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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of substituted benzo[d]thiazol-2-ylcarbamates as potential anticonvulsants

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Abstract A series of substituted benzo[d]thiazol-2-ylcarbamates **4a–g** and **5a–g** were synthesized and evaluated for anticonvulsant activity. The structures of the synthesized compounds were confirmed on the basis of their physical and spectral data. The compounds were evaluated for anticonvulsant activity using PTZ-induced convulsion and maximal electroshock models. The target compounds have shown significant activity in these models.

Keywords Benzothiazole · Carbamate · Anticonvulsant activity

Introduction

Epilepsy is not a disease, but a syndrome of different cerebral disorders of central nervous system (CNS), and is characterized by paroxysmal, excessive, and hypersynchronous discharges of large numbers of neurons. (Wasteralin *et al.*, 1989). It is a common neurological condition, affecting 0.5–1 % of the population worldwide (45–100 million people) and is characterized by recurrent seizure attacks. The prevalence of epilepsy in developing countries is usually higher than in developed countries. The incidence and prevalence rates are surprisingly similar to those in developed countries. A recent study conducted in Kolkata's urban population showed an annual incidence rate of 27.27 per 100,000 per year. (Banerjee *et al.*, 2010). There is a continuing demand for new anticonvulsant agents as several of the currently available antiepileptic drugs (AEDs) have been associated with severe side effects and fail to control seizures in about 30 % of epileptic patients. (Mc Namara, 2006; Kramer, 2001; Kwan and Brodie, 2000). Therefore, intensive research efforts are being devoted to find new anticonvulsant compounds with promising activity.

Benzothiazole is a bicyclic ring system with electron rich sulfur and nitrogen atom. Rana et. al (2000) in their review on benzothiazole have listed various pharmacological actions displayed by benzothiazole like antimicrobial, antitubercular, anticonvulsant, antitumor, antihyperglycemic, and HIV-1 integrase inhibition. Biologist's attention was drawn to the benzothiazole containing compounds with the discovery of riluzole. Du et. al 2007 determined the role of riluzole and lamotrigine on AMPA receptor localization.

In the recent years, several new drugs have been added to the list of therapeutic agents against epilepsy. (Fig. 1) Among these felbamate (Lemke and Williams, 2008), topiramate (Liberatore *et al.*, 2007), RWJ 333369 & meprobamate are carbamate derivatives with a broad spectrum of anticonvulsant activity.

These literature findings prompted us to synthesize benzo[d]thiazol-2-ylcarbamate derivatives **4a–g** and **5a–g** in the hope to develop compounds having significant anticonvulsant activity.

Experimental

The target compounds **4a–g** and **5a–g** were synthesized via two step pathway indicated in Scheme 1. All the chemicals used in the synthesis were of laboratory grade. Melting

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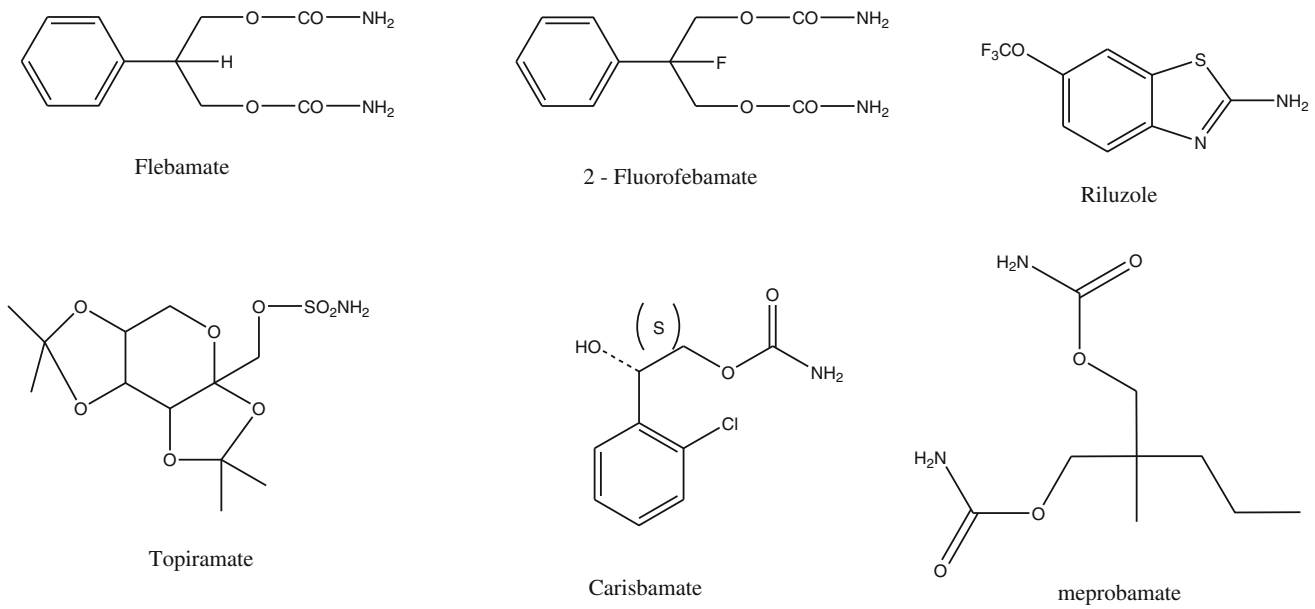


Fig. 1 Some examples of anticonvulsant agents

points were determined in open capillary on Veego (model: VMP-D) electronic apparatus and are uncorrected. The IR spectra of the synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO using NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are given in units as parts per million, downfield from Tetra Methyl Silane (TMS) as an internal standard. Mass spectra were taken on Schimatzu GC–MS spectrometer. To monitor the reactions, purity of reactants and products, thin layer chromatography was performed on precoated aluminum sheets (silica gel 60 F_{254}, 6 × 2.5 cm) using benzene: methanol solvent systems. The physical and spectral data are given in Tables 1 and 2, respectively.

General procedure for substituted benzo[d]thiazol-2-yl carbamate **4a–g** and **5a–g**

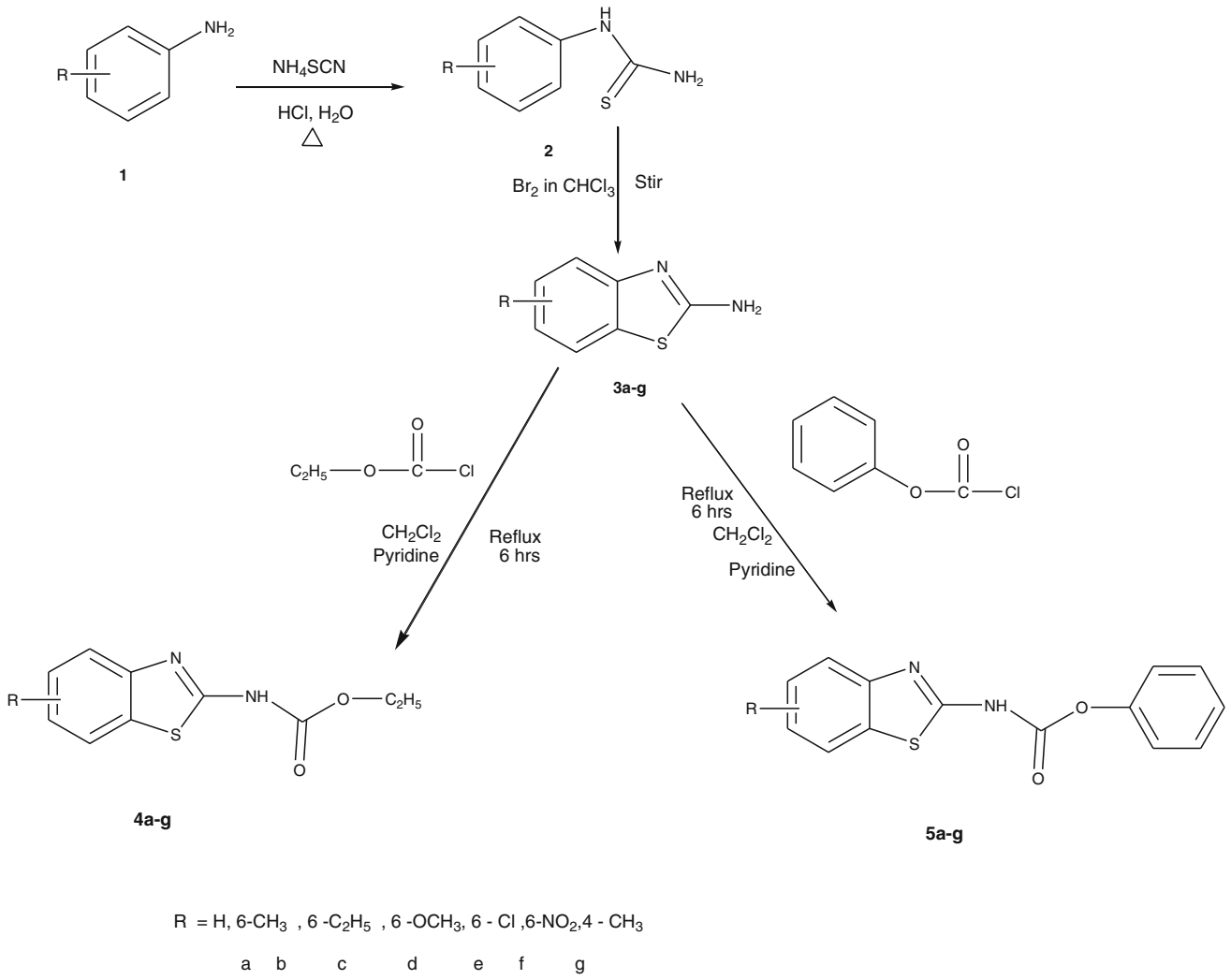
The target compounds **4a–g** and **5a–g** were synthesized as per scheme 1. Substituted 2-amino benzothiazole (**3a–g**) (0.1 mmol), synthesized as per reported procedure [Liberatore *et al.*, 2007] was dissolved in a 80 ml of dry dichloromethane containing pyridine (0.1 mmol). To this solution was added ethyl chloroformate (for **4a–g**) or phenyl chloroformate (0.1 mmol) (for **5a–g**) and the reaction mixture was refluxed for 6 h. The reaction mixture was then diluted with dichloromethane (200 ml) and washed with portion of 1 M sodium bicarbonate solution, followed by water and then brine. The organic layer was collected and dried over sodium sulfate. The solvent was removed under reduced pressure to yield the product which was recrystallized from toluene: methanol mixture.

Biology

The synthesized compounds were evaluated for anticonvulsant activity using PTZ and electroshock-induced convulsion models. Albino male Swiss mice (20–25 g) were housed (5 animals per cage) under the standard laboratory conditions (light period of 12 h/day, temperature 25 ± 2 °C, and humidity 55 ± 5 %) with free access to food (standard pellets chow, Lipton, India) and water. Food but not water was deprived overnight and during the experiment. Animals were dosed, one at a time.

Pentylenetetrazole (PTZ)-induced seizure (Vogel *et al.*, 2002)

The method employs PTZ to induce clonic convulsion in mice. Animals were divided into three groups, control, standard, and test group, each containing six animals. The control group received 0.1 % CMC suspension while the standard group received the standard drug (phenytoin) in 20 mg/kg dose. The test group was administered test compound **4a–g** and **5a–g** in a dose of 35 mg/kg, PTZ (60 mg/kg) was administered to the mice 60 min after the administration of test compounds and the standard. Mice were then observed over a period of 30 min. The absence of an episode of clonic spasm of at least 5 s duration



Scheme 1 Synthetic procedure for preparation of the target compound

indicated the compound's ability to abolish the effect of PTZ on seizure threshold.

Maximal electroshock (MES) seizures (Vogel *et al.*, 2002)

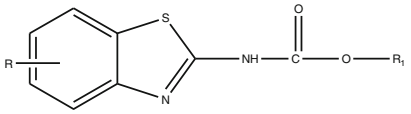
Convulsion in mice was produced using Electroconvulsometer. Similar to the above procedure, animals were divided into three groups, control, standard, and test group, each containing six animals. The control group received 0.1 % CMC suspension while the standard group received the standard drug (phenytoin) in 20 mg/kg dose. The test group was administered test compound **4a–g** and **5a–g** in a dose of 35 mg/kg. An alternating current (54 mA) was delivered via crocodile ear clip for 0.3 s 30 min after the administration of standard and the test compounds.. The percent protection and duration of hind limb extension were calculated.

Result and discussion

Chemistry

All the synthesized substituted ethyl benzo[d]thiazol-2-yl) carbamate **4a–g** and substituted phenyl benzo[d]thiazol-2-yl) carbamate **5a–g** were high melting solids (Table 1). These compounds were found to be soluble in DMSO. The solid state spectra (KBr, cm^{-1}) of (**4a–g**) (Table 2) reveal characteristic aromatic stretch at 2,900–3,000 $cm^{-1,}$ and N–H stretch at 3,100–3,300 cm^{-1}. The C=N group present in the benzothiazole ring reveals peaks at 1,600–1,500 cm^{-1}, while

Table 1 Physical data of compounds **4a–g** and **5a–g**



Compound	R	R_1	Yield	M.P. (°C)	R_f^a
4a	H	C_2H_5	80	209–212	0.52
4b	6-CH_3	C_2H_5	78	248–251	0.45
4c	6-C_2H_5	C_2H_5	65	210–212	0.45
4d	6-OCH_3	C_2H_5	75	225–227	0.55
4e	6-Cl	C_2H_5	80	235–237	0.5
4f	6-NO_2	C_2H_5	80	200–202	0.65
4g	4-CH_3	C_2H_5	75	205–207	0.63
5a	H	C_6H_5	75	230–233	0.45
5b	6-CH_3	C_6H_5	90	247–250	0.6
5c	6-C_2H_5	C_6H_5	90	210–212	0.75
5d	6-OCH_3	C_6H_5	85	225–228	0.5
5e	6-Cl	C_6H_5	80	270–272	0.7
5f	6-NO_2	C_6H_5	80	200–202	0.65
5g	4-CH_3	C_6H_5	75	230–232	0.7

[a] Solvent system: benzene : methanol

the carbonyl (C=O) peak of carbamate is seen at 1,700–1,750 cm^{-1} and C–O stretch at 1,000–1,100 cm^{-1}. The peak for C–N stretch is observed at 1,350–1,280 cm^{-1}. The ^1H NMR (δ) spectra of the (**4a–g)** were recorded in DMSO. A singlet of secondary amide proton at around 12 ppm and a quartet of methylene proton was observed at around 4 ppm. A doublet of methyl protons appeared around 2 ppm. The aromatic protons were observed at 7–8 ppm as multiplet.

IR spectra of (**5a–g**) show the stretching vibrations for secondary amide between 3,093 cm^{-1} and 3,141 cm^{-1}. The carbonyl C=O stretching was observed between 1,722 and 1,758 $cm^{-}1$, C=N at 1,574 cm^{-1}; C–N at 1,282 cm^{-1} and C–O at 1,053 cm^{-1}. The ^1H NMR spectra of **5a–g** was recorded in DMSO. The spectra reveal a peak by secondary amide proton at 12.65 ppm. The aromatic protons showed peaks at 7–8.5 ppm as multiplet. Therefore, the spectral data confirms the structure assigned to these compounds.

Biological activity

The synthesized compounds were tested for anticonvulsant activity using PTZ and electroshock-induced convulsion models. Phenytoin was used as standard. The results are reported in Tables 3 and 4.

All target compounds **4a–g** and **5a–g** exhibited significant anticonvulsant activity for both PTZ and MES models. While ethyl 6-methyl benzo[d]thizol-2-ylcarbamate **4b,** ethyl 6-methoxy benzo[d] thiazol-2yl carbamate **4d,** phenyl benzo [d]thiazole-2-yl carbamate **5a**, phenyl 6-methylbenzo[d]thiazol-2-ylcarbamate **5b**, phenyl 6-nitrobenzo[d]thiazol-2-ylcarbamate **5f** completely prevented the onset of clonic convulsions thereby providing 100 % protection in PTZ model. In the maximal electroshock- induced convulsions model also, compound **4b** and **5b** displayed activity very near to that of standard. The two compounds increased the latency of onset of clonus to more than 10 min. The compound ethyl 6-methylbenzo[d]thizol-2-ylcarbamate **4b** and phenyl 6-methylbenzo[d]thiazol-2-ylcarbamate **5b** has shown significant activity (Figs. 2, 3).

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The compound phenyl 6-methylbenzo[d]thiazol-2-ylcarbamate **5b** has been found to be active in both biological models. The compounds **4e** and **5d** were found to be least active in both models. So we may state that electron withdrawing group in benzothiazole ring shows significant activity and electron donating groups like chloro and methoxy show least activity.

Conclusion

The target compounds (**4a–g** and **5a–g**), carbamate derivatives of benzothiazole were synthesized using simple scheme

Table 2 Spectral data of compounds **4a–g** and **5a–g**

Compound	IR (cm^{-1})	^{1}H NMR(DMSO-d_6) δ ppm*	MS (*m/z*)
4a	ArCH(2963), NH(3141), C=O (1722), C=N(1606), C–N(1280), C–O(1060)	12(1H,s,CONH)7-8 (4H, m,ArCH), 4.2 (q, 2H, $J = 7.1$), 2.2(t, 3H, $J = 6.2$).	224(M+2),222(M+),177(M−47),150(M−72)
4b	ArCH(2962), NH(3165), C=O (1748), C=N(1610), C–N(1288), C–O(1057)	12(1H,s,CONH),7-8 (3H, m,ArCH), 4.2 (q, 2H, $J = 6.6$), 2.2(3H, s,CH3), 2.35(t, 3H, $J = 6.6$).	238(M+2),236(M+), (M+45),164(M−72)
4c	ArCH(2963), NH(3086), C=O (1749), C=N(1611), C–N(1300), C–O(1082)	11.90(s,1H,CONH),7-8 (3H, m,ArCH), 4.12 (q, 2H, $J = 6.9$) 1.24 (t, 3H, $J = 15.2$ Hz), 2.59(2H, q,CH_2), 1.30(t, 3H, $J = 6.5$)	252(M+2),250(M+),205(M−45),178(M−72)
4d	ArCH(2983), NH(3093), C=O (1748), C=N(1574), C–N(1283), C–O(1053)	11.59(1H,s,CONH),7-8 (3H, m,ArCH), 4.12 (q, 2H,$J = 7.2$)1.30(t, 3H, $J = 6.2$), 3.73(3H, s,CH_3)	252(M+),207(M−45) 180(M−72)
4e	ArCH(2849), NH(3066), C=O (1606), C=N(1500), C–N(1300), C–O(1150), Cl(700)	12.19(1H,s,CONH),7-8 (3H, m,ArCH), 4.12 (q, 2H, $J = 7.2$) 1.17 (t, 3H, $J = 6.2$).	256(M+),210(M−46) 183(M−73)
4f	ArCH(2849), NH(3066), C=O (1606), =N(1500), C–N(1300), C–O(1150), Cl(700)	12.06(1H,CONH,s),7-8 (3H, m,ArCH), (q, 2H, $J = 7.3$), 1.12(t, 3H, $J = 6.6$).	267(M+),222(M−45), 195(M−72)
4g	ArCH(2910), NH(3072), C=O (1720), C=N(1605), C–N(1209), C–O(1037)	12(1H,s,CONH),7-8 (3H, m,ArCH), 4.20 (q, 2H, $J = 7.2$) 1.24(t, 3H, $J = 6.5$),2.45(3H, s,CH_3)	236(M+),191(M−45), 164(M−72)
5a	ArCH(2983), NH(3093), C=O (1748), C=N(1574), C–N(1283), C–O(1053)	12.62(1H,s,CONH),7-8 (9H, m,ArCH)	270(M+),176(M−64), 148(M−122)
5b	ArCH(2922), NH(3086), C=O (1733), C=N(1574), C–N(1288), C–O(1150)	12.62(1H,s,CONH),7-8 (8H, m,ArCH), 2.40(3H, s,CH_3)	284.90(M+) 191(M−93),164(M−120)
5c	ArCH(2965), NH(3173), C=O (1758), C=N(1631), C–N(1250), C–O(1039)	12(1H,s,CONH),7-8 (8H, m,ArCH), 2.75(q, 2H, $J = 7.2$) 1.20 (t, 3H, $J = 6.1$)	298(M+),205.26(M−93),178(M−120)
5d	ArCH(2927), NH(3091), C=O (1733), C=N(1582), C–N(1274), C–O(1045)	12.30(1H,s,CONH),7-8 (8H, m,ArCH), 3.75(3H, s,CH_3),	300(M+),207(M−93), 180(M−120)
5e	ArCH(2983), NH(3141), C=O (1722), C=N(1564), C–N(1280), C–O(1060)	12.60(1H,s,CONH),7-8 (8H, m,ArCH)	304(M +),212(M−92), 184(M−120)
5f	ArCH(2983), NH(3141), C=O(1722), C=N(1564), C–N(1280), C–O(1060)	12.80(1H,s,CONH),7-8 (8H, m,ArCH)	315(M+),221(M−94) 195(M−120)
5g	ArCH(2983), NH(3141), C=O (1722), C=N(1564), C–N(1280), C–O(1060)	12.70(1H,s,CONH),7-8 (8H, m,ArCH), 2.60(3H, s,CH_3)	284(M+),190(M−94), 164(M−120)

* CONH proton at 12 δ ppm was found to be D_2O exchangeable

Table 3 Observation table for pentylenetetrazole (PTZ)-induced convulsion in mice

Group $n = 6$	Onset of clonic convulsions (sec)	Protection (%)	Death/recovery (%)
Control	59.166 ± 0.04216	0	All died
Standard(Phenytoin) 20 mg/kg	Absent	100	No death
4a (35 mg/kg)	86.66 ± 0.4216***	83.33	16.67
4b (35 mg/kg)	Absent	100	No death
4c (35 mg/kg)	83 ± 0.5164***	83.33	16.67
4d (35 mg/kg)	Absent	100	No death
4e (35 mg/kg)	71.83 ± 0.7032***	66.66	33.34
4f (35 mg/kg)	80.5 ± 0.03416***	83.33	16.67
4g (35 mg/kg)	85.166 ± 0.3073***	83.33	16.67
5a (35 mg/kg)	Absent	100	No death
5b (35 mg/kg)	Absent	100	No death
5c (35 mg/kg)	86 ± 0.5164***	83.33	16.67
5d (35 mg/kg)	80.5 ± 0.3416***	66.66	33.34
5e (35 mg/kg)	70.83 ± 0.4014***	66.66	33.34
5f (35 mg/kg)	Absent	100	No death
5g (35 mg/kg)	75.166 ± 0.1667***	83.33	16.67

Data were analyzed by one-way ANOVA followed by Dunnett's test. Values were expressed as Mean ± S.E.M

*** $P < 0.001$, as compared with control (0.1 % CMC suspension) group

Table 4 Observation table of maximal electroshock-induced convulsion

Group $n = 6$	Duration of tonic flexion sec.	Duration of tonic extension sec.	Latency of onset of clonus min.	Death/ recovery
Control	0	20.66 ± 0.8433	3.16 ± 0.0833	All died
Standard	5.34 ± 0.1261**	0	13.39 ± 0.1381**	No death
4a (35 mg/kg)	7.29 ± 0.1020**	0	11.18 ± 0.0628**	No death
4b (35 mg/kg)	6.24 ± 0.0988**	0	12.55 ± 0.1537**	No death
4c (35 mg/kg)	8.12 ± 0.1765**	0	10.415 ± 0.1061**	No death
4d (35 mg/kg)	6.40 ± 0.1350**	0	9.56 ± 0.1071**	No death
4e (35 mg/kg)	9.27 ± 0.1596**	0	5.40 ± 0.1506**	No death
4f (35 mg/kg)	7.44 ± 0.1650**	0	8.37 ± 0.1776**	No death
4g (35 mg/kg)	7.33 ± 0.1418**	0	10.36 ± 0.1364**	No death
5a (35 mg/kg)	9.54 ± 0.1518**	0	11.47 ± 0.1464**	No death
5b (35 mg/kg)	6.74 ± 0.2737**	0	13.28 ± 0.3741**	No death
5c (35 mg/kg)	5.2916 ± 0.1635**	0	7.59 ± 0.1117**	No death
5d (35 mg/kg)	11.08 ± 0.1183**	0	4.675 ± 0.1186**	No death
5e (35 mg/kg)	8.34 ± 0.06534**	0	11.20 ± 0.071**	No death
5f (35 mg/kg)	6.32 ± 0.1375**	0	10.34 ± 0.166**	No death
5g (35 mg/kg)	5.48 ± 0.1510**	0	9.58 ± 0.1291**	No death

Data were analyzed by one-way ANOVA followed by Dunnett's test. Values were expressed as Mean ± S.E.M

** $P < 0.01$, significant as compared with control (0.1 % CMC suspension) group

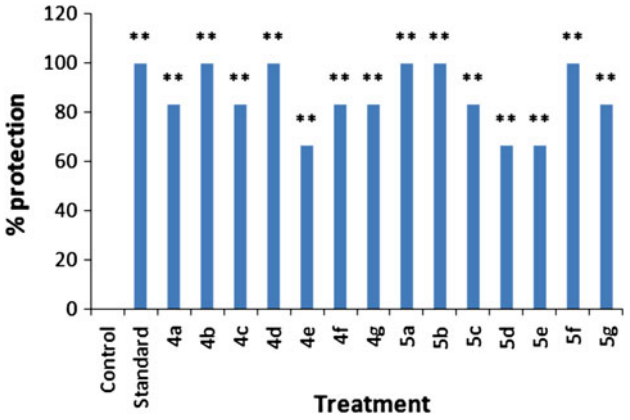

Fig. 2 Graph of % protection vs treatment given to the groups

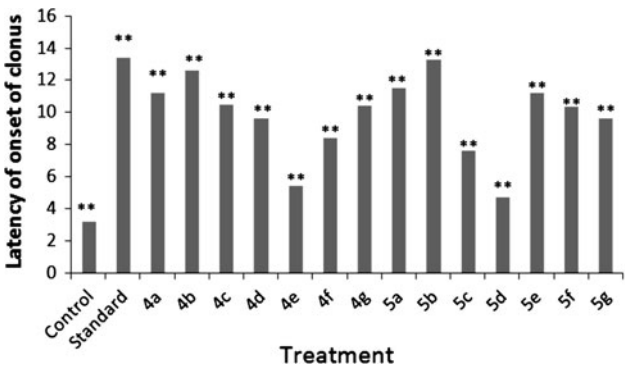

Fig. 3 Graph of latency of onset of clonus versus treatment given to the groups

and were evaluated for their anticonvulsant activity using two popular models, that is PTZ and maximal electroshock-induced convulsions. As evident from the biological activity data, all the compounds have displayed significant protection against the two types of convulsions. Compounds **4b, 4d, 5a, 5b**, and **5f** have shown 100 % protection and no animal death has been seen. Hence, we may conclude that the reported series of substituted benzo[d]thiazol-2-ylcarbamates holds promise for the development as potential anticonvulsant agents after further optimization.

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