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SYNTHESIS, ANTICONVULSANT AND NEUROTOXICITY EVALUATION OF 5-CARBOMETHOXYBENZOXAZOLE DERIVATIVES

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Abstract: A series of 5-carbomethoxybenzoxazole derivatives **(6a-t)** were prepared by using methyl-*p*-hydroxybenzoate. The identity of the compounds was confirmed on the basis of their elemental analysis and spectral data. In anti-MES test compounds **6b**, **6d**, **6h**, **6j**, **6m**, **6p**, **6q** and **6s** showed potent activity parallel to lipophilicity. Compounds **6b**, **6d**, **6k**, **6n** and **6s** successfully passed the rotorod test without any sign of neurological deficit.

Keywords: benzoxazole, phenyl isothiocyanates, anticonvulsant activity, neurotoxicity, lipophilicity

Since the past few decades, the literature has been enriched with progressive findings about the synthesis and pharmacological activities of various substituted benzoxazole derivatives. During recent years, there has been intense investigation of different classes of benzoxazole compounds and many of them were found to be pharmacologically active. The substituted benzoxazoles have attracted much attention due to their prominent utilization as anti-inflammatory (1), antiviral (2), antifungal (3), antibacterial (4), anticancer (5), antitubercular (6) and anticonvulsant (7) activity probably resulting from its planar and compact structure.

Benzoxazoles, heterocyclic compounds of varied biological activities were found to be one of the new classes of anticonvulsant agents as revealed by literature survey (8). In recent years, the field of antiepileptic drug development (ADD) has become quite dynamic, affording many promising research opportunities, and there is a continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with currently available antiepileptic drugs.

In the present work it was therefore thought to design and synthesize the first combination of benzoxazoles as a basic nucleus incorporated with substituted hydrazine carbothioamides moiety within a single molecule. Such combination is hoped to develop compounds with lipophilic character having potential anticonvulsant activity.

EXPERIMENTAL

Thin layer chromatography (TLC) was carried out using Silica gel G (Merck). TLC solvent systems used were: benzene : acetone (9 : 1, v/v) and (7 : 3, v/v), toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v). Iodine chamber and UV-lamp were used for visualization of TLC spots. Ashless Whatmann No. 1 filter paper was used for vacuum filtration. All the chemicals and solvents used were mostly of AR grade obtained from Merck, CDH and S. D. Fine. The melting points were determined in open glass capillaries using Kjedahl flask containing liquid paraffin and are uncorrected. The FT-IR spectra were recorded in KBr pellets on (BIO-RAD FTS), FT-IR spectrophotometer. The proton magnetic resonance spectra (^{1}H-NMR) were recorded on DRX-300 NMR spectrometer and BRUKER 400 Ultra Shield™. Chemical shifts (δ) are expressed in ppm in (DMSO-d_6) using TMS as an internal reference. The physical constants of the synthesized compounds are given in Table 1.

Anticonvulsant activity

Maximal Electroshock Seizure Test (MES)

The anticonvulsant screening of the final compounds was done according to the protocols of National Institute of Neurological Disorders and Stroke, NIH (USA). The compounds were screened for their anticonvulsant activity by electroshock

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seizure method (9-11). Supra-maximal electroshocks of current intensity of 50 mA, 60 Hz for 0.2 s duration were given to mice after administration with 30, 100 and 300 mg/kg doses of test compounds. The abolition of the hind limb tonic extensor spasm was recorded as anticonvulsant activity.

Neurotoxicity Screening (NT)

The minimal motor impairment was measured in mice by the rotorod test (12). The mice (20-25 g) were trained to stay on an accelerating rotorod (diameter 3.2 cm) that rotated at 10 rpm. Only those mice were taken for the test, which can stay on the revolving rod for at least one minute. Trained animals were injected *i.p.* with the test compounds at doses of 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibration on the rod for at least one minute.

Log P determination

The dependence of biological activity in the set of congeneric agents or lipophilic character has been shown in many types of drug action in particular, the reports by Lien and co-workers indicated that the anticonvulsant activity of different types of compounds were correlated with lipophilicity (13, 14). However, it has been observed that the maximum potency of the drugs that act on the central nervous system (CNS) is obtained with congeners having an optimum lipophilicity (log P) near 2. In this study, we attempted to correlate the anticonvulsant activity of the 5-carbomethoxybenzoxazole analogues with the calculated log P value, CLOGP (15). This experimental log P values were determined using chloroform phosphate buffer method (16) for compounds **(6a-t)**.

Synthesis of 4-carbomethoxy-2-nitrophenol **(2)**

The synthesis of 4-carbomethoxy-2-nitrophenol was carried out according to the procedure described elsewhere (17). To a solution of aluminium nitrate (40 g) in acetic acid : acetic anhydride (1 : 1, v/v) mixture (160 mL) 40 g of methyl-p-hydroxybenzoate (**1**) was added in small portions, while cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 h while shaking the contents intermittently to complete the nitration. The resulting brown solution was diluted

Table 1. Physical constants of compounds **6a-t**.

Comp. no.	R	R_1	Mol. Formula[a]	M. p[b] (°C)	Yield (%)	logP[c]	R_f[d] value
6a	H	H	$C_{21}H_{16}N_4O_2S$	112-115	60	1.43	0.69
6b	H	2-OCH_3	$C_{22}H_{18}N_4O_3S$	196-200	50	1.89	0.58
6c	H	4-OCH_3	$C_{22}H_{18}N_4O_3S$	198-201	75	0.38	0.60
6d	H	2-CH_3	$C_{22}H_{18}N_4O_2S$	153-156	65	1.95	0.51
6e	H	3-CH_3	$C_{22}H_{18}N_4O_2S$	155-161	75	1.19	0.55
6f	H	4-CH_3	$C_{22}H_{18}N_4O_2S$	160-165	75	0.42	0.59
6g	2-Cl	H	$C_{21}H_{15}ClN_4O_2S$	90-96	60	1.54	0.64
6h	2-Cl	2-OCH_3	$C_{22}H_{17}ClN_4O_3S$	187-190	75	1.98	0.68
6i	2-Cl	4-OCH_3	$C_{22}H_{17}ClN_4O_3S$	197-203	60	0.47	0.71
6j	2-Cl	2-CH_3	$C_{22}H_{17}ClN_4O_2S$	126-130	68	1.12	0.56
6k	2-Cl	3-CH_3	$C_{22}H_{17}ClN_4O_2S$	142-151	50	1.46	0.69
6l	2-Cl	4-CH_3	$C_{22}H_{17}ClN_4O_2S$	148-153	65	1.08	0.74
6m	4-Cl	H	$C_{21}H_{15}ClN_4O_2S$	106-113	68	0.32	0.65
6n	4-Cl	2-OCH_3	$C_{22}H_{17}ClN_4O_3S$	203-210	40	1.82	0.63
6o	4-Cl	4-OCH_3	$C_{22}H_{17}ClN_4O_3S$	193-206	50	1.56	0.69
6p	4-Cl	2-CH_3	$C_{22}H_{17}ClN_4O_2S$	133-140	75	0.67	0.58
6q	4-Cl	3-CH_3	$C_{22}H_{17}ClN_4O_2S$	138-145	75	0.92	0.73
6r	4-Cl	4-CH_3	$C_{22}H_{17}ClN_4O_2S$	145-158	76	1.01	0.75
6s	4-Br	H	$C_{21}H_{15}BrN_4O_2S$	197-209	60	1.59	0.74
6t	4-Br	2-OCH_3	$C_{22}H_{17}BrN_4O_3S$	210-216	66	0.32	0.72

[a] Solvent of crystallization – ethanol. [b] Melting point of the compounds at their decomposition, [c] Log P was calculated using absorbance data, chloroform / phosphate buffer at 28°C, [d] Solvent system – benzene : acetone (8 : 2, v/v), toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v). Elemental analyses for C, H, N were within ± 0.4 % of the theoretical value.

Table 2. Spectral data of compounds **6a-t**.

Compound no.	IR (KBr), cm^{-1}	NMR (DMSO-d_6), δ (ppm)
6a	3235 (NH str), 2897 (CH str), 1689 (C=O), 1555 (C=N, cyclic), 1486 (C=C, Ar), 1255 (C=S)	7.56 – 8.25 (m, 13H, Ar-H), 9.50 (s, 1H, -C(S)NH), 9.89 (s, 1H, NH-Ph) , 9.98 (s, 1H, -C(O)NH)
6b	3227 (NH str), 2958 (CH str), 1599 (C=O), 1530 (C=N, cyclic), 1483 (C=C, Ar), 1307 (C=S)	3.02 (s, 3H, OCH_3), 6.90 – 7.92 (m, 9H, Ar-H), 8.02 – 8.13 (m, 3H, benzoxazole), 9.12 (s, 1H, -C(S)NH), 9.33 (s, 1H, -C(O)NH), 9.59 (s, 1H, NH-Ph)
6c	3215 (NH str), 3007 (CH str), 1607 (C=O), 1545 (C=N, cyclic), 1463 (C=C, Ar), 1295 (C=S), 1028 (C-O-C)	3.75 (s, 3H, OCH_3), 6.81 – 7.38 (m, 9H, Ar-H), 8.02 – 8.13 (m, 3H, benzoxazole), 9.17 (s, 1H, -C(O)NH), 9.38 (s, 1H, -C(S)NH), 9.50 (s, 1H, NH-Ph)
6d	3225 (NH str), 3014 (CH str), 1688 (C=O), 1545 (C=N, cyclic), 1488 (C=C, Ar), 1298 (C=S)	2.75 (s, 3H, CH_3), 6.13 – 7.89 (m, 9H, Ar-H), 8.18 – 8.59 (m, 3H, benzoxazole), 9.02 (s, 1H, -C(S)NH), 9.26 (s, 1H, NH-Ph), 13.00 (s, H, -C(O)NH)
6e	3231 (NH str), 2935 (CH str), 1601 (C=O), 1563 (C=N, cyclic), 1488 (C=C, Ar), 1292 (C=S)	2.55 (s, 3H, CH_3), 6.61 – 7.65 (m, 9H, Ar-H), 8.20 – 8.61 (m, 3H, benzoxazole), 9.40 (s, 1H, -C(O)NH), 9.67 (s, 1H, -C(S)NH), 10.34 (s, 1H, NH-Ph)
6f	3188 (NH str), 3019 (CH str), 1543 (C=O), 1508 (C=N, cyclic), 1482 (C=C, Ar), 1311 (C=S)	2.51 (s, 3H, CH_3), 6.51 – 7.45 (m, 12H, Ar-H), 9.60 (s, 1H, -C(S)NH), 9.72 (s, 1H, NH-Ph), 10.04 (s, 1H, -C(O)NH)
6g	3205 (NH str), 3005 (CH str), 1725 (C=O), 1551 (C=N, cyclic), 1478 (C=C, Ar), 1341 (C=S), 746 (C-Cl)	6.91 – 7.56 (m, 12H, Ar-H), 9.60 (s, 1H, -C(S)NH), 9.72 (s, 1H, NH-Ph) , 9.86 (s, 1H, -C(O)NH)
6h	3228 (NH str), 2917 (CH str), 1668 (C=O), 5130 (C=N, cyclic), 1485 (C=C, Ar), 1332 (C=S), 1021 (C-O-C), 741 (C-Cl)	3.35 (s, 3H, OCH_3), 6.88 -7.90 (m, 8H, Ar-H), 8.02- 8.46 (m, 3H, benzoxazole), 9.35 (s, 1H, -C(S)NH), 9.72 (s, 1H, NH-Ph), 9.50 (s, 1H, -C(O)NH)
6i	3218 (NH str), 3007 (CH str), 1610 (C=O), 1545 (C=N, cyclic), 1463 (C=C, Ar), 1295 (C=S), 1027 (C-O-C), 743 (C-Cl)	3.59 (s, 3H, OCH_3), 6.64 – 7.55 (m, 8H, Ar-H), 8.09-8.19 (m, 3H, benzoxazole), 9.44 (s, 1H, -C(O)NH), 9.78 (s, 1H, -C(S)NH), 10.25 (s, 1H, NH-Ph)
6j	3235 (NH str), 3021 (CH str), 1690 (C=O), 1555 (C=N, cyclic), 1482 (C=C, Ar), 1300 (C=S), 747 (C-Cl)	2.50 (s, 3H, CH_3), 6.93 – 7.90 (m, 8H, Ar-H), 8.08 – 8.87 (m, 3H, benzoxazole), 9.24 (s, 1H, -C(S)NH), 9.50 (s, 1H, NH-Ph), 13.51 (s, 1H, -C(O)NH)
6k	3235 (NH str), 2979 (CH str), 1723 (C=O), 1561 (C=N, cyclic), 1485 (C=C, Ar), 1295 (C=S), 772 (C-Cl)	2.55 (s, 3H, CH_3), 6.61 – 7.69 (m, 11H, Ar-H), 8.21 (s, 1H, -C(S)NH), 9.42 (s, 1H, NH-Ph), 9.89 (s, 1H, -C(O)NH)
6l	3230 (NH str), 3027 (CH str), 1603 (C=O),1549 (C=N, cyclic), 1482 (C=C, Ar), 1309 (C=S), 748 (C-Cl)	2.53 (s, 3H, CH_3), 6.35 – 7.75 (m, 11H, Ar-H), 9.50 (s, 1H, -C(S)NH), 9.88 (s, 1H, NH-Ph), 10.28 (s, 1H, -C(O)NH)
6m	3215 (NH str), 3019 (CH str), 1680 (C=O), 1548 (C=N, cyclic), 1483 (C=C, Ar), 1295 (C=S), 746 (C-Cl)	6.93 – 7.57 (m, 12H, Ar-H), 9.35 (s, 1H, -C(S)NH), 9.72 (s, 1H, NH-Ph) , 9.86 (s, 1H, -C(O)NH)
6n	3256 (NH str), 3007 (CH str), 1687 (C=O), 1561 (C=N, cyclic), 1421 (C=C, Ar), 1291 (C=S), 1088 (C-O-C), 758 (C-Cl)	3.89 (s, 3H, OCH_3), 6.89 – 7.89 (m, 8H, Ar-H), 8.01 – 8.22 (m, 3H, benzoxazole), 9.05 (s, 1H, -C(S)NH), 9.52 (s, 1H, NH-Ph) , 10.53 (s, 1H, -C(O)NH)

Table 2. cont.

Compound no.	IR (KBr), cm^{-1}	NMR (DMSO-d_6), δ (ppm)
6o	3230 (NH str), 3001 (CH str), 1650 (C=O), 1530 (C=N, cyclic), 1448 (C=C, Ar), 1299 (C=S), 1011 (C-O-C), 746 (C-Cl)	3.50 (s, 3H, OCH_3), 6.88 – 7.67 (m, 8H, Ar-H), 8.45 – 8.98 (m, 3H, benzoxazole), 9.42 (s, 1H, C(O)NH), 9.72 (s, 1H, -C(S)NH), 9.98 (s, 1H, NH-Ph)
6p	3206 (NH str), 2968 (CH str), 1683 (C=O), 1524 (C=N, cyclic), 1479 (C=C, Ar), 1294 (C=S), 740 (C-Cl)	2.52 (s, 3H, CH_3), 6.93 – 7.95 (m, 11H, Ar-H), 8.87 (s, 1H, -C(S)NH), 9.21 (s, 1H, NH-Ph), 9.24 (s, 1H, -C(O)NH)
6q	3233 (NH str), 2975 (CH str), 1598 (C=O), 1561 (C=N, cyclic), 1485 (C=C, Ar), 1295 (C=S), 730 (C-Cl)	2.50 (s, 3H, CH_3), 6.45-7.31 (m, 11H, Ar-H), 9.39 (s, 1H, -C(S)NH), 9.72 (s, 1H, NH-Ph), 10.83 (s, 1H, -C(O)NH)
6r	3215 (NH str), 3007 (CH str), 1607 (C=O), 1545 (C=N, cyclic), 1463 (C=C, Ar), 1295 (C=S), 743 (C-Cl)	3.35 (s, 3H, OCH_3), 6.78 – 7.78 (m, 8H, Ar-H), 8.42-8.93 (m, 3H, benzoxazole), 9.12 (s, 1H, -C(O)NH), 9.89 (s, 1H, -C(S)NH), 10.34 (s, 1H, NH-Ph)
6s	3215 (NH str), 3031 (CH str), 1667 (C=O), 1545 (C=N, cyclic), 1479 (C=C, Ar), 1247 (C=S)	6.91 – 7.88 (m, 12H, Ar-H), 9.35 (s, 1H, -C(S)NH), 9.72 (s, 1H, NH-Ph) , 9.86 (s, 1H, -C(O)NH)
6t	3231 (NH str), 2912 (CH str), 1674 (C=O), 1583 (C=N, cyclic), 1483 (C=C, Ar), 1318 (C=S), 1063 (C-O-C), 545 (C-Br)	3.33 (s, 3H, OCH_3), 6.86 – 7.90 (m, 8H, Ar-H), 8.26 – 8.28 (m, 3H, benzoxazole), 9.57 (s, 1H, -C(S)NH), 9.85 (s, 1H, NH-Ph), 12.70 (s, 1H, -C(O)NH)

Table 3. Anticonvulsant and neurotoxicity evaluation of compounds **6a-t**.

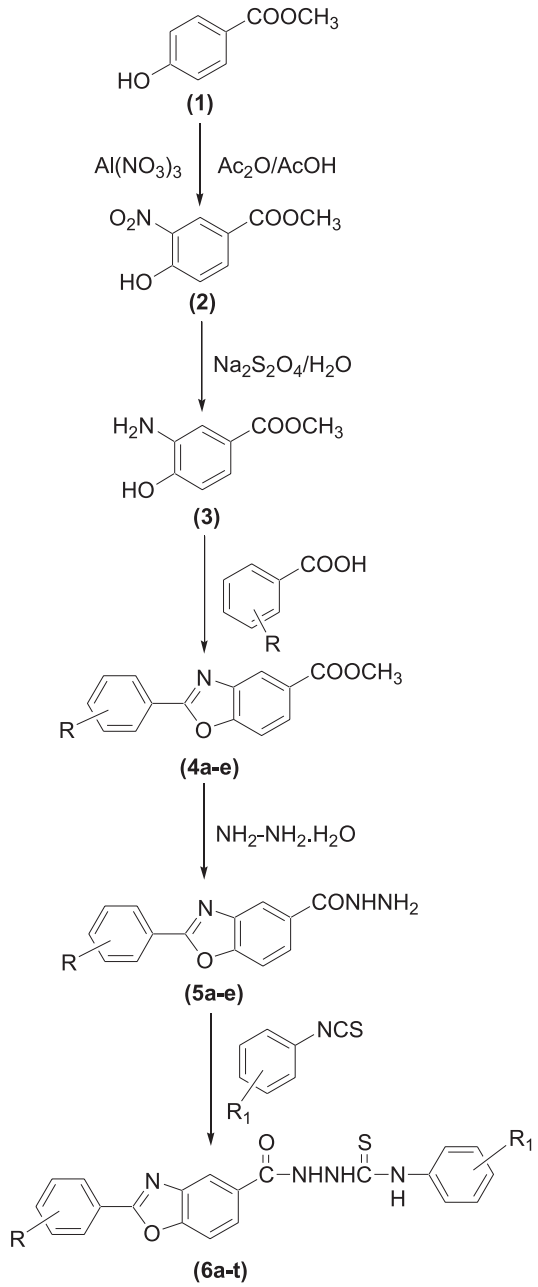
Compound	MES screen[a]		Neurotoxicity screen[a]	
no.	0.5 h	4 h	0.5 h	4 h
6a	100	300	300	—
6b	30	300	—	—
6c	100	300	300	—
6d	30	300	—	—
6e	100	300	—	300
6f	100	300	300	300
6g	—	300	300	—
6h	30	300	300	300
6i	100	300	—	300
6j	30	300	—	300
6k	100	300	—	—
6l	100	300	300	—
6m	30	300	—	300
6n	—	—	—	—
6o	100	—	300	—
6p	30	300	—	300
6q	30	300	—	300
6r	300	—	300	—
6s	30	—	—	—
6t	300	300	300	300
Phenytoin[b]	30	30	100	100
Carbamazepine[b]	30	100	300	300

[a] Doses of 30, 100 and 300 mg/kg were administered. The figures in the Table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice (n=6). The animals were examined 0.5 and 4 h after injections were made. The dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg). [b] Data from reference (22).

with ice cold water (500 mL) and acidified with conc. HNO_3 (40 mL) to get a bulky yellow precipitate of 4-carbomethoxy-2-nitrophenol.

Synthesis of 4-carbomethoxy-2-aminophenol **(3)**

The synthesis of 4-carbomethoxy-2-aminophenol was carried out according to the procedure described elsewhere (17). 4-Carbomethoxy-2-nitrophenol (**2**, 40 g) was dissolved in boiling ethanol (400 mL) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colorless. Then the solvent was reduced to one third of its volume by distillation and the residual liquid was triturated with ice cold water. The resulting colorless shiny product **(3)** was filtered, washed with cold water and dried.



R = H, 2-Cl, 4-Cl, 4-Br.

R_1 = H, 2- OCH_3, 4- OCH_3, 2-CH_3, 3-CH_3 ,4-CH_3.

Scheme 1. Synthesis of compounds **6a-t.**

Synthesis of methyl 2-substituted phenyl-1,3-benzoxazole-5-carboxylates **(4a-e)**

The synthesis of methyl-2-substituted phenyl-1,3-benzoxazole-5-carboxylates was carried out according to the procedure described elsewhere (18). 4-Carbomethoxy-2-aminophenol **(3)** (0.01mol) was refluxed with respective aromatic acids in excess under reflux for 15 h. The reaction mixture was cooled and poured onto the crushed ice with stirring to obtain the benzoxazole carboxylates.

Synthesis of 2-phenyl-1,3-benzoxazole-5-carbohydrazides **(5a-e)**

The synthesis of 2-phenyl-1,3-benzoxazole-5-carbohydrazides was carried out according to the procedure described elsewhere (19, 20). Benzoxazole carboxylates on heating under reflux with hydrazine hydrate (99%, 0.01 mol.) in absolute ethanol (25 mL) for 45-50 h yielded the acid hydrazides **(5a-e)** that were then separated out.

Synthesis of N-substituted phenyl-2-[(2-substituted phenyl-1,3-benzoxazol-5-yl)carbonyl]hydrazine carbothioamides **(6a-t)**

The synthesis of N-substituted phenyl-2-[(2-substituted phenyl-1,3-benzoxazol-5-yl)carbonyl]hydrazine carbothioamides was carried out according to the procedure described elsewhere (21). To a stirred solution of compound **(5a-e)** (0.002 mol) in absolute ethanol was added substituted phenyl isothiocyanate and refluxed for 2-4 h. The reaction mixture was concentrated and left over night. The crude product **(6a-t)** obtained was filtered, washed with petroleum ether, dried and recrystallized from absolute alcohol.

The synthetic route of the compounds is shown in Scheme 1.

RESULTS and DISCUSSION

In all the cases the TLC of the product showed the single spot confirming the chromatogram for only one product. The product with molecular formula R-C(O)NHNHC(S)NH-R_1 on warming with

alkaline lead acetate to go dehydrosulfurization indicating the thiocarbamoyl function attached to the R_1. Hence the product formed contains NH-C(=S)NH group having the structure (**6a-t**). The condensation has occurred on the exocyclic nitrogen atom.

The IR spectra of *N*-aryl substituted-2-[(2-aryl substituted -1,3-benzoxazol-5-yl)carbonyl]hydrazine carbothioamides **(6a-t)** showed absorption band at 3200-3100 cm^{-1} due to –NH stretching, 1350-1200 cm^{-1} due to C=S group, 1500-1400 cm^{-1} (C=C str., Ar), 500-700 cm^{-1} (monosubstituted phenyl). The ^{1}H NMR spectrum showed a multiplet at δ 6.9-7.9 ppm (8H-Ar) and broad singlet at 9.2-9.6 (1H) due to –NH adjacent to the phenyl ring. The spectral data of the titled compounds are summarized in Table 2.

In preliminary screening the test compounds dissolved in poly(propylene glycol) 400 were administered using an *i.p.* injection, at three dose levels (30, 100 and 300 mg/kg) in albino mice of either sex (Swiss strain) and the activity was examined after 0.5 and 4 h intervals against maximal electroshock-induced seizure (MES) threshold test. The anticonvulsant and neurotoxicity data of the compounds together with the literature data on standard drugs are summarized in Table 3.

The compounds that exhibited most potent anti-MES activity included **6b**, **6d**, **6h**, **6m**, **6p**, and **6q** which have activity comparable with that of phenytoin and carbamazepine.

Minimal motor impairment was measured by the rotorod test. Compounds **6b**, **6d**, **6k**, **6n** and **6s** successfully passed the rotorod test without any sign of neurological deficit, whereas compounds **6a**, **6c**, **6f**, **6g**, **6h**, **6l**, **6o**, **6r**, and **6t** exhibited neurological deficit at a dose of 300 mg/kg *i.p.*

Compounds **6b**, **6d**, **6h**, and **6n** were found to be more lipophilic having potent anticonvulsant activity. The other compounds **6a**, **6g**, **6k**, **6o**, and **6s** were also lipophilic having the same potency. Compounds **6e, 6j, 6l**, and **6r** were less lipophilic and were less active in MES test.

CONCLUSION

In conclusion, the present results have revealed that halosubstituted aryl at benzoxazole ring and alkyl or alkoxy substitutions at the carbothiomido aryl were essential for activity. Thus a number of *N*-aryl substituted-2-[(2-aryl substituted 1,3- benzoxazol-5-yl)carbonyl]hydrazine carbothiomides exhibited anticonvulsant activity in MES screen.

There were some compounds like **6b**, **6d**, **6h** and **6n** that showed more lipophilic character and were more active. The compounds **6a**, **6e**, **6g**, **6j**, **6k**, **6l**, **6o**, **6r** and **6s** were also lipophilic but were less active in MES test. Some of above mentioned compounds have shown higher degree of protection and obviously may have future commitment.

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