimalarials, antifungal, and antibacterial agents) belonging to the CAIs, targeting enzymes from various pathogens. It is thus, foreseeable that novel therapeutic applications will emerge in the near future (Sethi et al., 2011).



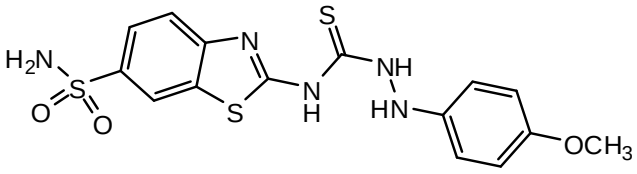
10a **10b** **10c**



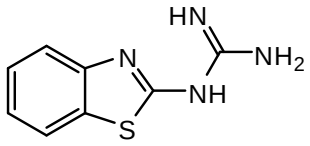
11a



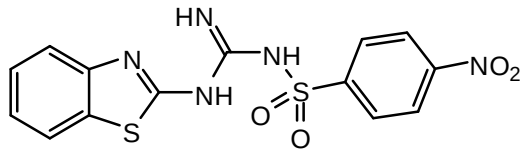
11b



11c



12a



12b

Discussion

Epilepsy affects 1% of world's population according to the epidemiological studies. Currently available AEDs produce satisfactory seizure control in 60–70% of patients (Perucen. 1996; Strine, et al., 2005). Several new AEDs like oxacarbazepine, vigabatrin, lamotrigine, gabapentin, topiramate, felbamate, rufinamide and levetiracetam have been put in clinical practice. Despite familiarity with established AEDs and the introduction of these new agents in the past decade, upto one third of epilepsy patients remain resistant to optimum drug treatment (Sabers and Gram. 2000). These facts triggered the search for newer more effective and less toxic AEDs. Only 75-80% of epileptic patients may be provided with adequate seizure control with the help of the available AEDs. The therapeutic failure in 20-25% of patients and serious side effects in the available AEDs have stimulated intensive research on novel AEDs (Spear. 2001; Bootsma et al., 2009; Kennedy and Lhatoo. 2008). The 1,2,4-triazole nucleus is incorporated in wide variety of therapeutically agents, such as antimicrobial (Eswaran et al., 2009; Bayrak et al., 2009), anticonvulsant (Chen et al., 2007; Deng et al., 2010) and enzyme inhibition activities (Zhou et al., 2009; Owen et al., 2007). Although the current drugs provide adequate seizure control in many patients, it is roughly estimated that up to 28-30% of patients are poorly treated with the available AEDs (Kwan and Brodie. 2000; Spear. 2001). Many AEDs have serious side effects (Rémi et al., 2010; Meador. 2003; Belcastro et al., 2010; Bootsma et al., 2009; Kennedy and Lhatoo. 2008; Penovich and Willmore. 2009), and lifelong medication may be required. Toxicity, intolerance, and lack of efficacy are the limitations of the current AEDs. Therefore, the continued search for safer and more effective new AEDs is necessary (Loscher and Schmidt. 1994; Scheuer and Pedley. 1990).

Conclusion

In past years the discovery and development of antiepileptic drugs (AEDs) have been the noticeable research fields. The search for new compounds combining strong antiepileptic activity is in progress. Many derivatives have been discovered as potent AEDs and the structure activity relationship studies have been reported. The antiepileptic activity of ten newly synthesized in MES models of seizures in rats was investigated. For several decades, AEDs research has focused on identifying new potential AEDs based on their activity against single acute seizures induced by various stimulators, usually in mice and rats. All established have antiepileptic activity in at least MES model. Thus, this test may, in some way distinguish the potential utility of compounds against different seizure types. Antiepileptic drugs have greatly improved the lives of people with epilepsy. Approximately 70% of the patients can achieve complete freedom from seizures with appropriate

treatment. The synthesized compounds confirmed the pharmacophore model requirements for the activity.

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