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Synthesis of New 2,5-Disubstituted-1,3,4-Thiadiazole Derivatives and Their in vivo Anticonvulsant Activity[1]

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Abstract—A series of 2,5-disubstituted-1,3,4-thiadiazole derivatives were synthesized by the reaction of 3-(2-cyanopropan-2-yl)-*N*-(5-(piperazine-1-yl)-1,3,4-thiadiazol-2-yl)benzamide with various sulfonyl chlorides and evaluated for their anticonvulsant activity in MES test. Rotorod method was employed to determine the neurotoxicity. The purity of the compounds is confirmed on the basis of their elemental analysis. The structures of all the new compounds are established on the basis of ^{1}H NMR and mass spectral data. Out of fifteen compounds, three were found to be potent anticolvunstants. The same compounds showed no neurotoxicity at the maximum dose administered (100 mg/kg).

Keywords: 1,3,4-thiadiazole, anticonvulsant, neurotoxicity

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INTRODUCTION

Epilepsy is usually described as a group of common chronic neurological disorders characterized by recurrent unprovoked seizures due to excessive neuronal firing or synchronous neuronal activity in the brain [1]. The known potential causes of epilepsy include brain tumors, infections, traumatic head injuries, perinatal insults, developmental malformations, cerebrovascular diseases, and febrile seizures [2]. The anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also being increasingly used in the treatment of bipolar disorder. Anticonvulsants are more accurately called antiepileptic drugs (AEDs), sometimes referred to as antiseizure drugs.

Several generations of anticonvulsants are available, such as phenytoin, phenobarbital, benzodiazepines, etosuximide, carbamazepine, and valproate. They are useful in the treatment of other diseases, such as neuropathic pain and bipolar disorders, conditions associated with significant morbidity and mortality [3–5]. The newest generation of anticonvulsants, including vigabatrin, lamotrigine, gabapentin, tiagabine, topiramate, felbamate, and zonisamide, represents a step forward toward better anticonvulsant drugs [6–9]. New anticonvulsant agents are discovered through conventional screening and/or structure modification rather than a mechanism driven design.

Five-member heterocyclic compounds showed various types of biological activities, among them 1,3,4-thiadiazoles are associated with diverse biological activities, probably by the virtue of –N=C–S– grouping [10]; some of them possess antibacterial [11], antifungal [12], and anticonvulsant [13] activities. Similarly, 2,5-disubstituted-1,3,4-thiadiazoles also display wide spectrum of activities such as antibacterial [14] and anticonvulsant [15]. The therapeutic importance of these rings have prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophore pattern to display higher pharmacological activity. In the present study, some new 2,5-disubstituted-1,3,4-thiadiazole derivatives (**VIIa–o**) have been synthesized and their anticonvulsant effects were determined through maximal electroshock (MES) seizure test.

RESULTS AND DISCUSSION

The new 2,5-disubstituted-1,3,4-thiadiazole derivatives (**VIIa–o**) were synthesized according to Scheme. We believe that this synthesizing approach represents the most efficient route to a diverse array of 2,5-disubstituted heterocycles yet reported [16–21]. Readily available starting materials and simple synthesizing procedures make this method very attractive and convenient for the synthesis of various thiadiazoles. Formation of products was confirmed by elemental analyses, ^{1}H NMR, and mass spectra. The ^{1}H NMR spectra of (**VIIg**) showed piperazine ring in the region of δ, 3.243.56. The mass spectra of

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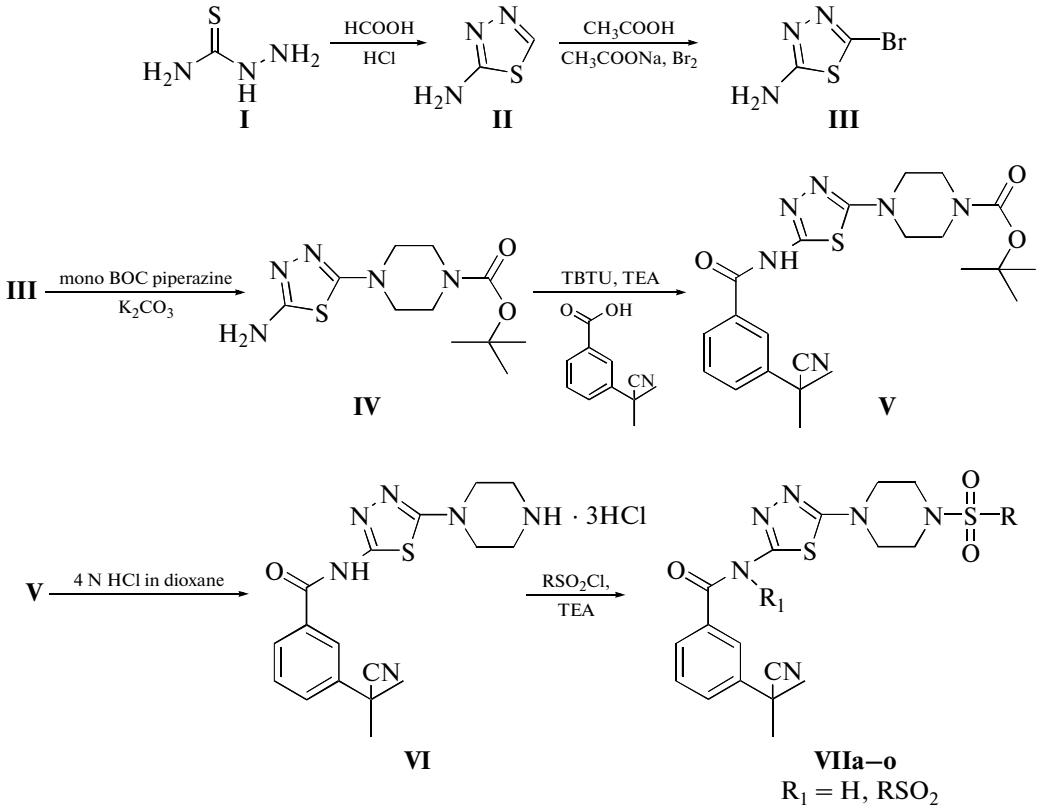
(**VIIg**) showed molecular ion peak at *m/z* 909.07, which is in agreement with the molecular formula, $C_{33}H_{24}F_{12}N_6O_5S_3$. The elemental analysis data showed good agreement (within ± 0.4%) between the experimentally determined values and the theoretically calculated values. The chemical structures and physical data of all the synthesized compounds are presented in Table 1.



Scheme. Synthetic route of 2,5-disubstituted-1,3,4-thiadiazole derivatives (**VIIa–o**).

In vivo Anticonvulsant Activity

All the synthesized thiadiazole analogues were screened for their anticonvulsant potential through MES model. For several decades, antiepileptic drug research has focused on identifying new potential drugs based on their anticonvulsant activity against a single acute seizure induced by various stimulators, usually in mice and rats. All the established antiepileptic drugs have anticonvulsant activity at least in the MES model [22]. In the present study, the anticonvulsant activity of the fifteen newly synthesized 2,5-disubstituted-1,3,4-thiadiazole derivatives (**VIIa–o**) was evaluated by MES model at the dose of 100 mg/kg and the results are summarized in Table 2. Compounds (**VIIg**), (**VIIj**), and (**VIIo**) demonstrated significant protective effect on MES induced seizure and the effect of (**VIIg**) was similar to that of the standard (phenytoin). Similarly, compounds (**VIIb**), (**VIId–f**), (**VIIi**), and (**VIIk–n**) also showed moderate protective effect and a significant difference in protectiveness was observed when compared to the standard group. Compounds (**VIIa, c, h**) have relatively low anticonvulsant potencies.

All the compounds were examined for their neurotoxicity using rotorod method given in the dose of 100 mg/kg. Except compounds (**VIIa**), (**VIIc**), and (**VIIh**) none of the compounds showed neurotoxicity. These compounds showed 25% toxicity compared to the standard 2 h after oral administration (Table 3).

From the results obtained, the structure activity relationship (SAR) can be drawn for the (**VIIa–o**) series. In this connection, different electron donating or electron withdrawing groups attached to phenyl ring as substituent linked to sulfonyl group are studied for anticonvulsant efficacy. In the present series of compounds, the active compounds possess all the requirements essential for anticonvulsant activity, as proposed by Dimmock et al. [23]. On correlating the structures of the synthesized compounds with their anticonvulsant activity, it has been observed that com-

Table 1. Chemical structure and melting range of 2,5–disubstituted-1,3,4–thiadiazole derivatives **(VIIa–o)**

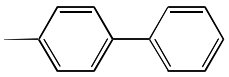
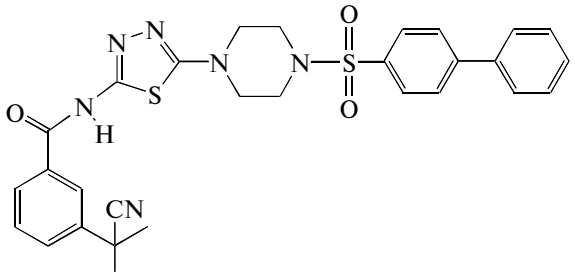
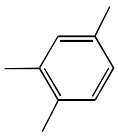
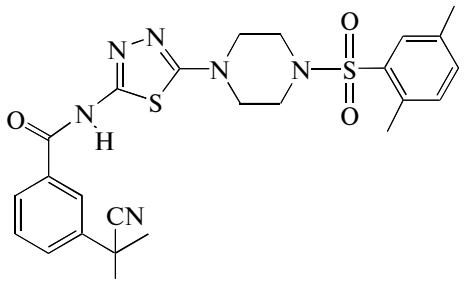
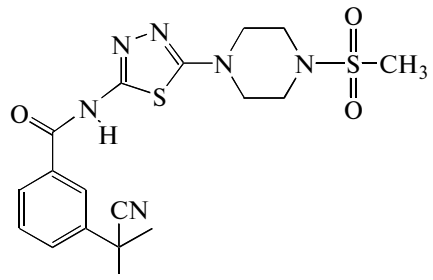
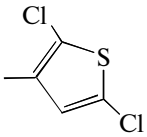
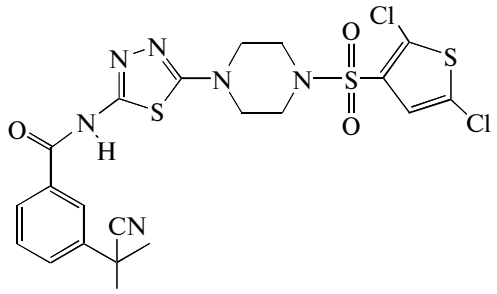
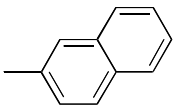
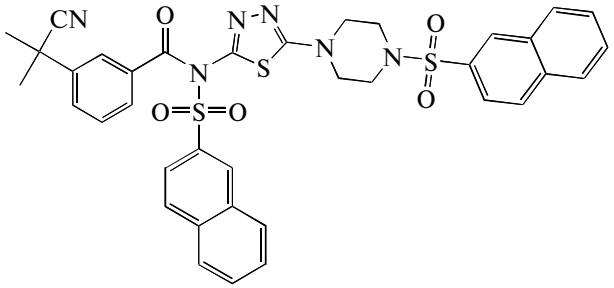
Compound	R	Structure	mp (°C)
(VIIa)			243–245
(VIIb)			212–214
(VIIc)	$-CH_3$		92–94
(VIId)			122–124
(VIIe)			162–164

Table 1. (Contd.)

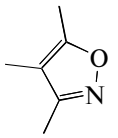
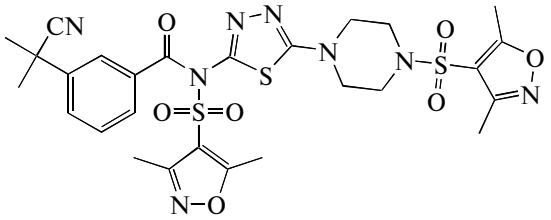
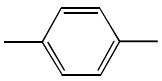
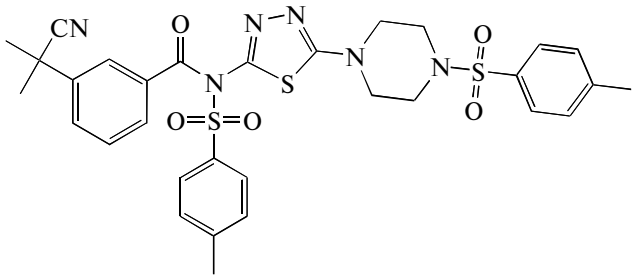
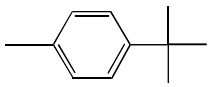
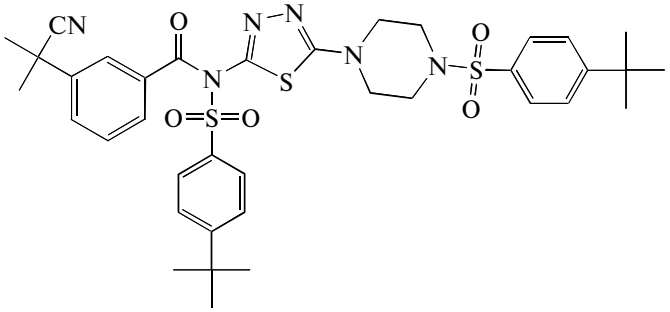
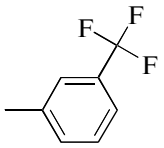
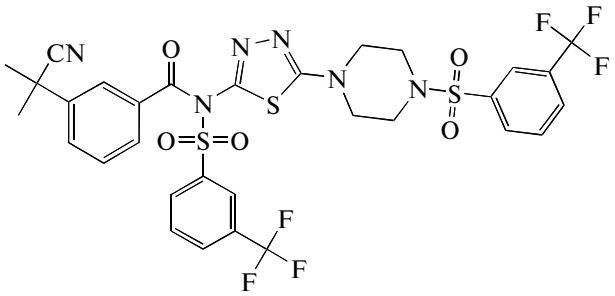
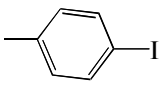
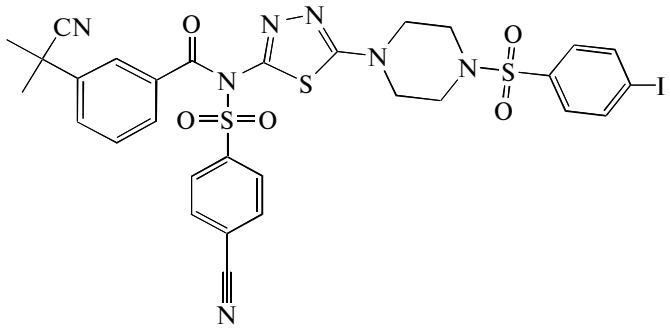
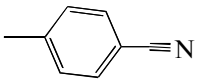
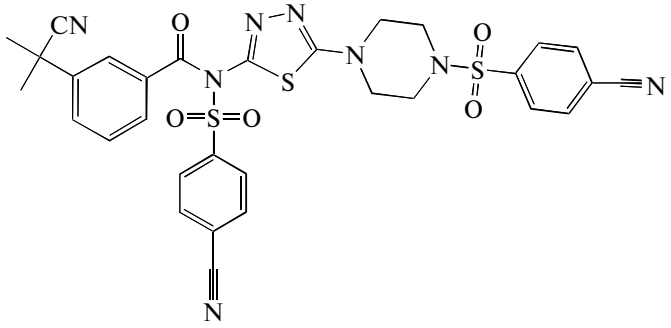
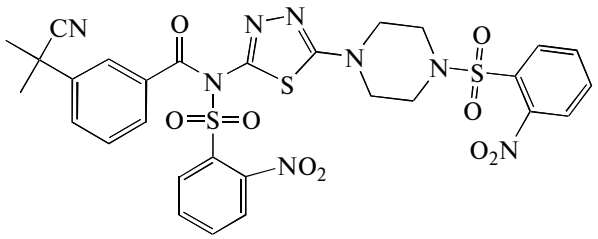
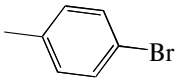
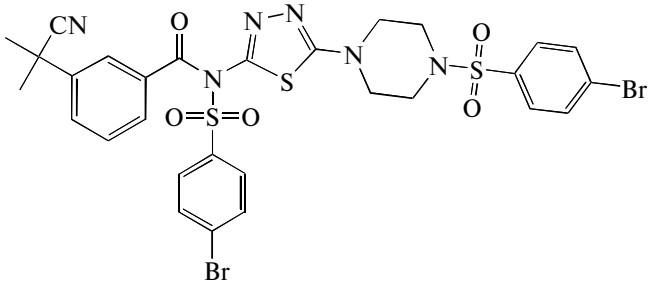
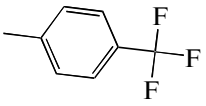
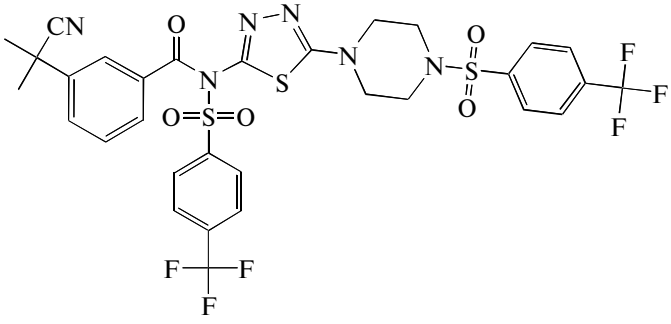
Compound	R	Structure	mp (°C)
(VIIf)			106–108
(VIIh)			100–102
(VIIi)			170–172
(VIIj)			149–141
(VIIk)			170–172

Table 1. (Contd.)

Compound	R	Structure	mp (°C)
(VIIl)			185–187
(VIIm)			162–164
(VIIn)			222–224
(VIIo)			154–156

pounds bearing the groups like nitro, phenoxy and halogens on phenyl ring possess high potency in MES. The SAR study of these compounds indicate that the introduction of a piperazine group at position 5 of thiadiazole ring and 3,5-bis(trifluoromethyl) positions of the benzenesulfonyl moiety (compound **(VIIg)**) showed the best anticonvulsant activity. Compounds **(VIIj)** and **(VIIo)** 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.

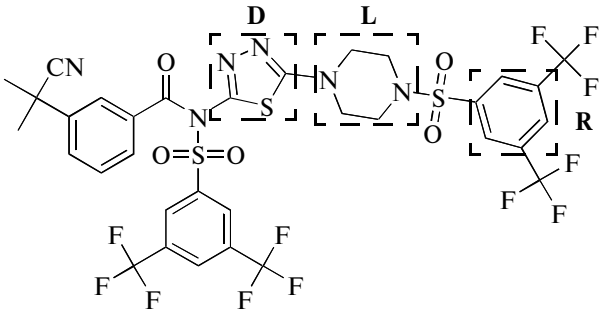
The presence of nitro group in **(VIIm)** and halogen groups in **(VIId)**, **(VIIk)**, and **(VIIn)** showed moderate anticonvulsant activity. The presence of cyano group in **(VIIl)** at aryl ring has moderate activity. Although naphthalene group in **(VIIe)**, dimethyl, in **(VIIb)**, and *tert*-butyl, in **(VIIi)** were moderately active in the MES test; compounds with phenyl ring in **(VIIa)** and **(VIIh)** exhibited considerable anticonvulsant activity in com-

Table 2. Effect of the tested compounds in the maximal electroshock seizure test

Treatment	E/F	% Protection
(VIIa)	7.32	12.00
(VIIb)	6.64	31.54
(VIIc)	8.14	10.13
(VIId)	5.48	59.64
(VIIe)	6.12	41.32
(VIIf)	2.97	69.25
(VIIg)	2.00	75.81
(VIIh)	7.00	17.31
(VIIi)	6.54	48.43
(VIIj)	2.21	71.23
(VIIk)	6.26	52.42
(VIIl)	6.50	48.12
(VIIm)	6.10	53.01
(VIIn)	6.35	50.03
(VIIo)	2.29	71.18
Standard	1.98	75.88
Control, vehicle	8.21	–

E/F = Extension/Flexion [Decrease in ratio of extension phase (in seconds)/flexion phase (in seconds]. % Protection = (control – test)/(Control) × 100.

parison to methyl group in (**VIIc**). These compounds ((**VIIa**), (**VIIc**), and (**VIIh**)) contribute to the 25% neurotoxicity at 2 h. Among the synthesized compounds (**VIIa–o**), all the compounds showed activity in the range of 10.13–75.81% in comparison to phenytoin, which completely inhibited the convulsions produced by electro-convulsometer, but compound (**VIIg**), having electron withdrawing groups, showed 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 donar (D)



(VIIg)

The pharmacophore model of (**VIIg**) for anticonvulsant activity.

system [23]. Thus the proposed pharmacophore model for (**VIIg**) includes all the above factors important for bioactivity (see figure).

In conclusion, a series of new 2,5-disubstituted-1,3,4-thiadiazole derivatives (**VIIa–o**) were synthesized in good yield, characterized by different spectral studies, and their anticonvulsant activity has been evaluated. Various thiadiazole derivatives with electron withdrawing groups showed potent anticonvulsant activity. Among the synthesized compounds, (**VIIg**), (**VIIj**), and (**VIIo**) showed excellent anticonvulsant activity. Therefore, the nature of groups in sulfonyl moiety is very important for anticonvulsant activity in MES model.

EXPERIMENTAL

Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were performed on VarioMICRO superuser V1.3.2 Elementar. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were recorded on Bruker DRX-500 spectrometer at 400 MHz using DMSO-d_6 as solvent and TMS as an internal standard. Mass spectral data were obtained by LC/MSD Trap XCT at 70 eV. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates.

1,3,4-Thiadiazol-amine (II). Thiosemicarbazide (**I**) (50.0 g, 0.5486 mol) was taken in 100 mL formic acid and the reaction mixture was stirred at room temperature for 1 h. After cooling the reaction mass, 100 mL conc. hydrochloric acid was added. Reaction completion was monitored by TLC. After cooling the reaction mass to 0°C, it was basified with ammonium hydroxide solution. The solid formed was filtered, washed with water, and dried to yield the above compound as a white solid. Recrystallization from methanol afforded 45.5 g (82%) (**II**). ^{1}H NMR: δ = 9.31 (s, 1 H), 4.21 (s, 2 H); MS: m/z = 102.14 (M^+).

5-Bromo-1,3,4-thiadiazol-2-amine (III). To a stirred solution of compound (**II**) (40.0 g) and sodium acetate (64.89 g) in 200 mL acetic acid (4% by vol.) bromine was added dropwise (37.92 g) at 10°C. The reaction mass was stirred at room temperature for 3 hours. The reaction mass was concentrated to syrup and basified with saturated sodium bicarbonate solution. The compound was extracted with ethyl acetate and the ethyl acetate layer was washed with water followed by brine, dried over sodium sulphate, and concentrated to syrup. The crude syrup was crystallized using ethyl acetate to yield the above compound as off-white solid. Recrystallization from methanol afforded 53.4 g (75%) (**III**). ^{1}H NMR: δ = 9.31 (s, 1 H), 4.21 (s, w, 2 H); MS: m/z = 181.10 (M^+).

***tert*-Butyl 4-(5-amino-1,3,4-thiadiazole-2-yl)piperazine-1-carboxylate (IV).** To a stirred solution of amine (**III**) (25.0 g, 0.1388 mol), potassium carbonate (57.57 g, 0.4165 mol) in dimethyl formamide (250 mL)

and *N*-Boc-piperazine (31.03 g, 0.1666 mol) were added, and the reaction mass was stirred for 10 h at room temperature. The reaction mass was quenched in ice water (2.0 L) and stirred at room temperature for 1 h. The solid formed was filtered and dried to yield the above compound as off-white solid. Recrystallization from ethanol afforded 33.6 g (85%) (**IV**). ^{1}H NMR: δ = 4.21 (s, 2 H), 3.77 (t, *J* = 5.36, 4 H), 3.10 (t, *J* = 4.80, 4 H), 1.41 (s, 9 H); MS: *m/z* = 286.03 (M^+).

***tert*-Butyl-4-(5-(3-(2-cyanopropane-2-yl)benzamido)-1,3,4-thiadiazol-2-yl) piperazine-1-carboxylate (V).** To a stirred solution of carbonate (**IV**) (25.0 g, 0.0876 mol) in dichloromethane (250 mL), triethylamine (26.59 g, 0.2628 mol), 3-(2-cyanopropan-2-yl)benzoic acid (19.89 g, 0.1051 mol), and TBTU (33.75 g, 0.1051 mol) were added. The reaction mass was stirred overnight at room temperature and the reaction completion was monitored by TLC. The reaction mass was washed with saturated bicarbonate solution followed by 1.0 N HCl, water and brine. The organic layer was dried over sodium sulphate, concentrated to syrup, and crystallized using dichloromethane to yield the above compound as off-white solid. Recrystallization from dichloromethane afforded 33.99 g (85%) (**V**). ^{1}H NMR: δ = 11.45 (s, 1 H), 8.33 (s, 1 H), 8.02 (d, *J* = 8.00, 1 H), 7.79 (d, *J* = 7.88, 1 H), 7.66 (t, *J* = 7.60, 1 H), 3.59 (t, *J* = 5.20, 4 H), 3.50 (t, *J* = 4.40, 4 H), 2.07 (s, 6 H),1.48 (s, 9 H); MS: *m/z* = 457.00 (M^+).

3-(2-Cyanopropan-2-yl)-N-(5-(piperazine-1-yl)-1,3,4-thiadiazol-2-yl)benzamide hydrochloride (VI). To a stirred solution of carboxylate (**5**) (20 g, 0.0438 mol) in 1,4-dioxane at 0–5°C, 4 N HCl in dioxane (80.0 mL) was added. The reaction mixture was stirred at room temperature for 10 h. The solid was filtered, washed with diethyl ether, and packed in air tight container to yield the above compound as pale yellow hygroscopic solid 16.9 g (90%) (**VI**). ^{1}H NMR: δ = 9.81 (s, 2 H), 8.21 (s, 1 H), 8.02 (d, *J* = 8.00, 1 H), 7.79 (d, *J* = 7.92, 1 H), 7.60 (t, *J* = 7.80, 1 H), 3.77 (t, *J* = 5.36, 4 H), 3.21 (t, *J* = 4.00, 4 H), 1.73 (s, 6 H); MS: *m/z* = 357.05 (M^+).

General procedure for the synthesis of 2,5-disubstituted-1,3,4-thiadiazole derivatives (VIIa–o). To a mixture of (**VI**) (1.0 eq) and triethyl amine (4.5 eq) in dichloromethane (10 vol), substituted sulphonyl chloride (2.4 eq) was added at 5–10°C and stirred overnight at room temperature. Reaction completion was confirmed through TLC (R_f value 0.30 to 0.38). The reaction mixture was poured into separating funnel, washed with water followed by brine solution, dried over anhydrous sodium sulphate, and concentrated to syrup. Crude syrup was purified by crystallization using ethyl acetate to yield the thiadiazol substituted sulfonamide as white to pale yellow solids.

***N*-(5-((1,1'-Biphenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazol-2-yl)-3-(2-cyanopropan-2-yl)benzamide (VIIa).** Yield: 1.06 g (80%); white solid; ^{1}H NMR: δ = 12.71 (s, 1 H), 8.19 (s, 1 H), 7.96–8.01 (m, 3 H), 7.84–7.90 (m, 2 H), 7.72–7.80 (m, 3 H), 7.58–7.62 (m, 1 H), 7.50–7.54 (m, 2 H), 7.45 (t, *J* = 7.32, 1 H), 3.77 (t, *J* = 5.36, 4 H), 3.21 (t, *J* = 4.00, 4 H), 1.74 (s, 6 H); MS: *m/z* = 573.18 (M^+).

Table 3. Neurotoxicity screening of the compounds (**VIIa–o**)

Compound	Neurotoxicity screen			
	0.5 h	1 h	2 h	4 h
(**VIIa**)	0/4	0/4	1/4	1/4
(**VIIb**)	0/4	0/4	1/4	1/4
(**VIIc**)	0/4	0/4	1/4	1/4
(**VIId**)	0/4	0/4	0/4	0/4
(**VIIe**)	0/4	0/4	0/4	0/4
(**VIIf**)	0/4	0/4	0/4	0/4
(**VIIg**)	0/4	0/4	0/4	0/4
(**VIIh**)	0/4	0/4	0/4	0/4
(**VIIi**)	0/4	0/4	0/4	0/4
(**VIIj**)	0/4	0/4	0/4	0/4
(**VIIk**)	0/4	0/4	0/4	0/4
(**VIIl**)	0/4	0/4	0/4	0/4
(**VIIm**)	0/4	0/4	0/4	0/4
(**VIIn**)	0/4	0/4	0/4	0/4
Standard	0/4	0/4	0/4	0/4

The data in the table represent ratio between the numbers of the animals that exhibited neurotoxicity against the number of tested animals.

3-(2-Cyanopropan-2-yl)-*N*-(5-(4-((2,4-dimethylphenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazol-2-yl)benzamide (VIIb). Yield: 0.99 g (81%); white solid; ^{1}H NMR: δ = 9.6 (s, 1 H), 8.64 (s, 1 H), 8.21–8.24 (m, 3 H), 8.02 (d, *J* = 8.00, 1 H), 7.79 (d, *J* = 7.92, 1 H), 7.45 (t, *J* = 7.32, 1 H), 3.77 (t, *J* = 5.36, 4 H), 3.20 (t, *J* = 4.10, 4 H), 3.06 (s, 3 H), 1.73 (s, 6 H), 1.18 (s, 3 H); MS: *m/z* = 525.18 (M^+).

3-(2-Cyanopropane-2-yl)-*N*-(methylsulfonyl)-*N*-5-(4-(methylsulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)benzamide (VIIc). Yield: 0.89 g (75%); white solid; ^{1}H NMR: δ = 8.16 (s, 1 H), 7.95–7.98 (m, 1 H), 7.82–7.85 (m, 1 H), 7.70 (t, *J* = 7.85, 1 H), 3.40 (t, *J* = 5.10, 4 H), 3.10 (t, *J* = 4.32, 4 H), 2.84 (s, 3 H), 2.81 (s, 3 H), 1.72 (s, 6 H); MS: *m/z* = 513.09 (M^+).

3-(2-Cyanopropan-2-yl)-*N*-(5-(4-((2,5-dichlorothiophen-3-yl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)benzamide (VIId). Yield: 1,05 g (79%); white solid; ^{1}H NMR: δ = 9.23 (s, 1 H), 8.28 (s, 1 H), 8.01–8.08 (m, 1 H), 7.79–7.85 (m, 1 H), 7.63 (t, *J* = 7.48, 1H), 7.42 (s, 1 H), 3.60 (t, *J* = 4.84, 4 H), 3.31 (t, *J* = 4.00, 4 H), 1.74 (s, 6 H); MS: *m/z* = 572.01 (M^+).

3-(2-Cyanopropan-2-yl)-*N*-(naphthalene-2-ylsulfonyl)-*N*-(5-(4-(naphthalene-2-ylsulfonyl) piperazine-1-yl)-1,3,4-thiadiazol-2-yl)benzamide (VIIe). Yield:

1.28 g (75%); pale yellow solid; ^{1}H NMR: δ = 8.93 (s, 1 H), 8.48 (s, 1 H), 8.31 (s, 1 H), 8.18–8.24 (m, 3 H), 8.07–8.10 (m, 3 H), 8.01 (d, *J* = 8.12, 1 H), 7.94 (dd, *J* = 1.92, 8.76 Hz, 1 H), 7.66–7.73 (m, 6 H), 7.60 (t, *J* = 7.76, 1 H), 3.57 (t, *J* = 5.04, 4 H), 3.13 (t, *J* = 5.00, 4 H), 1.72 (s, 6 H); MS: *m/z* = 737.16 (M^+).

3-(2-Cyanopropane-2-yl)-*N*-((3,5-dimethylisoxazol-4-yl)sulfonyl)-*N*-(5-(4-((3,5-dimethylisoxazol-4-yl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazol-2-yl)benzamide (VIIf). Yield: 1.25 g (80%); white solid; ^{1}H NMR: δ = 8.21 (s, 1 H), 8.02 (d, *J* = 7.72, 1 H), 7.80 (d, *J* = 7.76, 1 H), 7.61 (t, *J* = 7.80, 1 H), 3.56 (t, *J* = 4.84, 4 H), 3.24 (t, *J* = 4.32, 4 H), 2.64 (s, 3 H), 2.43 (s, 3 H), 2.36 (s, 3 H), 2.23 (s, 3 H), 1.75 (s, 6 H); MS: *m/z* = 675.15 (M^+).

***N*-((3,5-Bis(trifluoromethyl)phenyl)sulfonyl)-*N*-(5-(4-((3,5-bis(trifluoromethyl)phenyl)sulfonyl) piperazine-1-yl)-1,3,4-thiazol-2-yl)-3-(2-cyanoprppan-2-yl)benzamide (VIIg).** Yield: 1.58 g (75%); pale yellow solid; ^{1}H NMR: δ = 8.89 (s, 1 H), 8.57 (s, 2 H), 8.32 (s, 2 H), 8.19 (s, 1 H), 8.12 (s, 1 H), 7.99 (d, *J* = 7.60, 1 H), 7.78 (d, *J* = 8.00, 1 H), 7.59 (t, *J* = 8.00, 1 H), 3.56 (t, *J* = 4.84, 4 H), 3.24 (t, *J* = 4.32, 4 H), 1.73 (s, 6 H); MS: *m/z* = 909.07 (M^+).

3-(2-Cyanopropan-2-yl)-*N*-tosyl-*N*-(5-(4-tosylpiperazine-1-yl)-1,3,4-thiadiazol-2-yl)benzamide (VIIh). Yield: 1.23 g (80%); pale yellow solid; ^{1}H NMR: δ = 8.36 (s, 1H), 8.11 (d, *J* = 7.76, 1 H), 8.04 (d, *J* = 6.88, 2 H), 7.81 (dd, *J* = 0.92, 4.86 Hz, 1 H), 7.42–7.48 (m, 3 H), 7.09–7.11 (m, 4 H), 3.52 (t, *J* = 5.20, 4 H), 3.03 (t, *J* = 4.84, 4 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.73 (s, 6 H); MS: *m/z* = 665.15 (M^+).

***N*-((4-(*tert*-Butyl)phenyl)sulfonyl)-*N*-(5-(4-((-tert-butyl)phenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)-3-(2-cyanopropane-2-yl)benzamide (VIIi).** Yield: 1.30g (79%); pale yellow solid; ^{1}H NMR: δ = 8.37 (s, 1 H), 8.10 (d, *J* = 7.68, 1 H), 8.05 (d, *J* = 8.48, 2 H), 7.82 (d, *J* = 7.60, 1 H), 7.62–7.68 (m, 7 H), 3.51 (t, *J* = 4.80, 4 H), 3.00 (t, *J* = 4.00, 4 H), 1.75 (s, 6 H), 1.29 (s, 9 H), 1.19 (s, 9 H); MS: *m/z* = 749.25 (M^+).

3-(2-Cyanopropan-2-yl)-*N*-((3-(trifluoromethyl)phenyl)sulfonyl)-*N*-(5-(4-((3-(trifluoromethyl) phenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)benzamide (VIIj). Yield: 1.35 g (75%); white solid; ^{1}H NMR: δ = 8.43 (s, 1 H), 8.38 (s, 1 H), 8.34 (d, *J* = 7.36, 1 H), 8.17 (t, *J* = 8.76, 2 H), 8.08 (d, *J* = 7.72, 2 H), 7.95 (s, 1 H), 7.92 (d, *J* = 7.88, 1 H), 7.83 (d, *J* = 6.36, 2 H), 7.63 (t, *J* = 8.04, 1 H), 3.51 (t, *J* = 4.80, 4 H), 3.00 (t, *J* = 4.00, 4 H), 1.73 (s, 6 H); MS: *m/z* = 773.09 (M^+).

3-(2-Cyanopropan-2-yl)-*N*-((4-iodophenyl)sulfonyl)-*N*-(5-(4-((4-iodophenyl)sulfonyl) piperazine-1-yl)-1,3,4-thiadiazole-2-yl-)benzamide (VIIk). Yield: 1.57 g (76%); white solid; ^{1}H NMR: δ = 8.34 (s, 1 H), 8.05–8.11 (m, 5 H), 7.82–7.86 (m, 3 H), 7.65 (t, *J* = 7.80, 1 H), 7.52 (d, *J* = 8.44, 2 H), 3.51 (t, *J* = 4.80, 4 H), 3.00 (t, *J* = 4.00, 4 H), 1.74 (s, 6 H); MS: *m/z* = 888.92 (M^+).

***N*-((4-Cyanophenyl)sulfonyl)-*N*-(5-(4-((4-cyanophenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)-3-(2-cyanopropane-2-yl)benzamide (VIIl).** Yield: 1.20 g (75%); white solid; ^{1}H NMR: δ = 8.32 (s, 1 H), 8.11 (d, *J* = 7.76, 1 H), 8.04 (d, *J* = 6.98, 2 H), 7.81 (dd, *J* = 0.92, 4.86 Hz, 1 H), 7.43–7.48 (m, 3 H), 7.09–7.11 (m, 4 H), 3.52 (t, *J* = 5.20, 4 H), 3.03 (t, *J* = 4.84, 4 H), 1.73 (s, 6 H); MS: *m/z* = 687.78 (M^+).

3-(2-Cyanopropane-2-yl)-*N*-((2-nitrophenyl)sulfonyl)-*N*-(5-(4-((2-nitrophenyl)sulfonyl) piperazine-1-yl)-1,3,4-thiadiazole-2-yl)benzamide (VIIm). Yield: 1.32 g (78%); off-white solid; ^{1}H NMR: δ = 8.36 (s, 1 H), 8.10 (d, *J* = 7.68, 1 H), 8.05 (d, *J* = 8.48, 2 H), 7.82 (d, *J* = 7.60, 1 H), 7.62–7.68 (m, 7 H), 3.52 (t, *J* = 4.80, 4 H), 3.10 (t, *J* = 4.00, 4 H), 1.75 (s, 6 H); MS: *m/z* = 727.01 (M^+).

***N*-((4-Bromophenyl)sulfonyl)-*N*-(5-(4-((4-bromophenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)-3-(2-cyanopropane-2-yl)benzamide (VIIn).** Yield: 1.39 g (75%); white solid; ^{1}H NMR: δ = 8.20 (s, 1 H), 8.01 (d, *J* = 7.68, 2 H), 7.89 (dd, *J* = 1.56, 8.40 Hz, 2 H), 7.79 (d, *J* = 7.84, 2 H), 7.71 (dd, *J* = 1.56, 6.92 Hz, 2 H), 7.60 (t, *J* = 7.80 Hz, 1 H), 7.53 (d, *J* = 0.92 Hz, 2 H), 3.51 (t, *J* = 4.80 Hz, 4 H), 3.00 (t, *J* = 4.00 Hz, 4 H), 1.74 (s, 6 H); MS: *m/z* = 792.94 (M^+).

3-(2-Cyanopropan-2-yl)-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)-*N*-(5-(4-((4-(trifluoromethyl) phenyl)sulfonyl)piperazine-1-yl)-1,3,4-thiadiazole-2-yl)benzamide (VIIo). Yield: 1.35 g (75%); white solid; ^{1}H NMR: δ = 8.32 (s, 1 H), 8.04–8.10 (m, 5 H), 7.83–7.87 (m, 3 H), 7.65 (t, *J* = 7.80, 1 H), 7.52 (d, *J* = 8.44, 2 H), 3.51 (t, *J* = 4.80, 4 H), 3.10 (t, *J* = 4.00, 4 H), 1.74 (s, 6 H); MS: *m/z* = 773.10 (M^+).

Anticonvulsant evaluation. Male Wistar rats (190–220 g) procured from National Institute of Nutrition, Hyderabad, were used in the present study. The animals were kept in individual cages for one week to acclimatize for the laboratory conditions. They were allowed to access water and food freely.

All the experimental procedures were carried out in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The study was reviewed and approved by the Institutional Animal Ethics Committee, G Pulla Reddy College of Pharmacy, Hyderabad, India.

Maximal electroshock seizure model was used in the present study to evaluate the anticonvulsant activity of the compounds on male Wistar rats. Seizures were induced in rats by delivering electroshock of 150 mA for 0.2 s by means of a convulsiometer through a pair of ear clip electrodes. The test compounds (100 mg/kg) were administered by oral route in the form of solution (the compounds were dissolved in 1% sodium carboxymethyl cellulose), 30 minutes before the maximal electroshock seizure test. The animals were observed closely for 2 min. The percentage of inhibition of sei-

zure relative to control was recorded and calculated [24]. Phenytoin (100 mg/kg) was used as a standard drug.

The minimal motor impairment, reflecting acute neurological toxicity, was measured in mice by the rotorod test [24]. The mice were trained to stay on the accelerating rotorod that rotates at 10. The rod diameter was 3.2 cm. Trained animals were administered with the test compounds at dose of 100 mg/kg. Neurotoxicity was evidenced by the inability of the animal to maintain equilibrium on the rod for at least one minute in each of the three trails. Phenytoin was used as a standard drug.

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