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Research Article

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Anticonvulsant and toxicity screening of newly synthesized 1,2,4-triazole-3(4H)-thione derivatives

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ABSTRACT

A series of new 2-substituted benzyl-5-methyl-4-aryl-2H-1,2,4-triazole-3(4H)-thione (4a-r) were produced by reacting 5-methyl-4-aryl-2H-1,2,4-triazole-3(4H)-thione with substituted benzyl chloride. Final compounds were analyzed by their infra-red spectroscopy, proton NMR and elemental studies. MES and scPTZ animal models were selected for the activity of newly synthesized compounds against anticonvulsant activity. 4c, 4e, 4i, 4k and 4m showed inspiring anticonvulsant profile. Rotorod and ethanol potentiation test have been performed to examine any neurotoxicity. Most potent compounds were passed through an assay of GABA-transaminase inhibition to diagnose the mechanism involved in the anticonvulsant screening. Utmost compounds were found to be less harmful and can be selected as lead compounds for forthcoming research.

Keywords: *Triazole; Anticonvulsant activity; MES; sc.PTZ; Neurotoxicity*

INTRODUCTION

Epilepsy is progressive condition considered by the episodic and random incidence of seizures that are produced by irregular release of huge amount of neurons. Up to 5% people of the world population develops epilepsy in their lifespan [1]. Heterocyclic with nitrogen atom is paying attention to large number of pharma industries [2]. In literatures, pharmacological action of nitrogen holding heterocyclic structure is stated in varied collection. In medicinal chemistry now days 1, 2, 4-triazol ring is proved to be as diverse therapeutic agents [3]. Triazole ring linked with other heterocyclic nucleus is a great thrust for chemist to explore its hidden potentials. Heterocyclic having nitrogen are present in plenty of therapeutic compounds. Triazole ring attached with hydrophobic aryl group increases the lipophilicity of intact compound and in different literature it shows successful anticonvulsant, antiviral and anticancer activities. Pandeya *et al* recommended the pharmacophoric features crucial for anticonvulsant activity [4]. These groups are available in many presently used medicines. Pharmacophoric elements necessary for good anticonvulsant activity like hydrophobic area (A), hydrogen bonding domain (HBD), electron donor moiety (D) and distal hydrophobic area (C) are present in the final structure and are shown in Figure 1 [5]. By considering the broad features of triazole ring, a series of newer 2-substituted benzyl-5-methyl-4-aryl-2*H*-1,2,4-triazole-3(4*H*)-thione (4a-r) have been synthesized in hope to be better anticonvulsant with lesser side effects. Elemental analyses were done using the software. Characterizations of compounds were done by using infra-red spectroscopy and proton NMR techniques.

Anticonvulsant and toxicity screening were seen against MES and sc. PTZ models. Rotorod and ethanol potentiation tests have been performed to check any neurotoxicity.

GABA-transaminase inhibition assay was performed for few selected active compounds to confirm the mechanism pathways.

2. MATERIALS AND METHODS

2.1. Chemistry

Chemicals for the experiment were obtained from s.d. Fine Chemicals, India. Paraffin was used to check the melting points. ^{1}H NMR spectra were obtained using Bruker 300 MHz instrument. Chemical shifts are shown as ppm relative to tetramethylsilane (TMS). The Infra-red spectra of compounds were recorded in KBr (cm^{-1}) on a Bio-Rad FTIR instrument.

Synthesis of Acetohydrazide (1)

First of all hydrazine hydrate (10 ml) and ethyl acetate (0.004 mol) was taken in flask. To this mixture dry ethanol was added and heated at refluxing condition for 20–22 h. At the end ethanol was removed by distillation process. Crystals of acetohydrazide (1) was obtained after cooling the final compounds.

Synthesis of 1-acetyl-4-substituted phenyl thiosemicarbazide (2a-f):

Mixture of compound 1 (0.01 mol) and substituted phenylisothiocyanates (0.01 mol) was refluxed for 5-6 hrs in presence of absolute ethanol. Compounds were crystallized and purified by using ethanol.

Synthesis of 5-methyl-4-substituted phenyl-1,2,4-triazole-3(4H)-thione (3a-f)

Mixture of compounds 2a-f (0.004 mol) and 30 mL of 2% NaOH solution was heated for 6 hours. Precipitate was filtered and crystallized with the help of ethanol/water.

Synthesis of 2-substituted benzyl-5-methyl-4-aryl-2H-1, 2, 4-triazole-3(4H)-thione (4a-r)

Benzyl chloride (0.01mol) was slowly added to the mixture of compound 3a-f (0.01 mol) and anhydrous K_2CO_3 (0.01 mol) in presence of acetone (30 ml). Mixture was stirred for 7-8 hrs. At the end it was transferred into water. Finally synthesized compounds (4a-r) were recrystallized with ethanol.

2-Benzyl-5-methyl-4-phenyl-2H-1, 2, 4-triazole-3(4H)-thione (4a)

IR: 3347(Ar-CH), 2389(Aliphatic-CH), 1658(C=N), 1566(C=C), 1263(C=S), 1013(N-N). ^{1}H NMR: 6.2-7.3(m, 10H, Ar-H), 4.38(s, 2H, CH_2), 1.24(s, 3H, CH_3).

2-Benzyl-5-methyl-4-o-tolyl-2H-1,2,4-triazole-3(4H)-thione (4b)

IR: 3264(Ar-CH), 2302(Aliphatic-CH), 1613(C=N), 1543(C=C), 1395(C=S), 1060(N-N). ^{1}H NMR: 6.7-7.3(m, 9H, Ar-H), 4.43(s, 2H, CH_2), 2.34(s, 3H, Ar-CH_3), 0.89(s, 3H, CH_3).

2-Benzyl-4-(2-chlorophenyl)-5-methyl-2H-1,2,4-triazole-3(4H)-thione (4c)

IR: 3273(Ar-CH), 2364(Aliphatic-CH), 1632(C=N), 1628(C=C), 1425(C=S), 1051(N-N), 690(C-Cl). ^{1}H NMR: 7.2-8.1(m, 9H, Ar-H), 4.62(s, 2H, CH_2), 0.89(s, 3H, CH_3).

2-Benzyl-5-methyl-4-p-tolyl-2H-1,2,4-triazole-3(4H)-thione (4d)

IR: 3231(Ar-CH), 2384(Aliphatic-CH), 1644(C=N), 1646(C=C), 1326(C=S), 1105 (N-N). ^{1}H NMR: 6.9-7.3(m, 9H, Ar-H), 4.72(s, 2H, CH_2), 2.17(s, 3H, Ar-CH_3), 0.87(s, 3H, CH_3).

2-Benzyl-5-methyl-4-(4-nitrophenyl)-2H-1,2,4-triazole-3(4H)-thione (4e)

IR: 3355(Ar-CH), 2360(Aliphatic-CH), 1655(C=N), 1645(C=C), 1402(-NO_2), 1295(C=S), 1013(N-N). ^{1}H NMR: 6.5-7.5(m, 9H, Ar-H), 4.71(s, 2H, CH_2), 0.97(s, 3H, CH_3).

2-Benzyl-4-(2-methoxyphenyl)-5-methyl-2H-1,2,4-triazole-3(4H)-thione (4f)

IR: 3452(Ar-CH), 2320(Aliphatic-CH), 1600(C=C), 1545(C=N), 1258(C=S), 1058(C-O-C), 1010 (N-N). ^{1}H NMR: 6.4-7.4(m, 9H, Ar-H), 4.71(s, 2H, CH_2), 3.76(s, 3H, Ar-OCH_3), 0.87(s, 3H, CH_3).

2-(2-Chlorobenzyl)-5-methyl-4-phenyl-2H-1,2,4-triazole-3(4H)-thione (4g)

IR: 3258(Ar-CH), 2362(Aliphatic-CH), 1640(C=N), 1620(C=C), 1258(C=S), 1195(N-N), 680(C-Cl). ^{1}H NMR: 6.7-7.1(m, 9H, Ar-H), 4.38(s, 2H, CH_2), 0.89(s, 3H, CH_3).

2-(2-Chlorobenzyl)-5-methyl-4-o-tolyl-2H-1,2,4-triazole-3(4H)-thione (4h)

IR: 3310(Ar-CH), 2320(Aliphatic-CH), 1632(C=N), 1621(C=C), 1294(C=S), 1056(N-N), 670(C-Cl). ^{1}H NMR: 6.6-7.3(m, 8H, Ar-H), 4.43(s, 2H, CH_2), 2.34(s, 3H, Ar-CH_3), 0.89(s, 3H, CH_3).

2-(2-Chlorobenzyl)-4-(2-chlorophenyl)-5-methyl-2H-1,2,4-triazole-3(4H)-thione (4i)

IR: 3386(Ar-CH), 2396(Aliphatic-CH), 1648(C=N), 1616(C=C), 1368(C=S), 1152(N-N), 740(C-Cl). ^{1}H NMR: 6.9-7.4(m, 8H, Ar-H), 4.72(s, 2H, CH_2), 0.87(s, 3H, CH_3).

2-(2-Chlorobenzyl)-5-methyl-4-p-tolyl-2H-1,2,4-triazole-3(4H)-thione (4j)

IR: 3329(Ar-CH), 2340(Aliphatic-CH), 1614(C=N), 1580(C=C), 1320(C=S), 1120(N-N), 750(C-Cl). ^{1}H NMR: 6.4-7.3(m, 8H, Ar-H), 4.66(s, 2H, CH_2), 2.38(s, 3H, Ar-CH_3), 1.22(s, 3H, CH_3).

2-(2-Chlorobenzyl)-5-methyl-4-(4-nitrophenyl)-2H-1,2,4-triazole-3(4H)-thione (4k)

IR: 3385(Ar-CH), 2260(Aliphatic-CH), 1630(C=N), 1601(C=C), 1489(-NO_2), 1290(C=S), 1064(N-N), 795(C-Cl). ^{1}H NMR: 7.3-8.1(m, 8H, Ar-H), 4.62(s, 2H, CH_2), 0.91(s, 3H, CH_3).

2-(2-chlorobenzyl)-4-(2-methoxyphenyl)-5-methyl-2H-1,2,4-triazole-3(4H)-thione (4l)

IR: 3370(Ar-CH), 2267(Aliphatic-CH), 1620(C=N), 1610(C=C), 1489(-NO_2), 1290(C=S), 1064(N-N), 1058(C-O-C),795(C-Cl). ^{1}H NMR: 7.3-8.1(m, 8H, Ar-H), 4.62(s, 2H, CH_2), 3.76(s, 3H, Ar-OCH_3, 0.91(s, 3H, CH_3).

2-(2-Methoxybenzyl)-5-methyl-4-phenyl-2H-1,2,4-triazole-3(4H)-thione (4m)

IR: 3362(Ar-CH), 2310(Aliphatic-CH), 1665(C=N), 1568(C=C), 1483(C=S), 1063(C-O-C), 1093(N-N). ^{1}H NMR: 6.5-7.5(m, 9H, Ar-H), 3.71(s, 2H, CH_2), 3.61 (s, 3H, OCH_3), 0.97(s, 3H, CH_3).

2-(2-methoxybenzyl)-5-methyl-4-o-tolyl-2H-1,2,4-triazole-3(4H)-thione (4n)

IR: 3310(Ar-CH), 2300(Aliphatic-CH), 1605(C=N), 1566(C=C), 1473(C=S), 1073(C-O-C), 1083(N-N). ^{1}H NMR: 6.3-7.4(m, 8H, Ar-H), 3.61(s, 2H, CH_2), 3.55 (s, 3H, OCH_3), 0.95(s, 3H, CH_3).

2-(2-methoxybenzyl)-4-(2-chlorophenyl)-5-methyl-2H-1,2,4-triazole-3(4H)-thione (4o)

IR: 3290(Ar-CH), 2350(Aliphatic-CH), 1625(C=N), 1506(C=C), 1463(C=S), 1033(C-O-C), 1063(N-N), 790(C-Cl). ^{1}H NMR: 6.1-7.2(m, 8H, Ar-H), 3.56(s, 2H, CH_2), 3.46 (s, 3H, OCH_3), 0.85(s, 3H, CH_3).

2-(2-Methoxybenzyl)-5-methyl-4-p-tolyl-2H-1,2,4-triazole-3(4H)-thione (4p)

IR: 3459(Ar-CH), 2342(Aliphatic-CH), 1665(C=N), 1659(C=C), 1527(C=S), 1079(N-N), 1042(C-O-C). ^{1}H NMR: 6.2-8.5(m, 8H, Ar-H), 4.53(s, 2H, CH_2), 3.57(s, 3H, OCH_3), 2.17(s, 3H, Ar-CH_3), 0.87(s, 3H, CH_3).

2-(2-methoxybenzyl)-5-methyl-4-(4-nitrophenyl)-2H-1,2,4-triazole-3(4H)-thione (4q)

IR: 3400(Ar-CH), 2322(Aliphatic-CH), 1625(C=N), 1600(C=C), 1512(C=S), 1480(-NO_2), 1069(N-N), 1022(C-O-C). ^{1}H NMR: 6.1-8.2(m, 8H, Ar-H), 4.23(s, 2H, CH_2), 3.52(s, 3H, OCH_3), 0.87(s, 3H, CH_3).

2-(2-Methoxybenzyl)-4-(2-methoxyphenyl)-5-methyl-2H-1,2,4-triazole-3(4H)-thione (4r)

IR: 3326(Ar-CH), 2352(Aliphatic-CH), 1632(C=C), 1590(C=N), 1425(C=S), 1190(C-O-C), 1026 (N-N). ^{1}H NMR: 6.1-7.3(m, 8H, Ar-H), 4.43(s, 2H, CH_2), 3.73(s, 3H, OCH_3), 0.81(s, 3H, CH_3).

2.2. Pharmacology

2.2.1. Anticonvulsant activity

Screening was performed on albino mice having weight in between 25-30 g. Experiment was done on fasting mice. Different groups of six mice were selected. Prior to administration, compounds (4a-r) were dissolved in PEG. Dosages of 30, 100 and 300 mg/kg ip were given to the animals. Screening was done following the Antiepileptic Drug Development Program protocol by Epilepsy, NIH, USA [6]. Animal screening was done according to protocol of CPCSEA and earlier approval was taken from IAEC of Translam Institute of Pharmaceutical Education & Research, Meerut-250001, Uttar Pradesh, INDIA. Registration number and date of registration is 1207/PO/c/2008/CPCSEA.

2.2.1.1. Maximal Electroshock Seizure (MES) test

Current of 50 mA with pulse of 60 Hz for 0.25 s was given to produce seizure. Mice were injected earlier with the compounds ip. Elimination of tonic extension of hind limb was noted as the end point. Anticonvulsant activity was judged after 0.5 hr and 4 hr intervals against the doses of 30, 100 and 300 mg per kg ip [7].

2.2.1.2. Subcutaneous Pentylenetetrazole Test (scPTZ)

The sc PTZ test was done following the established protocol. Pentylenetetrazole at the dose of 75 mg/kg subcutaneously administered in the posterior midline. This induces seizures in more than 95 % of mice. Failure to show even a single episode of clonic spasm was considered as protection [7].

2.2.2. Toxicity studies

2.2.2.1. Rotorod Test

Rotorod test was performed to check the toxicity. Prior to this test, training was given to mice to stay on revolving rod with 3.2 cm diameter. Compounds were administered intra peritoneal at dosages of 30, 100, 300 mg per kilogram body weight. Inability to stay for at least 1 minute on rod is checked as end point for this test. This loss of balance is due to muscle relaxant properties. The amount of drug at which fifty percent of the mice were lost the balance and dropped from the revolving rod was noted [8].

2.2.2.2. Ethanol Potentiation Test

Mice treated with test compounds were administered by 2.5 gram per kilogram ip dose of ethanol after 1h. In control mice, this dose of drug usually did not put the mice in lateral position. In this test the number of animals that were found in the lateral position after getting ethanol was noted down [9].

2.2.3. GABA-Transminase inhibition study

Most of the drugs display anticonvulsant action due to carbon dioxide retaining followed by inhibition of some enzymes. In present study potent analogues were examined in *vitro* against the GABA-T enzyme [10]. Test was achieved for 4 h as per as standard protocols [11].

3. RESULTS & DISCUSSION

3.1. Chemistry

Reaction steps for titled compounds (4a-r) are presented in Scheme 1. Acetohydrazide (1) is obtained by the reaction of hydrazine hydrate with ethyl acetate in presence of dry ethanol after 20–22 h refluxing. A mixture of compound (1) and aryl isothiocyanates in presence of 99% ethanol was heated for 5–6 h through refluxing to give the compound 1-acetyl-4-substituted aryl thiosemicarbazide (2a-f). A mixture of compound (2a-f) and NaOH solution was heated for 6 h to give the compounds 5-methyl-4-substituted aryl-1,2,4-triazole-3(4*H*)-thione (3a-f). Benzyl chloride was added slowly to the mixture of compounds (3a-f) and anhydrous potassium carbonate. After 8 hrs of stirring the mixture was transferred into water. In presence of vacuum it was concentrated to obtained final pure compound 2-substituted benzyl-5-methyl-4-aryl-2*H*-1, 2, 4-triazole-3(4*H*)-thione (4a-r). The physical and chemical features of all produced compounds are shown in Table 1.

3.2. Pharmacology

Anticonvulsant assessment and toxicity screening of final compounds (4a-r) are presented in Table 2. Rotorod and ethanol potentiation tests have been done to check any neurotoxicity. In present study Anticonvulsant activity was done against the most established models MES and scPTZ. For the reference anticonvulsant drugs phenytoin and carbamazepine were selected [12]. All of the screening compounds exhibited motivating results.

4c, 4e, 4f, 4i, 4k, 4m and 4q displayed 50 % or more protection at a dosage of 30 mg per kilogram after half an hour and have found to be potent as compared to phenytoin and carbamazepine in MES test. Compounds, 4c, 4e, 4k, 4m and 4q at the dose of 100 mg kg^{-1} showed protection even after 4h. At 30 mg kg^{-1} compound 4i displayed protection both after 0.5 h and 4 h. After 0.5 h of administration compound 4b, 4g, 4j, 4n, and 4r displayed protection at the dosage of 100 mg kg^{-1}. .

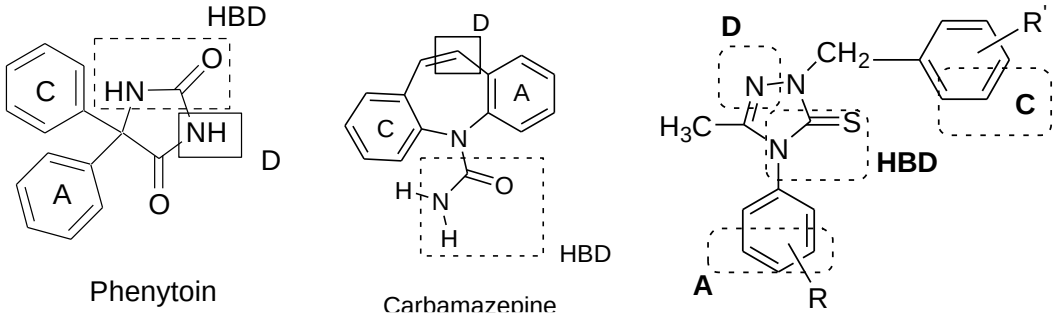
Compounds 4d, 4e 4h, 4j, 4k, 4m and 4o displayed 50 % or even high protection at a dosage of 30 mg per kilogram after half an hour in scPTZ test. Compounds 4d and 4m at the dose of 100 mg kg^{-1} displayed protection even after 4 hours. At 30 mg kg^{-1}, compound 4k displayed protection both after 0.5 h and 4 h and at a dose of 100 mg kg^{-1} compounds 4c, 4g, 4i, 4n, 4q and 4r showed protection after half an hour. Five compounds 4c, 4e, 4i, 4k and 4m were found to be very much promising results.

Ethanol potentiation and rotorod tests have been performed to establish any neurotoxicity. Compounds 4f, 4i, 4j, 4k and 4o potentiated the effect of ethanol and brought the mice in lateral position. In rotorod test, most of compounds confirmed to be less neurotoxic or even lack of any toxicity.

Optimum lipophilicity is required for the drug acting on CNS. The lipophilicity of potent compound 4e appeared to be least Log P value while other active compound 4i exhibited moderately high Log P.

Compounds 4c, 4e, 4i, 4k and 4m were passed through GABA-transaminase inhibition assay to establish the mechanism involved. GABA-transaminase enzyme helps to metabolize GABA and reduces its concentration. Inhibition of this enzyme definitely raises the GABA in brain and would be beneficial in seizure patients. The outcomes of the assay are shown in Table 3. All these compounds reduce GABA-T enzyme level after 2h, 3h and 4h time interval. Compound 4c showed effective in inhibition of GABA for long time.

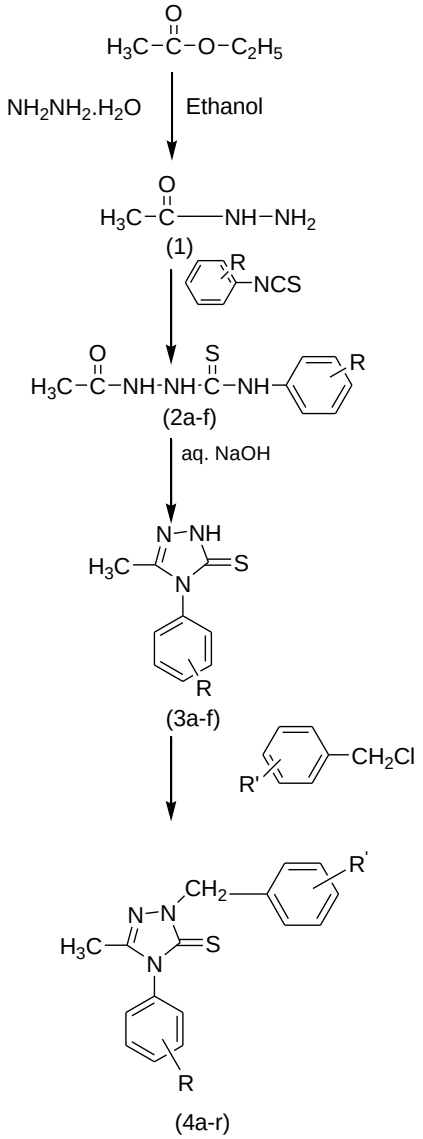
Compounds with electron withdrawing chloro and nitro substituent at the ortho and para position respectively to hydrophobic aryl group led to increase in anticonvulsant activity. While Compound with an electron withdrawing chloro substituent at the ortho position to hydrophobic aryl group and non-substituted benzyl group exhibited inhibition of GABA for long time.



(4a-r)

Hydrophobic area: A; Hydrogen bonding domain: HBD; electron donor moiety: D; distal hydrophobic area: C

Figure 1. Pharmacophoric elements essential for Anticonvulsants



Scheme-1

R = H, 2 -CH_3, 2-Cl, 4-CH_3, 4-NO_2, 2-OCH_3
R1= H, 2 -Cl, 2-OCH_3

Table 1. Physico-chemical properties of the compounds (4a-r)

Cmpd. No.	R	R′	Molecular Formula	R_f value	Log P	%age Yield	m.p. (°C)	Elemental analysis (%)		
								C	H	N
4a	H	H	$C_{16}H_{15}N_3S$	0.68	4.32	68	234-237	67.84	5.88	14.42
4b	2-CH_3	H	$C_{17}H_{17}N_3S$	0.62	4.81	64	268-271	68.63	6.35	13.71
4c	2-Cl	H	$C_{16}H_{14}ClN_3S$	0.74	4.88	66	276-279	61.40	3.96	13.87
4d	4-CH_3	H	$C_{17}H_{17}N_3S$	0.70	4.81	70	258-261	69.76	5.37	14.72
4e	4-NO_2	H	$C_{16}H_{14}N_4O_2S$	0.69	3.58	65	270-273	59.39	4.89	17.66
4f	2-OCH_3	H	$C_{17}H_{17}N_3OS$	0.66	4.20	69	298-301	64.91	6.13	13.96
4g	H	2-Cl	$C_{16}H_{14}ClN_3S$	0.71	4.88	67	286-289	61.25	3.92	13.89
4h	2-CH_3	2-Cl	$C_{17}H_{16}ClN_3S$	0.67	5.37	71	270-273	62.48	4.41	12.20
4i	2-Cl	2-Cl	$C_{16}H_{13}Cl_2N_3S$	0.65	5.44	66	254-257	54.18	3.22	12.54
4j	4-CH_3	2-Cl	$C_{17}H_{16}ClN_3S$	0.72	5.37	68	258-261	62.41	4.39	12.23
4k	4-NO_2	2-Cl	$C_{16}H_{13}ClN_4O_2S$	0.66	4.20	64	260-265	53.90	3.15	16.04
4l	2-OCH_3	2-Cl	$C_{17}H_{16}ClN_3OS$	0.70	4.75	72	256-262	59.55	5.19	12.65
4m	H	2-OCH_3	$C_{17}H_{17}N_3OS$	0.73	4.20	69	265-270	65.77	6.17	13.02
4n	2-CH_3	2-OCH_3	$C_{18}H_{19}N_3OS$	0.68	4.68	66	234-237	66.98	6.36	12.47
4o	2-Cl	2-OCH_3	$C_{17}H_{16}ClN_3OS$	0.61	4.75	63	301-306	59.64	5.21	12.67
4p	4-CH_3	2-OCH_3	$C_{18}H_{19}N_3OS$	0.65	4.68	72	254-257	66.93	6.38	12.47
4q	4-NO_2	2-OCH_3	$C_{17}H_{16}N_4O_3S$	0.70	3.72	69	247-251	57.79	5.09	15.26
4r	2-OCH_3	2-OCH_3	$C_{18}H_{19}N_3O_2S$	0.72	4.07	68	257-261	62.86	5.11	12.87

Elemental analysis and Log P was done using software ACD lab version 8. Solvent system used for TLC; Toluene: Ethyl acetate: Formic acid (5:4:1)

Table 2. Anticonvulsant and toxicity data of compounds (4a-r)

Comp. No.	**Intraperitoneal injection on mice**						
	MES screen		**scPTZ screen**		**Rotorod test**		**Ethanol Potentiation Test**
	0.5h	**4h**	**0.5h**	**4h**	**0.5h**	**4h**	
4a	300	-	300	300	300	-	X
4b	100	300	300	-	300	-	X
4c	30	100	100	300	100	300	(+)
4d	300	-	30	100	100	100	(+)
4e	30	100	30	300	300	-	X
4f	30	300	300	-	-	100	(-)
4g	100	300	100	300	-	-	(+)
4h	-	100	30	-	-	100	X
4i	30	30	100	-	100	-	(-)
4j	100	100	30	-	-	100	(-)
4k	30	100	30	300	-	-	(-)
4l	300	-	-	-	-	-	X
4m	30	100	30	100	-	-	(+)
4n	100	300	100	100	100	-	(+)
4o	-	100	30	-	-	100	(-)
4p	300	-	-	30	100	30	X
4q	30	100	100	300	300	-	X
4r	100	-	100	-	30	-	X
Phenytoin	30	30	-	-	100	100	X
Carbamazepine	30	100	300	100	300	-	X

Figures in the table display the minimum dose on which protection showed in mice. The (–) indicates the absence of activity at 300 mg kg^{-1}. The 'X' indicates not tested.

Ethanol Potentiation test; The (+) indicates animals passed the test while (-) indicates Failed.

Table 3. *In vitro* GABA-T inhibition assay

Compounds	**Percentage inhibition of GABA-T[a]**				
	0.5 h	**1.0 h**	**2.0 h**	**3.0 h**	**4.0 h**
Control	—	—	—	—	—
4c	4	7	9	10	11
4e	—	—	5	4	8
4i	—	11	14	17	28
4k	—	6	10	12	15
4m	—	10	13	18	30

4. CONCLUSIONS

Compounds 4a-r exhibited remarkable anticonvulsant activity with lesser neurotoxicity. Among the synthesized derivatives, 4c, 4e, 4i, 4k and 4m displayed promising anticonvulsant against both the MES and sc. PTZ seizure models. Most of them were to be less neurotoxic against rotorod and ethanol potentiation test. The above five potent compounds were established as GABA-transaminase inhibitor. These encouraging molecules can be explored for upcoming examinations.

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Conflicts of Interest

The authors declare no conflict of interest.

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