

Recent Update on 1,3,4-Thiadiazole Derivatives: As Anticonvulsant Agents

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Abstract

1,3,4-thiadiazole is one of the most potent heterocyclic containing carbonic anhydrase and antibacterial inhibitor from the natural and synthetic origin. It possessed potent anticonvulsant activity in wide range preclinical in vitro and in vivo models. Recently, various 1,3,4-thiadiazole derivatives have been synthesized and evaluated their anticonvulsant activity. This review is a demonstration to compile the medicinal chemistry, anticonvulsant screening and their structural activity relationship as well as pharmacophoric pattern of various synthesized 1,3,4-thiadiazole derivatives.

Keywords: 1,3,4-thiadiazole; Anticonvulsant; Structure activity relationship; Mechanism of action

Abbreviations: CNS: Central nervous system; CA: Carbonic anhydrase; SRB: Sulforhodamine B; AAZ: Acetazolamide; MZA: Methazolamide; SAR: Structure-activity relationship; 3D-QSAR: Three dimensional quantitative structure-activity relationships; GABA: γ -Aminobutyric acid; NMDA: N-Methyl-D-aspartic acid; ED50: Effective dose for 50 percent; MES: Maximal electroshock seizure; PTZ: Pentylentetrazol

Introduction

In the last few years, heterocyclic compounds were not only used for development the heterocyclic derivatives, but also argumentation of the application in pharmaceutical and chemical field. Till date various heterocyclic compounds had been synthesized and evaluated for their significance. Firstly, Fischer was introduced 1,3,4-thiadiazole in 1882, whereas Freund and Kuh were described the true nature of the ring. In addition, thiadiazole is a widespread and important five-member heterocyclic system which contains two nitrogen atoms and a sulfur atom. 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole isomer of thiadiazole was discovered and evaluated for the biological activity.

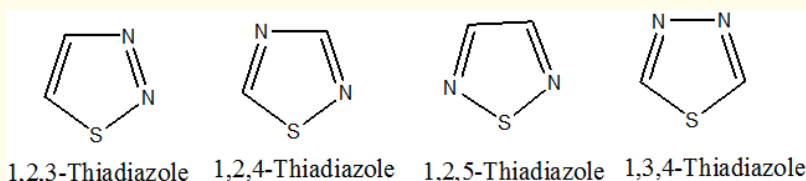


Figure 1: Structural formulae of isomers of thiadiazole.

As per previous literature survey indicated that 1,3,4-thiadiazole have been most promised isomer than the other. Due to the sulfur atom of 1,3,4-thiadiazole ring produced the inductive effect, in this way shown very weak base property and possesses relatively high aromaticity [1-3].

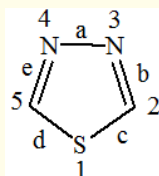


Figure 2: Numbering of the 1,3,4-thiadiazole ring system.

In addition, the nitrogen atoms of 1,3,4-thiadiazole ring is also shown to be very electron underprovided due to the electron-withdrawing effect and comparatively still toward electrophilic substitution, but susceptible to nucleophilic attack. Thus, possessing the substitution into the 2' or a 5' position of this ring and these substitutions involves highly activating reaction.

Till date many 1,3,4-thiadiazole nucleus containing drugs are available in the market such as acetazolamide, methazolamide, megazol and whereas 1,2,4-thiadiazole ring containing drug is the antibiotic cefozopran [4,5].

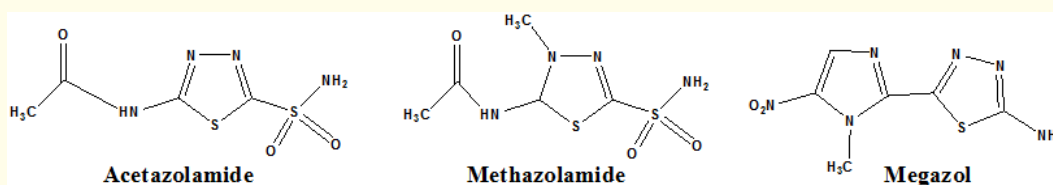


Figure 3: Structural formula of 1,3,4-thiadiazole containing marketed drugs.

Among their isomer, particularly the 1,3,4-thiadiazoles possessed a broad spectrum of biological activities including antimicrobial [6] antituberculosis [7] antioxidant [8] anti-inflammatory [9] anticonvulsants [10] antidepressant and anxiolytic [11] antihypertensive [12] anticancer [13] and antifungal activity [14].

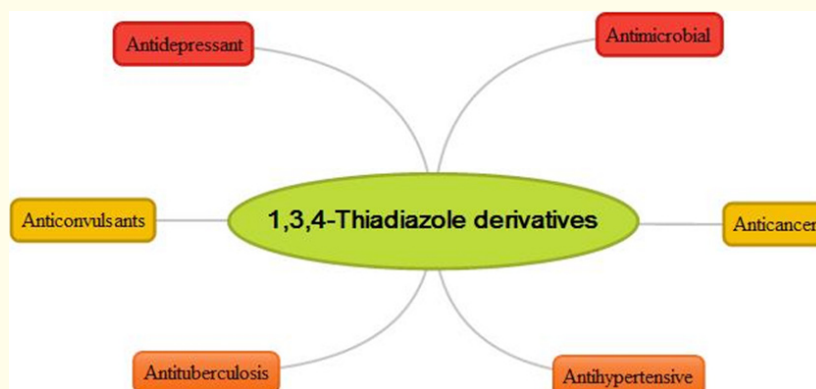


Figure 4: Biological activity of 1,3,4-thiadiazole derivatives.

In this review, We give an overview to synthesis as well as the structure activity relationship of 1,3,4-thiadiazole derivatives. On the basis of the literature survey of cited references 1,3,4-thiadiazole ring contain compound shown the medicinal importance to treatment the epileptic condition.

Mechanism of action of 1,3,4-thiadiazole

Till date various molecular target had been investigated for the treatment of epilepsy as following

Nonsynaptic mechanisms

1. Alterations in ionic microenvironment; e.g., increased extracellular K^+ , decreased extracellular Ca^{++}
2. Decreases in size of extracellular space
3. Failure of ion transport: Na^+ , K^+ pump or Cl^- , K^+ co-transport
4. Presynaptic terminal bursting
5. Ephaptic interactions

Synaptic mechanisms

1. Depression of GABAergic inhibition
2. NMDA receptor activation; voltage-dependent EPSPs
3. Frequency potentiation of EPSPs
4. Actions of modulators

These molecular targets related to blockage of voltage dependent sodium channels to inhibit release of excitatory neurotransmitters, enhanced GABAergic transmission, inhibition of T-type calcium channels or kainite/AMPA receptors and a combination of the above actions [2].

Another approach has been identified in 1952. In which, 1,3,4-thiadiazole containing acetazolamide AZA targets carbonic anhydrase, in the brain has a significant role in the neuroglia metabolic relationship. Carbonic anhydrase acted on the seizure by the mechanism that CAs catalyzes interconversion of CO_2 and HCO_3^- the latter of which combines with hydrogen exchange across the glial membrane for sodium and chloride as well as contributed the current through the γ -amino butyrate A (GABAA) receptors. CAs are also involved in the maintenance of Cl^- and K^+ concentrations in glial cells [15-17].

Essential Pharmacophore for anticonvulsant activity

A pharmacophore based approach is one of the few applicable tools in modern drug design. Which is essential to develop new ligands with high affinity of binding to a given protein receptor. Whereas, this is the 3D arrangement of features in the biologically active compound that is responsible for it's against a particular protein target. On the facts, if the 3D structure is available for several ligands bound to the same binding site of the same protein and in this way, observing their common arrangement of ligands into the binding site of a protein, referred to as the pharmacophore. Thiadiazole ring expressed diverse biological activities, might be due to the presence of N-C-S moiety [18].

SN Pandeya [19] proposed that the following features are important for anticonvulsant activity.

1. Hydrophobic aryl ring (Ar),
2. A hydrogen bonding domain (HBD),
3. An electron-donor group (D) and
4. Another distal hydrophobic site

Review literature of 1,3,4-thiadiazole derivatives as an anticonvulsant

Christopher B Chapleo., *et al.* (1986) [20] synthesized a series of 2-aryl-5-hydrazino-1,3,4-thiadiazole derivatives and evaluated them for anticonvulsant activity. Among them, N-methylhydrazine 1 shown potent anticonvulsant activity in rodent models of grand mal epilepsy and it has neither produced neurotoxicity nor cardiovascular actions occur at anticonvulsant doses.

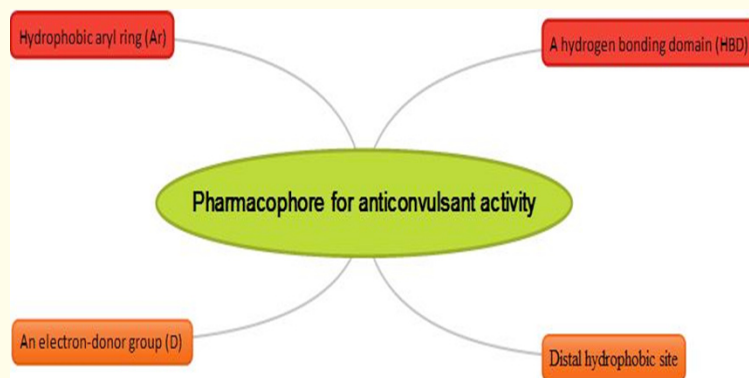


Figure 5: Essential pharmacophoric requirements for anticonvulsant activity.

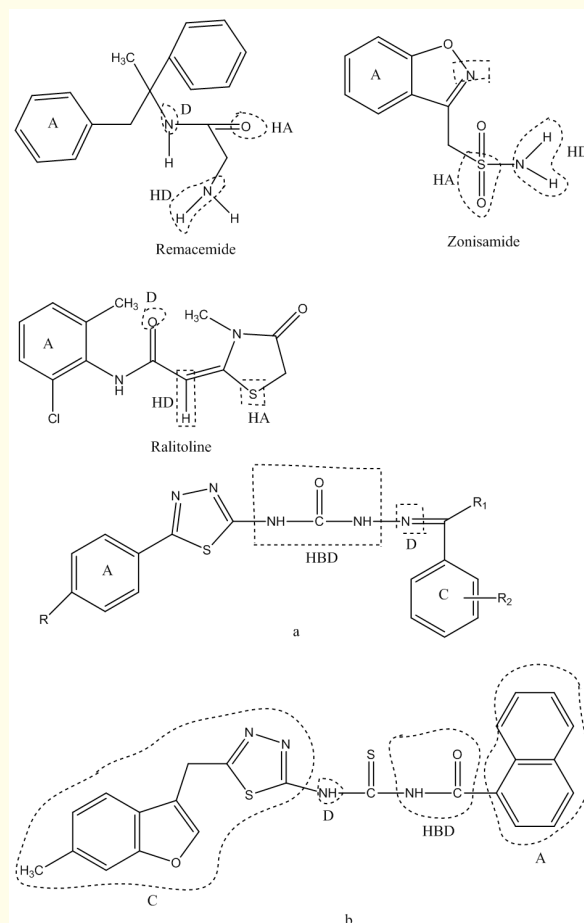


Figure 6: Pharmacophoric pattern of well-known antiepileptic drugs.

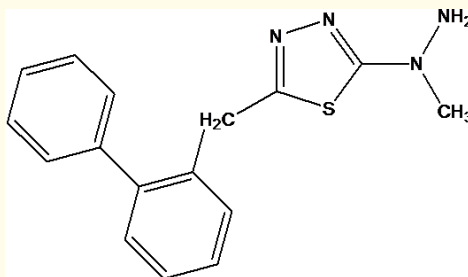
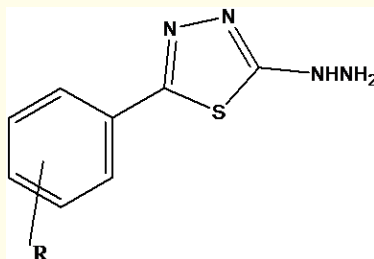


Figure 7: Structure formulae of 2-aryl-5-hydrazino-1,3,4-thiadiazole derivatives.

The SAR study of synthesized compounds reveals that the introduction of aromatic substituted in the 2-position tied with alkyl on the hydrazine moiety led to a number of potent compounds lacking sedation, ataxia, or lethality like as 5-(2-Biphenyl)-2-(1-methylhydrazino)-1,3,4-thiadiazole (1).

(a) Unsubstituted Compounds

Substituent in the 2-position of the aromatic ring produced compounds (i.e., 2-6) shown desirable anticonvulsant activity with significantly reduced neurotoxicity in comparison to the 2-CH₃ compound 2 and replacement of the 2-phenyl group (4) by a 4-phenyl (6) shown a complete loss of activity.

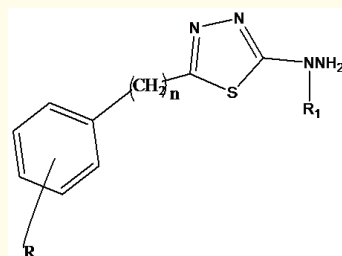


Compounds	R
2	-2-CH ₃
3	2-Cl
4	2-Ph
5	2-C ₆ H ₁₃ O
6	4-Ph

Figure 8: Structure formulae of unsubstituted thiadiazole derivatives.

(b) N'-Monosubstituted Compounds

The one side substitution at N1 in the 2-chloro and 2-phenyl series resulted in a decrease or loss of activity (i.e., CH₃, i-Pr, n-Bu, Ph, CH₂Ph, CH₂CH₂Ph, cyclohexyl). One except benzyl derivative, which possessed a good profile of activity the ether containing group CH₂OCH₃, in place of CH₃ would enhance the activity. The methylhydrazines had shown the most potent anticonvulsant activity in this series, especially the benzyl (7), 2-phenyl (8), and 2-hexyloxy (9) derivatives, although the latter produced sedation as observed in the rotorod screen.

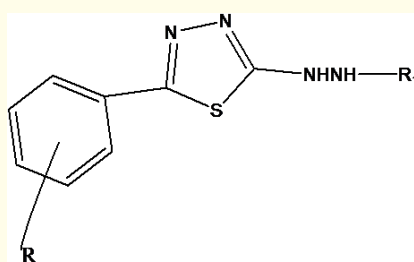


Compounds	R	R ₁	n
7	H	CH ₃	1
8	2-Ph	CH ₃	0
9	2-C ₆ H ₁₃ O	CH ₃	0

Figure 9: Structure formulae of mono substituted thiadiazole derivatives.

(c) N₂-Monosubstituted Compounds

The isopropyl derivatives 10, 11 and 12 shown significant anticonvulsant activity; loss of activity observed when introduces 2-hexyloxy substitution in the 13 compound. Unexpectedly, the methyl derivative 14 was shown the loss of anticonvulsant activity in the 2-CH₃ series and retained some of the antihypertensive activity. From the above suggestion, that better activity could be expected if the isopropyl group was replaced by cyclopentyl or benzyl groups.

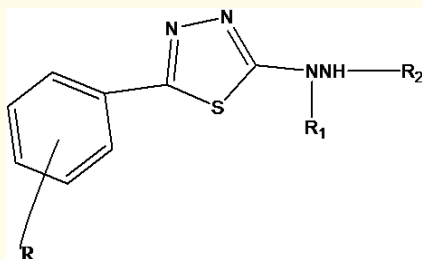


Compounds	R	R ₁
10	2-CH ₃	i-Pr
11	2-Cl	i-Pr
12	2-Ph	i-Pr
13	2-C ₆ H ₁₃ O	i-Pr
14	2-CH ₃	CH ₃

Figure 10: Structure formulae of N₂-Monosubstituted thiadiazole derivatives.

(d) N', N₂-Disubstituted Compounds

Potent anticonvulsant activity was produced when the disubstitution with lower alkyl groups in the 2-CH₃ and 2-C₁ series compounds. Although, in the 2-phenyl and 2-hexyloxy series (i.e., 14-17) the potency was somewhat reduced and sedation was not apparent. The position of the isopropyl group in attached to N₂, shown the activity in the following compounds 15,16,18,19, and excepted then 20,21. When the isopropyl group was replaced by the more lipophilic cyclopentyl group (i.e, 22 and 23), then the activity was reduced.

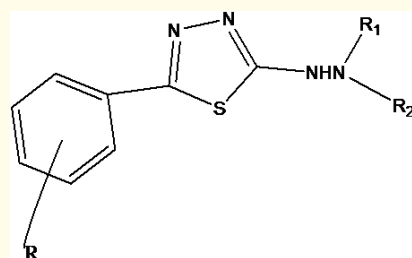


Compounds	R	R ₁	R ₂
15	2-Ph	CH ₃	i-Pr
16	2-C ₆ H ₁₃ O	CH ₃	CH ₃
17	2-C ₆ H ₁₃ O	CH ₃	i-Pr
18	2-CH ₃	CH ₃	i-Pr
19	2-Cl	CH ₃	i-Pr
20	2-CH ₃	i-Pr	CH ₃
21	2-Cl	i-Pr	CH ₃
22	2-CH ₃	CH ₃	c-C ₅ H ₉
23	2-Cl	CH ₃	c-C ₅ H ₉

Figure 11: Structure formulae of *N',N₂*-Disubstituted thiadiazole derivatives.

(e) N₂-Disubstitution

Reduction in activity was found when disubstitution on the terminal nitrogen atom with the respective CH₃-series.

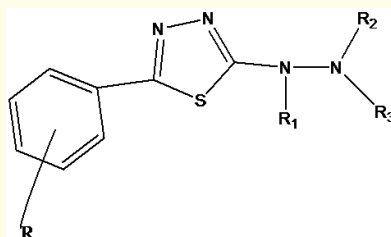


Compounds	R	R ₁	R ₂
24	2-CH ₃	CH ₃	CH ₃
25	2-CH ₃	CH ₃	i-Pr

Figure 12: Structure formulae of *N₂*-Disubstitution thiadiazole derivatives.

(f) Trisubstitution

It was observed that the trimethylated derivatives 26, 27 and 28 have somewhat anticonvulsant activity compared than other compounds of this series. Substitution of the methyl group on *N'* by larger groups considerably reduced this activity as seen with 29 and 30. Among of all the hydrazines examined, the most promising profile of activity is found in compounds based on the 2-Ph series.



Compounds	R	R ₁	R ₂	R ₃
26	2-CH ₃	CH ₃	CH ₃	CH ₃
27	2-CH ₃	PhCH ₃	CH ₃	CH ₃
28	2-Cl	CH ₃	CH ₃	CH ₃
29	2-Cl	i-Pr	CH ₃	CH ₃
30	2-CH ₃	CH ₃	CH ₃	CH ₃

Figure 13: Structure formulae of Trisubstitution thiadiazole derivatives.

Michael R Stillings, *et al.* (1986) [21] synthesized a series of substituted 1,3,4-thiadiazoles derivatives and evaluated for the anti-convulsant activity. Among them, the most potent 2-(aminomethyl)-5-(2-biphenyl)-1, 3, 4-thiadiazole (31) compound showed anti-convulsant activity in both rats and mice and compared with the standard anticonvulsant drugs phenytoin, phenobarbital, and carbamazepine. This compound was produced 6.5 protective index (PI) (TD_{50} divided by ED_{50} i.p. at time of peak effect) as the compared phenytoin, phenobarbital, and carbamazepine were 7, 4.8, and 11, respectively.

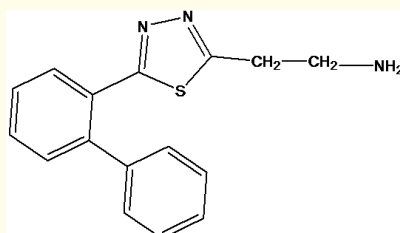
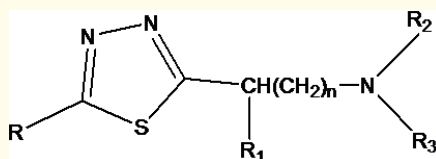


Figure 14: Structure formulae of 1,3,4-thiadiazole derivatives.

SAR study of the synthesized compounds reveals that the introduction of alkylation of the side-chain nitrogen atom produced the potent compound. However, aryl substitution or chain lengthening decrease the activity. Replacement of 2-biphenyl group by phenyl or benzyl caused loss of anticonvulsant activity. Whereas, the n-propylamino derivative (32) was devoid of anticonvulsant activity. The branched-chain substitution of derivative (33) still retained significant activity. Further introduction of aryl group in compound 34 and another 2-biphenyl group of substitution in the phenyl (35) and benzyl (36) derivatives shown the lack of another approach was found if the 2-phenyl group into the benzyl derivative to give the biphenylmethylene compound (19) caused a marked increase in activity. Introduction of the 2-biphenyl moiety in compounds 16 and 17, which showed some anticonvulsant activity.



Compounds	R	R ₁	R ₂	R ₃	n
32		H	H	CH ₃	0
33		H	H	H	2
34		CH ₃	H	H	0
35		H	H		0
36		H	H	H	0
37		H	H	CH ₃	0
38		H	H	H	0
39		H	H	H	0

Figure 15: Structure formulae of Substituted 1,3,4-Thiadiazoles.

Christopher B Couple., *et al.* (1987) [22] synthesized a series of 2-aryl-5-guanidino-1,3,4-thiadaizole derivatives and screened them for anticonvulsant activity. Among them unsubstituted guanidine (40) showed potent anticonvulsant activity in the rat MES model and the level of neurotoxicity shown in acceptable range.

SAR study of synthesized compounds reveals that 40 is the most potent anticonvulsant agent than the other compounds of this series. Considerable of substituted guanidines is an essential key to the reduction or loss of activity of synthesized derivatives. Inter-tilization of the guanidine group into an imidazoline ring also resulted in a loss of activity. However, with the exception of methylated derivative 41, the terminal of methyl group with the substituted guanidines were found to reduction or complete loss of activity and the guanidine grouping into an imidazoline ring also devoid of anticonvulsant activity.

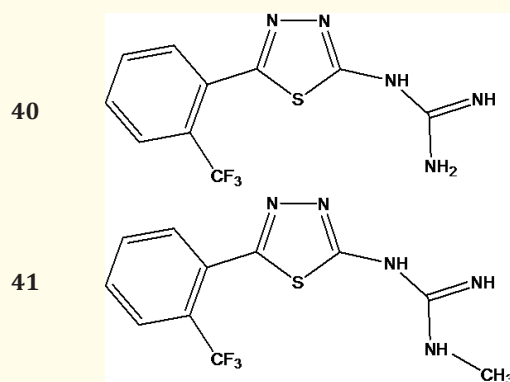
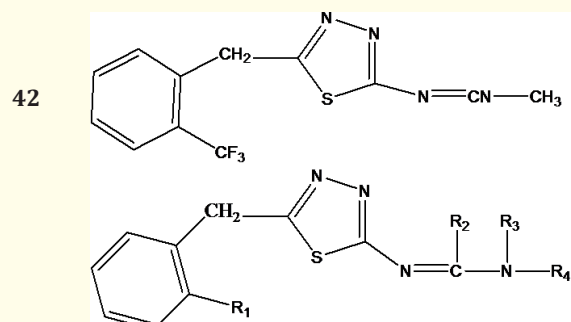


Figure 16: Structure formulae of 2-aryl-5-guanidino-1,3,4-thiadaizole derivatives.

Christopher B Chapleo., *et al.* (1988) [23] synthesized two novel series of 2-aryl-1, 3, 4-thiadiazole amidines and evaluated for anticonvulsant activity using by MES model. Among them the most potent 42 compound occurred in the 5-[2 (trifluoromethyl) phenyl] series, but the level of sedation was also high. Whenever, the 2-methyl series it was found that the N-butyl analogue 43 possessed higher anticonvulsant activity and lesser neurotoxic effects than the parent amidine 44. The N-substituted analogues 45-47 are also more significant effect in the MES test than 44, but less so than 43. However, in the 2-trifluoromethyl series, the parent amidine containing possessed slightly higher anticonvulsant activity than the N-butyl analogue, although both compounds possessed a similar level of neurotoxicity. A similar finding was observed in the 2-phenyl series 48-49 (MES test).

HN Dogan., *et al.* (2002) [24] synthesized two new series of 2,5-disubstituted-1,3,4-thiadiazoles derivatives and evaluated them for anticonvulsant activity. Among these compounds, 50 (90%) and 51 (70%) showed maximum protection at a dose of 100 mg/kg i.p. against pentylenetetrazole induced convulsions. The ED₅₀ values of the most effective compounds, 50 and 51 were 33 and 66 mg/kg, respectively. The lower dose (50 mg/kg) was ineffective (50: 50% and 51: 40%) and the higher dose (150 mg/kg) did not increase the efficiency (50: 90% and 51: 70%). Therefore the dose of 100 mg/kg was selected as the best one.

Archana., *et al.* (2002) [25] synthesized a series of 3-[[5-(alkylbenzylideneamino)-1,3,4-thiadiazol-2-yl]methylamino]-2-methyl-6-monosubstituted quinazolin-4(3H)-one and evaluated them anticonvulsant activity using by in MES models and PTZ model also. Among them the most active compound was 3-[[4-[2-(m-methoxy-phydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl]methylamino]-2-methyl-6-bromo-quinazolin-4(3H)-one (52).



Compounds	R ₁	R ₂	R ₃	R ₄	n
43	CH ₃	CH ₃	nBu	H	0
44	CH ₃	CH ₃	H	H	0
45	CH ₃	CH ₃	Ph	H	0
46	CH ₃	CH ₃	C ₂ H ₅	C ₂ H ₅	0
47	CH ₃	CH ₃		C ₂ H ₅	0
48	Ph	CH ₃	H	H	0
49	Ph	CH ₃	nBu	H	0

Figure 17: Structure formulae of 2-aryl-1, 3, 4-thiadiazole amidines.

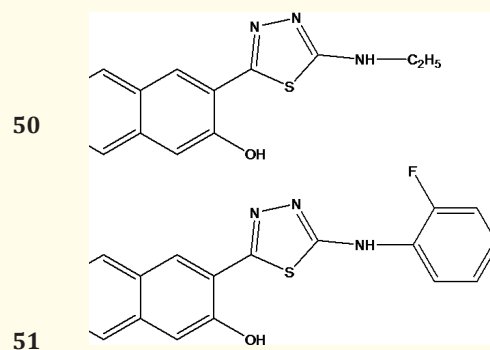


Figure 18: Structure formulae of 2,5-disubstituted-1,3,4-thiadiazoles derivatives

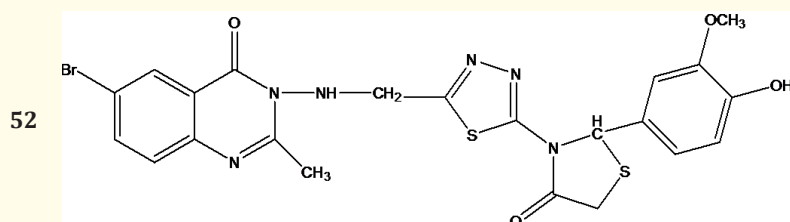


Figure 19: Structure formulae of 3-[[5-(alkylbenzylideneamino)-1,3,4-thiadiazol-2-yl]methylamino]-2-methyl-6-monosubstituted quinazolin-4(3H)-one

Hatice N Dogan., *et al.* (2002) [26] synthesized two new series of 2,5-disubstituted-1,3,4-thiadiazoles and evaluated them for anticonvulsant activity. Among them, compounds 53 (90%) and 54 (70%) showed maximum protection. The acetylation of thiadiazoles retained anticonvulsant effectiveness to a lesser degree. The ED₅₀ values of these compounds were 33 and 66 mg/kg, respectively. Therefore the dose of 100 mg/kg was selected as the best one.

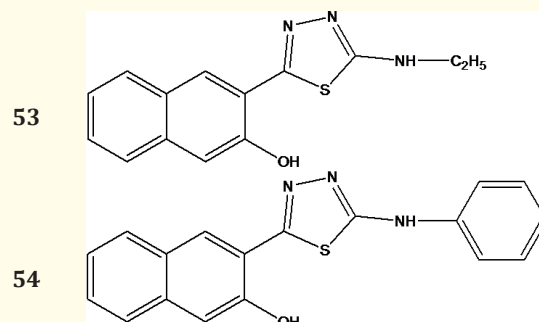


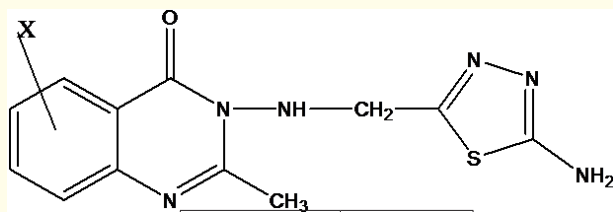
Figure 20: Structure formulae of 2,5-disubstituted-1,3,4-thiadiazole.

Archana., *et al.* (2004) [27] synthesized a novel series of substituted quinazolinonyl-2-oxo/thiobarbituric acid and performed screened for their anticonvulsant activity in MES and PTZ models. Among them the most potent compound 66, showed activity (90%) compared than the standard drug. Compounds 55-58 showed more potent activity (40–60% in MES and 40–50% in PTZ models). Whereas, compounds 59-66 produced good percentage protection ranging from 60 to 90% in both models (MES and PTZ). Among them, compound 66 is the most potent anticonvulsant compound which possess same percentage protection at lower doses of 17.5 and 25 mg/kg i.p. (20 and 40% protection in MES model, respectively) and different inhibition of seizures at a higher dose at 50 mg/kg i.p. (80 and 90% inhibition in MES model, respectively). This compound, in PTZ model in three graded doses was exhibited protection of 20, 30, 80% and 20, 50, 90%, respectively.

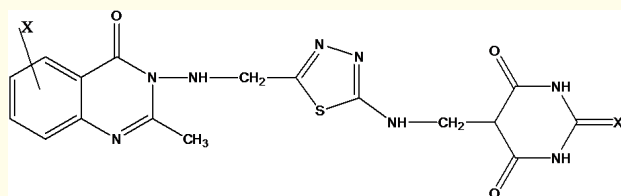
The SAR study of the synthesized compound reveals that the introduction dibromo group at the 6th and 8th positions of quinazolinone nucleus was found to increase the anticonvulsant activity. Whenever, cyclization of intermediate into corresponding thiadiazole was found to be fruitful as the presence of this five membered ring showed considerable increase in Percentage inhibition of seizures. Furthermore, incorporation of 2-oxo/thiobarbituric acid in 55-58 was found to increase the potency of these compounds and resulted into the formation of 59-66, respectively, with high anticonvulsant activity.

MA Ilies., *et al.* (2004) [28] synthesized a series of aromatic/heterocyclic sulfonamides incorporating adamantyl moieties and evaluated for the anticonvulsant activity using by a MES test in mice. After intraperitoneal injection (30 mg kg⁻¹), among them compound 67 exhibited a high protection against electrically induced convulsions at a dosage of: 20,10,5 and 2.5 mg/kg. (> 90%). Their ED₅₀ was 3.5 mg kg⁻¹.

KM Dawood., *et al.* (2006) [29] synthesized newly benzotriazole derivatives and screened them for anticonvulsant activity in maximal electroshock seizure (MES) and subcutaneous metrazole (ScMet) test in mice. Among them compounds 68 and 69 were found to be active in ScMet only, whereas the test compounds 70 was active in MES.



Compounds	X
55	H
56	6-I
57	6-Br
58	6,8-Br ₂



Compound	X	X ¹
59	H	O
60	6-I	O
61	6-Br	O
62	6,8-Br ₂	O
63	H	S
64	6-I	S
65	6-Br	S
66	6,8-Br ₂	S

Figure 21: Structure formulae of substituted quinazolinonyl-2-oxo/thiobarbituric acid.

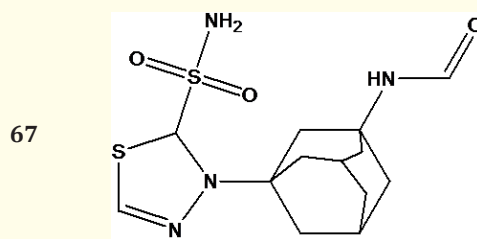


Figure 22: Structure formulae of 5-(Adamantan-1-yl-carboximido)-4-methyl-Δ2-1,3,4-thiadiazoline-2-sulfonamide

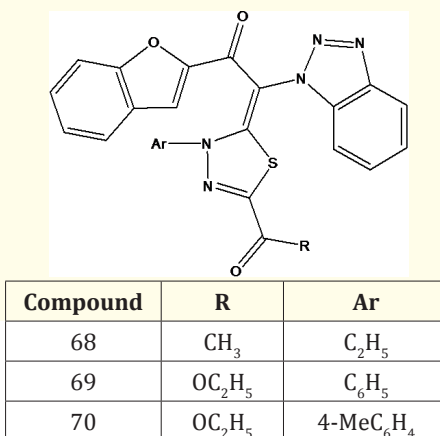


Figure 23: Structure formulae of benzotriazole derivatives.

Foroumadi A., *et al.* (2007) [30] synthesized a series of a novel 2-amino-5-[4-chloro-2-(2-chlorophenoxy)phenyl]-1,3,4-thiadiazole derivatives and evaluated for their anticonvulsant activity by a lethal doses of pentylenetetrazole (PTZ) and maximal electroshock (MES). Among them the synthesized compounds, 5-[4-chloro-2-(2-chlorophenoxy)phenyl]-N-ethyl-1,3,4-thiadiazol-2-amine 71 was the most active compound in both MES and PTZ tests with an ED₅₀ of 20.11 and 35.33 mg/kg, respectively. Whereas, Compound 5-(4-chloro-2-(2-chlorophenoxy) phenyl)-N-ethyl-1,3,4-thiadiazol-2-amine 72 was the most active compound in both MES (ED₅₀ = 20.11) and PTZ (ED₅₀ = 35.33) tests.

The SAR study of synthesized compounds reveals that the introduction of unsubstituted amino group exerted inactive in both PTZ and MES tests. The replacement of the amino group with a methyl group led to slight increase in the activity of the compound in MES, as similar the presence of ethyl group increased the activity in both MES and PTZ. On the other hand, substitution of the amino group by a phenyl moiety produced inactive compounds in both tests. These result concluded that in 2-amino-1,3,4-thiadiazoles substituted by a hydroxynaphthyl group at position 5, showed the higher protection.

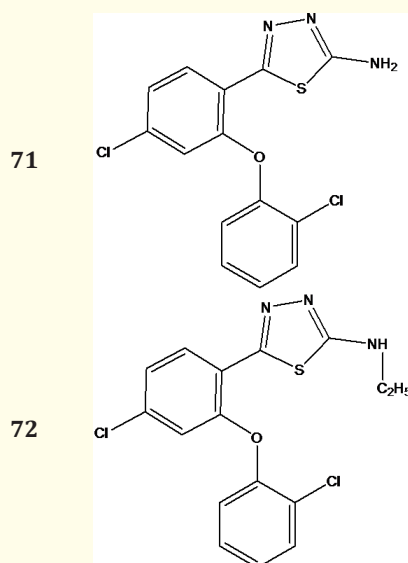
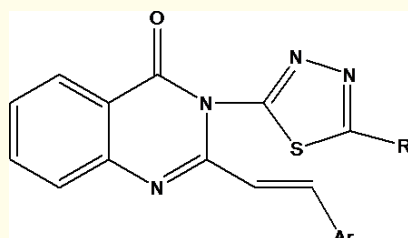


Figure 24: Structure formulae of 2-amino-5-[4-chloro-2-(2-chlorophenoxy)phenyl]-1,3,4-thiadiazole

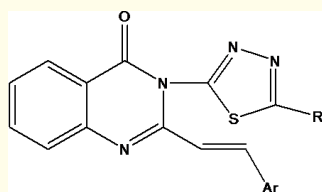
Sushil Kashaw, *et al.* (2008) [31] synthesized a series of novel 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones derivatives and evaluated them for anticonvulsant activity employing two model (the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models) in mice at doses of 30, 100, and 300 mg/kg body weight. Compounds 73,74,75,76,77 and 78 were found to exhibit anticonvulsant activity in MES screen, among of them, compound 73 showed potency similar to standard drug (phenytoin, carbamazepine) without any neurotoxicity. Whereas, compound 74 showed activity in the MES screen after 0.5h (100 mg/kg). This compound exhibited rapid onset of action and long duration of activity.



Compound	Ar	R
73	C ₆ H ₅	C ₆ H ₅
74	C ₆ H ₅	p-ClC ₆ H ₅
75	C ₆ H ₅	m-ClC ₆ H ₅
76	p-OCH ₃ C ₆ H ₅	p-OCH ₃ C ₆ H ₅
77	p-OCH ₃ C ₆ H ₅	m-ClC ₆ H ₅
78	p-CH ₃ C ₆ H ₅	p-ClC ₆ H ₅

Figure 25: Structure formulae of 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones derivatives

Sushil Kashaw, *et al.* (2008) [32] synthesized a new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones derivatives and screening them for anticonvulsant activity after i.p. injection doses 0.01 ml/g body weight for mice or 30, 100, and 300 mg/kg body weight for rat and examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. Among them, compounds 79,80 and 81 showed anticonvulsant activity in one or more test models.



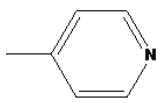
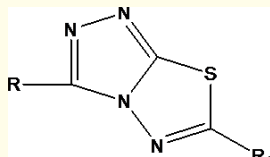
Compounds	Ar	R
79	p-ClC ₆ H ₄	C ₆ H ₅
80	p-ClC ₆ H ₄	m-ClC ₆ H ₄
81		p-ClC ₆ H ₄

Figure 26: Structure formulae of 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones derivatives.

Asif Husain, *et al.* (2009) [33] synthesized a series of 3,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives and evaluated for their anticonvulsant activity and neurotoxicity. In anti-MES activity compounds 82,83,84 and 86 showed potent activity comparable to that of standard drugs: phenytoin and carbamazepine. Compound 84 successfully passed the rotorod test without any sign of neurological deficit. SAR study of the synthesized compounds reveals that the halo-substituted aryl (bromophenyl) in position 6 of the triazolothiadiazole ring was essential for the activity. Thus a number of 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives exhibited anticonvulsant activity in the MES screen. Some compounds like 82, 83, 84, 85, 86 and 87 showed more lipophilic character and were more active.



Compounds	R	R1
82	C ₆ H ₅ CH ₂ -	2-Br C ₆ H ₄ -
83	C ₆ H ₅ CH ₂ -	C ₁₀ H ₇ CH ₂
84	C ₆ H ₅ OCH ₂ -	4-Br C ₆ H ₄ -
85	C ₆ H ₅ OCH ₂ -	C ₈ H ₆ NCH ₂ -
86	2-OHC ₆ H ₄ -	3-BrC ₆ H ₄
87	2-OHC ₆ H ₄ -	C ₁₀ H ₇ CH ₂ -

Figure 27: Structure formulae of 3,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives.

Mohammad Shahar Yar, *et al.* (2009) [34] synthesized a series of five membered heterocyclics and evaluated for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer. Among the synthesized compounds, (88) 2-(4-chlorophenyl) amino-5-(4-pyridyl)-1,3,4-thiadiazole was found promising compounds of the series after administration of 25 mg/kg of test compounds.

88

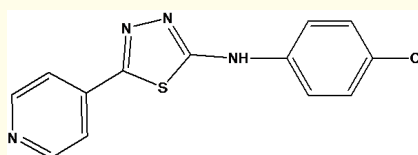


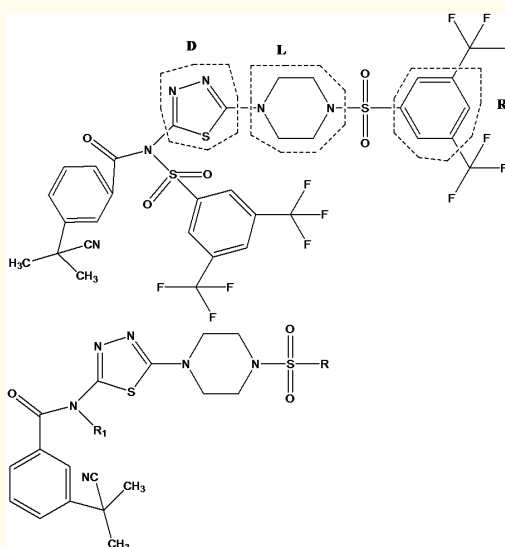
Figure 28: Structure formulae of 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole.

Nadeem Siddiqui, *et al.* (2009) [35] synthesized a series of 2,5-disubstituted-1,3,4-thiadiazole derivatives and evaluated for their anticonvulsant activity in MES test. Whenever, Rotorod method was used to determine the neurotoxicity. Among them compounds (89), (90), and (91) produced significant protective effect on MES induced seizure. Whereas other remains compounds showed moderate protective effect. All the compounds were evaluated for their neurotoxicity using rotorod method given in the dose of 100 mg/kg. None of the compounds showed neurotoxicity.

The SAR study of synthesized compounds reveals that different electron donating or electron withdrawing groups attached to phenyl ring as substituent linked to sulfonyl group are studied for anticonvulsant efficacy. It has been investigated that compounds bearing the groups like nitro, phenoxy and halogens on phenyl ring possess high potency in MES. The result of these compounds concluded that the introduction of a piperazine group at position 5 of thiadiazole ring and 3,5-bis(trifluoromethyl) positions of the benzenesulfonyl

moiety (compound (89)) showed the best anticonvulsant activity. Whereas, compounds (90) and (91) possessing trifluoromethyl substituent at different positions of the benzenesulfonyl moiety showed good anticonvulsant activity in the MES model. Both compounds did not exhibit neurotoxicity at the highest administered dose. Further introduction of nitro group and halogen groups showed moderate anticonvulsant activity. The presence of cyano group at aryl ring has moderate activity. Although naphthalene group, dimethyl, and tert-butyl, were moderately active in the MES test; compounds with phenyl ring exhibited considerable anticonvulsant activity in comparison to methyl group.

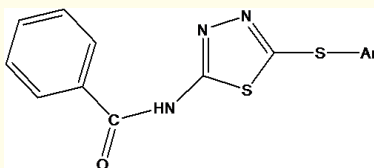
These observation suggested that compound having electron withdrawing groups, produced excellent anticonvulsant activity. It has been established that there are at least three parameters for anticonvulsant drugs, that is (i) lipophilic domain (L), (ii) hydrophobic unit (R), and (iii) electron donor (D) system. Thus the proposed pharmacophore model for (89) includes all the above factors important for bioactivity. Therefore, the nature of groups in sulfonyl moiety is very important for anticonvulsant activity in MES model.



Compounds	R	R1
89		
90		
91		

Figure 29: Structure formulae of 2,5-disubstituted-1,3,4-thiadiazole derivatives.

Priyabrata Pattanayak, *et al.* (2009) [36] synthesized a series of thiadiazole derivatives and evaluated them for the anticonvulsant activity. Among the synthesized compounds 92,93 and 94 were found to possess significant anticonvulsant activity in both models.

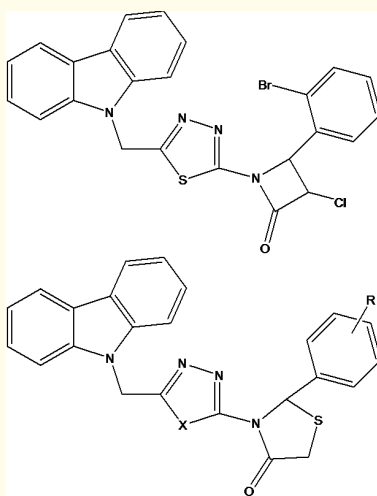


Compounds	Ar
92	4-C ₆ H ₄ SO ₂ Cl
93	4-C ₆ H ₄ SO ₂ NH ₂
94	4-C ₆ H ₄ F

Figure 30: Structure formulae of 2-amino-5-sulfanyl-1,3,4-thiadiazoles.

Hemlata Kaur, *et al.* (2010) [37] synthesized a novel series of substituted oxa/thiadiazolylazetidinyll/ thiazolidinonylcarbazoles derivatives and screened for anticonvulsant activities. In the synthesized series compound 99 showed promising anticonvulsant activity. Thiadiazole ring containing compounds was showed better biological activities than compounds having oxadiazole ring. In these compounds, 100 showed potent (80%) anticonvulsant activity as well as compounds 95-99 showed good anticonvulsant response when compared to the other compounds and the reference drugs.

100



Compounds	R	X
95	4-OH	S
96	2,4-OH	S
97	4-OH,3-OCH ₃	S
98	4-N(CH ₃) ₂	S
99	2-Br	S

Figure 31: Structure formulae of substituted oxa/thiadiazolylazetidinyll/thiazolidinonylcarbazoles

Harish Rajak., *et al.* (2010) [38] synthesized a novel series of N1-{5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]}-N4-(4-substituted benzaldehyde)-semicarbazones, N1-{5-[(1H-indol-3-yl methyl)-1,3,4-thiadiazol-2-yl]}-N4-[1-(4-substituted phenyl)ethanone]-semicarbazones and N1-{5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]}-N4-[1-(4-substituted phenyl) (phenyl) methanone]-semicarbazones and evaluated for their anticonvulsant potential using maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) models. The minimal motor impairment (neurotoxicity) evaluated by rotorod test. Among them, compound N1-{5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]}-N4-[1-(4-hydroxyphenyl)(phenyl) methanone]-semicarbazone 101 showed the most active compound in maximal electroshock seizure (at 100 mg/kg after 0.5h and at 300 mg/kg after 4.0h) and subcutaneous pentylenetetrazole model (at 300 mg/kg after 4.0h) without any neurotoxicity (up to 300 mg/kg after 4.0h).

The SAR study of synthesized compounds reveals that the introduction of hydroxy and nitro group on distant phenyl ring showed high potency in MES and scPTZ tests, whereas replacement of these groups with methoxy and chloro groups on the distant phenyl ring has resulted in compounds with a decrease in anticonvulsant activity. These results concluded that anticonvulsant activity of test compounds changes on varying *p*-substituted group on aryl moiety as follows: hydroxy > nitro > methoxy > chloro > methyl group.

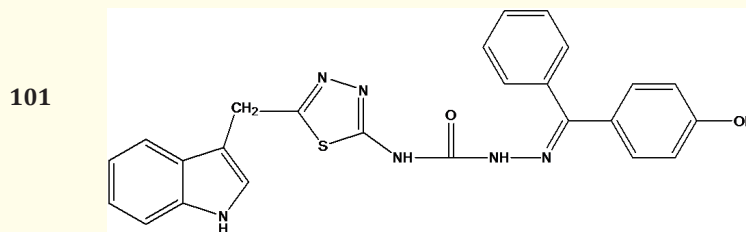


Figure 32: Structure formulae of 2,5-disubstituted 1,3,4-thiadiazoles.

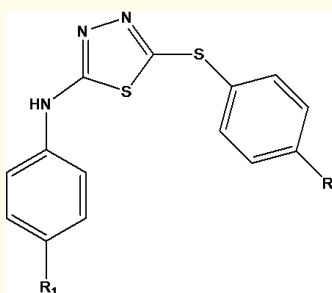
Rajesh Sharma., *et al.* (2011) [39] synthesized a new series of 2-amino-5-sulfanyl-1,3,4-thiadiazole and screened for anticonvulsant activity. Among them compounds 102,103,104,105 and 106 exhibited significant anticonvulsant activity.

The SAR study of synthesized compounds reveals that substitution of sulphonamide group on R position and chloride group on R1 position in compound 102, appreciable anxiolytic and anticonvulsant activity but little effect on antidepressant activity. Whereas compound 103 having sulphonamide group on R position and fluoride group on R1 position produced significant effects on CNS (antidepressant, anxiolytic and anticonvulsant). Compound 104 having sulphonyl chloride group on R position and trifluoro methyl group on R1 position exerted maximum activity among all compounds. Among the halogen (electron-withdrawing group) substituted compounds only compound having fluoride or trifluoromethyl group and up to some extent chloride group (compound 102 showed anxiolytic and anticonvulsant activity) on R1 position possessed significant central nervous system activity, the possible reason could be a fluorine atom are small in size, lipophilic in nature and ability to form strong hydrogen bond. Further compound 105 having methyl (electron donating) group on R1 position produced broad range of central nervous system activity (antidepressant, anxiolytic and anticonvulsant).

But in the compound 106 having sulphonyl chloride group on R1 position and sulphonamide group on R position also produced significant CNS (antidepressant, anxiolytic and anticonvulsant).

Nadeem Siddiqui., *et al.* (2011) [40] synthesized a series of thiazole-substituted thiadiazole derivatives using and evaluated them for anticonvulsant activity by using maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) models. Among them three compounds 107,108 and 109 were showed the potent anticonvulsant activity in both the models at the lowest dose 30 mg/kg after 0.5h with comparable ED₅₀ and better TD₅₀ values than some standard drugs. These compounds showed protective indices of 25.8, 11.3, and 43.6 respectively. These compounds were not showed the neurotoxicity but exert lesser toxic effects on liver. Compound 107 and 109 possessed good anti-MES activity with ED₅₀ of 19.1 and 12.6 mg/kg, respectively. The much higher TD₅₀ values exhibited

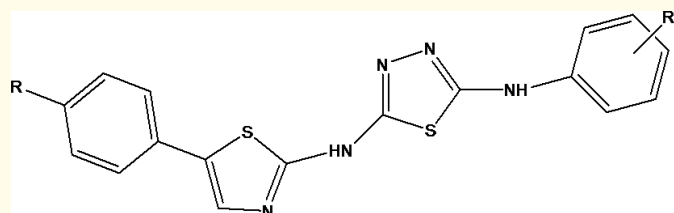
by the compounds 107 as well as in the scPTZ screen compound 107 displayed better ED_{50} values than most of the standard drugs with higher PI.



Compounds	R	R ₁
102	-SO ₂ NH ₂	-Cl
103	-SO ₂ NH ₂	-F
104	-SO ₂ NH ₂	CH ₃
105	-SO ₂ Cl	-CF ₃
106	-SO ₂ NH ₂	-SO ₂ Cl

Figure 33: Structure formulae of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives.

SAR study reveal that the phenyl ring attached to the thiazole moiety was substituted with electron withdrawing groups (NO₂\Br\Cl) effect the activity and the phenyl ring attached to the thiadiazole moiety was substituted with different electron releasing groups at different positions does not have marked effect on the activity. The bromo-substituted derivatives were comparatively more neurotoxic than the other derivatives of the series.

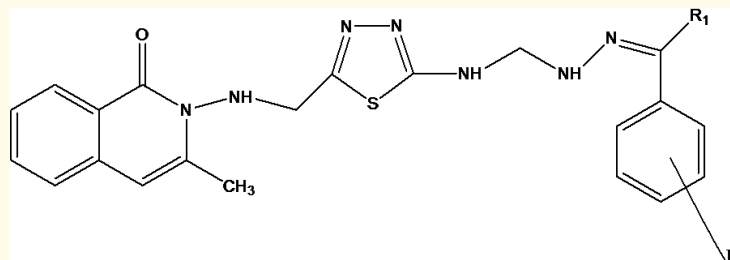


Compounds	R	R ₁
107	Br	4-OCH ₃
108	NO ₂	4-CH ₃
109	NO ₂	4-OCH ₃

Figure 34: Structure formulae of thiazole-substituted thiadiazole derivatives.

Harish Rajak, *et al.* (2012) [41] synthesized a series of novel semicarbazones containing 1,3,4-Thiadiazole and Quinazoline ring and evaluated them for anticonvulsant activity. Among them compounds i.e., 110 and 113-121 produced anticonvulsant activity in the MES screening as compared to 57% of the compounds i.e., 111, 112-114, 116, 117, 119 and 120 in the scPTZ test. Thus, the compounds exhibited some MES selectivity indicating their effectiveness in generalized seizures of the tonic-clonic (grand mal) type. The most potent N1-{5-[[[2-methyl-4-oxoquinazolin-3(4H)-yl] amino]methyl]-1,3,4-thiadiazol-2-yl}-N4-[1-(4-nitrophenyl) (phenyl) methanone] semicarbazone 120 investigated, in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0h) and subcutaneous pentylenetetrazole model (at 300 mg/kg after 4.0 h) without any neurotoxicity (up to 300 mg/kg after 4.0h).

SAR study of synthesized compounds reveals that the introduction of nitro or chloro on distant phenyl ring possesses high potency in MES and scPTZ tests. However, replacement of these substituent with methyl or methoxy groups on the distant phenyl ring show with a decrease in anticonvulsant activity. The result concluded that the antiepileptic activity of test compounds changes on varying p-substituted group on aryl moiety as follows: nitro > chloro > hydroxy > methoxy > methyl group.



Compounds	R	R1	MES Activity	ScPTZ Activity
110	H	4-NO ₂	MES	-
111	H	4-OH	-	ScPTZ
112	H	4-OCH ₃	-	ScPTZ
113	H	4-Cl	MES	ScPTZ
114	CH ₃	4-OH	MES	ScPTZ
115	CH ₃	4-OCH ₃	MES	-
116	CH ₃	4-NO ₂	MES	ScPTZ
117	CH ₃	4-Cl	MES	ScPTZ
118	C ₆ H ₅	H	MES	-
119	C ₆ H ₅	4-OH	MES	ScPTZ
120	C ₆ H ₅	4-NO ₂	MES	ScPTZ
121	C ₆ H ₅	4-OCH ₃	MES	-

Figure 35: Structure formulae of semicarbazones containing 1,3,4-Thiadiazole and Quinazoline ring

Hemlata Kaur, *et al.* (2012) [42] synthesized two series of 2-((2-((5-benzylideneamino)-1,3,4-oxa/thiadiazol-2-yl)methyl)hydrazinyl) methyl)-benzo[b][1,4]oxa/thiazepin-4(5H)-ones, 2-((2-((5-(4-oxo-2-substitutedphenyl)thiazolidin-3-yl)-1,3,4-oxa/thiadiazol-2-yl)methyl)hydrazinyl) methyl)benzo [b] [1,4]oxa/thiazepin-4(5H)-ones and 2-((2-((5-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl)-1,3,4-oxa/thiadiazol-2-yl)methyl)hydrazinyl) methyl) benzo[b][1,4] oxa/thiazepin-4(5H)-ones and evaluated them for the anticonvulsant activity. Among them compound 122 showed the most compound (having 2-bromophenyl ring at 2nd position of thiazolidinone ring) having 90% anticonvulsant activity.

Kikkeri P, *et al.* (2013) [43] synthesized a new pyrazine substituted 1,3,4-thiadiazole derivatives and evaluated for their anticonvulsant activity against maximal electroshock (MES) seizure method at the dose of 100 mg/kg. Neurotoxicity was performed by Rotarod method and the compounds 123 and 124 produced highly significant protective effect similar to that of standard (phenytoin).

The SAR study of these compounds indicate that the introduction of a piperazine group of pyrazine ring and 3, 5-bis(trifluoromethyl) positions of the benzenesulfonyl moiety showed the best anticonvulsant activity in 123. Another approach of substitution in compound 124 contains halogen and thiophene group showed good anticonvulsant activity in the MES model. Both compounds did not exhibit neurotoxicity at the highest administered dose. The results concluded that the introduction of phenyl ring exhibited more anticonvulsant activity in comparison to methyl group.

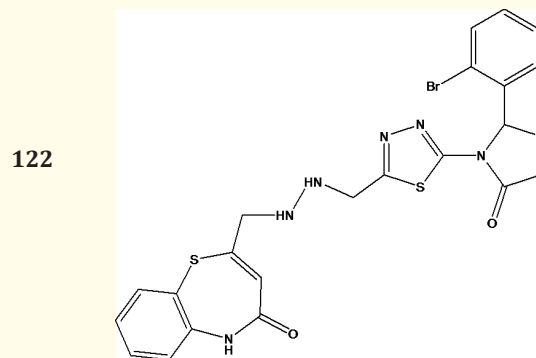


Figure 36: Structure formulae of substituted benzoxazepine and benzothiazepine.

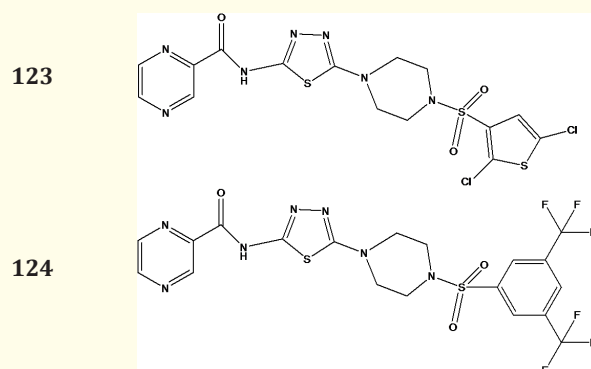


Figure 37: Structure formulae of pyrazine substituted 1,3,4-thiadiazole derivatives.

Kikkeri N Mohana., *et al.* (2013) [44] synthesized a new series of indazole substituted-1,3,4-thiadiazole derivatives and evaluated them for the anticonvulsant activity against maximal electroshock (MES) seizure model in male Wistar rats. Among them, compounds 125 and 126 showed the most potent of this series and no neurotoxicity was found at the maximum dose administered (100 mg/kg).

The SAR study of synthesized compounds reveals that the nature of groups in sulfonyl moiety is very important for anticonvulsant. Different electron donating or electron withdrawing groups attached to phenyl ring as substituent linked to sulfonyl group are investigated for anticonvulsant efficacy. The result concluded compounds bearing the groups like nitro and halogens on phenyl ring possess high potency in MES. The structural activity relationship study of these compounds indicate that the introduction of a piperazine group of thiadiazole ring and 3,5-bis(trifluoromethyl) positions of the benzenesulfonyl moiety exerted best anticonvulsant activity in 125. Compound 126 contains halogen and thiophene group produced good anticonvulsant activity in the MES model activity in MES model.

S Botros., *et al.* (2013) [45] synthesized Hybrids between phenytoin and thiosemicarbazide, 1,3,4-thiadiazole and evaluated them for anticonvulsant activity by using standard maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens in mice. The neurotoxicity was determined applying the rotarod test. All test compounds (127-131) showed varying degree (20-60 %) of anticonvulsant activity in the scPTZ and MES model.

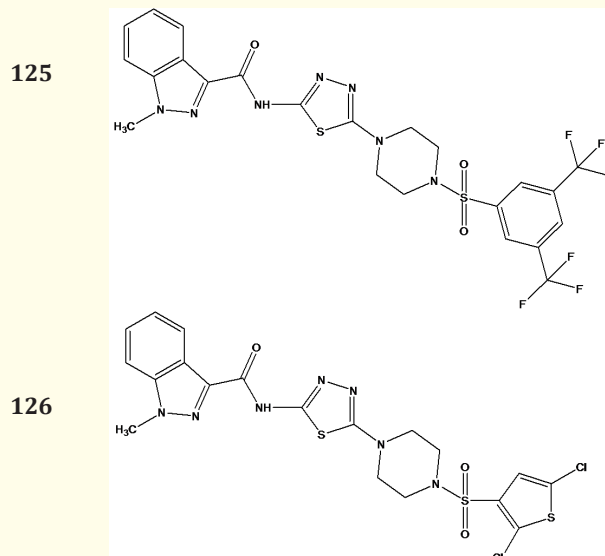
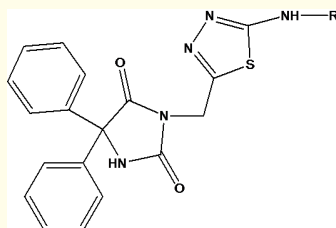


Figure 38: Structure formulae of indazole substituted-1,3,4-thiadiazole derivatives



Compounds	R
127	C ₂ H ₅
128	C ₆ H ₅
129	4-CH ₃ C ₆ H ₄
130	4-OCH ₃ C ₆ H ₄
131	4-ClC ₆ H ₄

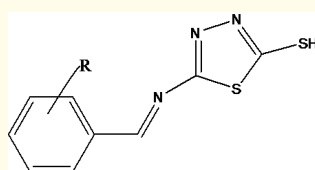
Figure 39: Structure formulae of new phenytoin derivatives.

Mohammad Yusuf, *et al.* (2013) [46] synthesized a novel imines derived and evaluated for anticonvulsant activity. Among them 5-amino-1,3,4-thiadiazole-2-thiol exhibited shows potential anticonvulsant activity. The compounds 5-[1-(4-Chlorophenyl)-3-[4-(methoxy-phenyl)-prop-2-en-1-ylidene]amino]-1,3,4-thiadiazole-2-thiol (139), 5-[[1-(4-chloro-phenyl)]-3-[4-(dimethyl-amino-phenyl)-prop-2-en-1-ylidene]amino]-1,3,4-thiadiazole-2-thiol (140) and 5-[[1-(4-chloro-phenyl)]-3-[(4-amino-phenyl)-prop-2-en-1-ylidene]amino]-1,3,4-thiadiazole-2-thiol(143) showed 100% activity in comparison with standard Acetazolamide drug. Neither compound 140 nor 143 had shown the neurological toxicity in Rotarod and Ethanol Potentiation tests.

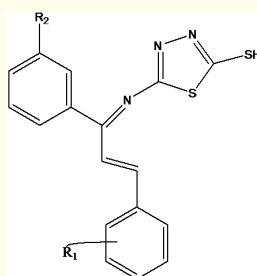
SAR study of the synthesized compounds indicated that thiadiazole ring, free thiol and imine group are part of the main pharmacophore responsible for exhibiting the anticonvulsant activity.

Thiadiazole ring have two nitrogen's at 1, 2 position which formed mesoionic complex with the hydrogen of the hydroxyl group of amino acids threonine (Thr), positioned as Thr-200 and Thr-199 in the polypeptide chain of the hCA-II enzyme. Further investigation of compounds in 132-137 possessed chloro, fluoro and nitro electron withdrawing groups at positions 2 and 4 of the benzyl ring and exhibited average levels of bioactivity. However, compounds 133 and 137 were active at 50% and above in anticonvulsant tests.

Whereas, the compounds in (138-144) shown potent anticonvulsant activity as per sequences-N(CH₃)₂, -NH₂ and OH substitutions, although the introduction by H, OCH₃ and Cl groups reduced the activity. The R₁ substitution at para-position was preferred in comparison with substitution at position 3 (meta) of the C₆ aromatic ring which did not showed enough potency levels. The results concluded that the presence of electron rich and comparatively bulky group with availability of free electrons, such as OCH₃, -N(CH₃)₂ and -NH₂ in comparison with OH, CH₃ and Cl atom at position 4 of the benzene ring away from thiadiazole moiety as preferred substitutions for producing higher biological activity for (138-144) compound. Whenever, the 132-137 compounds having electron-withdrawing group at R position of the benzene ring showed good anti-convulsant activity but in the compounds (138-144), the electron-donating groups at R₁ position and electron-withdrawing groups at R₂ position showed potent anticonvulsant activity.



Compounds	R
132	2-Cl
133	4-Cl
134	2-NO ₂
135	4-NO ₂
136	2-F
137	4-F



Compounds	R ₁	R ₂
138	H	H
139	4-OCH ₃	Cl
140	4-N(CH ₃) ₂	Cl
141	4-Cl	Cl
142	3-OH	Cl
143	4-NH ₂	Cl
144	4-CH ₃	Cl

Figure 40: Structure formulae of 5-Amino-1,3,4-Thiadiazole-2-Thiol Conjugated Imine Derivatives

Rajesh Sharma, *et al.* (2014) [47] synthesized a series of 2-(2-(3-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)yl)acetyl)hydrazine carbothioamide and 2-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-6-(4-chlorophenyl)-4,5-dihydropyridazin-3(2H)-one derivatives and evaluated them for anticonvulsant activity. Among them the compound 145 (85.44 %) showed promising anticonvulsant activity by protection against tonic hind limb extensor phase in maximal electroshock model (MES) at (50 mg/kg) compared to standard drug phenytoin and also showed significant anticonvulsant activity by protection against pentylenetetrazole-induced generalized convulsions in pentylenetetrazole model (PTZ) at (100 mg/kg) compared to standard drug diazepam shown significant anticonvulsant activity against MES and PTZ induced seizure in albino mice after IP administration of 50 and 100 mg/kg body weight dose, respectively.

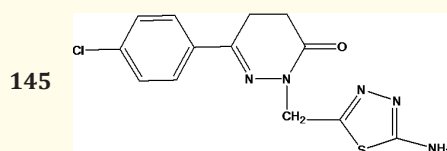
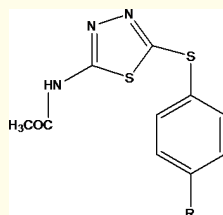


Figure 41: Structure formulae of substituted 1,3,4-thiadiazoles.

K P Harish, *et al.* (2014) [48] synthesized a series of 2-amino-5-sulphonyl-1,3,4-thiadiazole derivatives and evaluated for the anticonvulsant activity. Among them, compounds 146, 147 and 148 exhibited excellent anticonvulsant activity in comparison to the reference drugs.



Compounds	R
146	SO ₂ NH ₂
147	CF ₃
148	F

Figure 42: Structure formulae of 2-amino-5-sulphonyl-1,3,4-thiadiazole derivatives.

Conclusion

Thiadiazole is belong to the triheterocycle template which composed of two electron-deficient carbon atoms these are interconnected with nitrogen atoms, and a sulfur atom with lone electron pairs. However, this compound has an electron-deficient nature and pretty high thermotic stability. Due to this properties, it can hardly react whenever the introduction on the C3' or C5' position of 1,3,4-thiadiazoles are highly reactive. Hence, the nitrogen atoms tend to nucleophilic attack, and the carbon atoms can suffer both nucleophilic substitutions and electrophilic attacks. The introduction of common leaving susitution on the 1,3,4-thiadiazole possessed very higher reactivity.

1,3,4-thiadiazoles exhibit versatile pharmacological activity, specially wide range of derivative shown the most potent anticonvulsant effect against a variety of in vivo animal models. Structure activity relationship of 1,3,4-thiadiazole derivatives indicated that 1,3,4-thiadiazole ring essential for the anticonvulsant activity. Substitution of halogens group containing phenyl on the 1,3,4-thiadiazole derivatives possessed anticonvulsant activity against MES and PTZ models. These results reveal that 1,3,4-thiadiazole and

substituted electrophilic containing phenyl linked with 1,3,4-thiadiazole are the essential pharmacophore for the anticonvulsant activity. On the behalf of existing literature the mechanism of action of 1,3,4-thiadiazole may be demonstrated that means these derivatives increase GABA pathway via release the chloride ions and further control and prevent the firing of neurons in the Brain.

For the development 1,3,4-thiadaizole derivative may be a potent anticonvulsant agent via introducing different kinds of substitution on the nitrogen atoms and ring sulfur atom as well as amino groups and mercapto groups attached to the ring carbon atoms. 1,3,4-thiadiazole is the essential heterocycle which will certainly contribute in medicinal chemistry to the development of new anticonvulsant drug. The continuing focus of chemist to developing the thiadiazole scaffold and used of essential pharmacophores to make low molecular weight medicine with high efficacy and low side effects on the epileptic patient.

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