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Rapid microwave-assisted solution phase synthesis of 6, 8-disubstituted- 2-phenyl-3-(substituted-benzothiazole-2-yl) – 4-[3*H*]-quinazolinone as novel anticonvulsants#

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Abstract

A fast and highly efficient microwave accelerated solution phase procedure for the synthesis of a series of 2-phenyl-3-(substituted-benzothiazole-2-yl) - 4[3*H*]-quinazolinone is developed and title compound was characterized by elemental analyses and spectral (IR, 1H NMR and EI-MS) data. The anticonvulsant activity of all the title compounds (**3a-m** &**4a-m**) were evaluated against Maximum Electroshock (MES) induced seizures and further more the compounds were evaluated against subcutaneous pentylenetetrazole (PTZ) induced seizures model in mice. The neurotoxicity was assessed using Rotorod procedure. All the test compounds were administered intraperitoneally at a various dose levels ranging from 7-200 mg/Kg body wt and the median toxic dose (TD_{50}) and protection index (PI) values were determined and reported. In general compounds **3a-m** were found to be more potent compared to compounds **4a-m**. Among the compound tested , the compound **3e** in 2-phenyl-3-(substituted-benzothiazole-2-yl) – 4-[3*H*]-quinazolinones series and compound **4l** in 6,8, dibromo 2-phenyl-3-(substituted-benzothiazole-2-yl) – 4-[3*H*]-quinazolinones series were found to be the most potent.

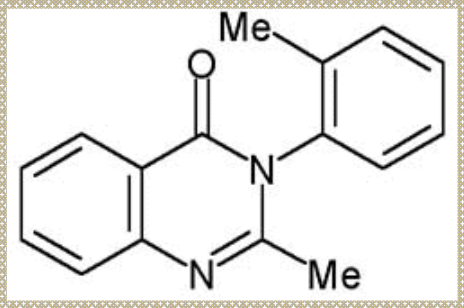
Keywords: Anticonvulsant, 4[3*H*]-quinazolinone, Microwave irradiation, 6,8-disubstituted-2-phenyl-3- (substituted benzothiazole-2-yl)-4[3*H*]-quinazolinone, Neurotoxicity.

Introduction

The development of novel agents, particularly compounds effective against complex seizures, remains a major focus of

antiepileptic drug research[1]. Literature survey reveals that 2-amino benzothiazole derivatives possessed potent anticonvulsant activity[2, 3]. In 1985, Riluzole (6-(trifluromethoxy)-2-benzothiazolamine) (Figure 1.) was reported as potent anticonvulsant agents that function by action on voltage-dependent sodium channels[3-5]**.** Similarly the sedative hypnotic (neurotoxic) properties of another pharmacophore 4[3*H*]-quinazolinones are well-documented [6-18]. The prototype sedative hypnotic in this class is Methaqualone (2-methyl-3-o-tolyl-4[3*H*] - quinazolinone) (Figure 1.) [19]. In spite of the fact that literally thousands of quinazolinone and 2-amino benzothiazole related compounds have been synthesized and tested for central nervous system depressant and anticonvulsant activity, no attempt have been made to incorporate benzothiazole moiety in quinazoline nucleus in single molecular framework.

We previously reported[20] conventional method for synthesis of 6, 8-disubstituted-2-phenyl-3-(substituted-benzothiazole-2-yl) - 4[3*H*]-quinazolinone which involves the fusion of 2-amino benzothiazole with 2-phenyl-3, 1[*H*] - benzoxazine-4-one in pyridine. This procedure usually needs high temperatures and requires lengthy and tedious conditions. Microwave irradiation is known to allow a striking reduction in reaction times and good yields than the purely thermal procedures. In this paper, we report the benefits associated with this new methodology and we identify standard experimental conditions. Following the strategy previously reported by us[20] for the synthesis of 6, 8-disubstituted-2-phenyl-3-(substituted-benzothiazole-2-yl) - 4[3*H*]-quinazolinone involves long heating (several hours) of the 2-amino benzothiazole with 2-phenyl-3, 1[*H*] - benzoxazine-4-one in pyridine at reflux temperature. So in this paper, the synthesis of 6, 8-disubstituted- 2-phenyl-3- (substituted-benzothiazole-2-yl)-4[3*H*]-quinazolinone (**3a-m** & **4a-m**) was realized under microwave irradiation with the aim to develop original and environmentally friendly procedures. Also aim is to evaluate their anti convulsant activity.



Methaqualone

Figure 1

Results and Discussion

Chemistry

Synthesis of the title compounds 3a-m and 4a-m has been carried out as depicted in Scheme 1. The starting 2-amino benzothiazole[21] (**1a-m**), 2-phenyl-3, 1[*H*] - benzoxazine-4-one[22] (**2a**) and 6, 8-dibromo-2-phenyl- 3, 1 [*H*] - benzoxazine-4-one[22] (**2b**) were prepared according to known procedures from commercially available substituted anilines, antharanilic acid and 3,5, dibromo anthranilic acid. Mixtures of 2-amino-benzothaizole 1a and 2-phenyl-3, 1[*H*] - benzoxazine-4-one 2a in dry pyridine were irradiated in a scientific microwave oven at reflux temperature (power input: 210 W). The products were isolated by pouring solution in a beaker containing crushed ice and little amount of conc. HCl. The solid separated (**3a**) was filtered, dried and recrystallised from appropriate solvent. The reaction mechanism for the synthesis of title compound had been reported[20]. The proposed work-up is fast, easy and clean and presents an advantage of less time and better yields than the conventional method. The transformation proceeded very clean, without any traces of side products. The results, which are summarized in Table 1, show that quantitative conversions were achieved after 10-20 min irradiation in the most part of the cases.

All of the synthesized compounds were characterized by their physical, analytical and spectral data. The IR, EI MS and ^{1}H NMR spectral data of all the synthesized compounds were in conformity with the structure assigned.

Pharmacology

The anticonvulsant activity of all the title compounds were evaluated against Maximum Electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (PTZ) induced seizures in mice[23]. Using Rotorod procedure the neurotoxicity of the all test compounds were assessed in mice (30). All the test compounds were administered intraperitoneally at various dose levels ranging from 7-200 mg/kg body wt., and the median effective dose (ED_{50}), median toxic dose (TD_{50}) and protection index (PI) values were determined. Suspensions of the test compounds in polyethylene glycol were administered to mice at 0.5 hour or 4 hours before evaluation of their activity. The result of anticonvulsant activity and neurotoxicity are presented in Table 2 &3

The anti MES and Anti sc PTZ activity (ED50 values in table 2 & 3) indicated significant anticonvulsant activity for the test compounds **3a-m** and **4a-m**. However, they were found less potent when compared with the reference standard phenytoin (ED50: 6.48 and 7.1 at t = 0.5 and 4 h in MES model). The different substituents on the aromatic ring exert a significant influence on the biological activity by modulating the lipophilicity and thereby facilitating penetration across the blood-brain barrier. The presence of electron withdrawing groups (halogen and nitro) on the aromatic ring in general decreases the potency of test compounds compared to compounds having electron-donating groups. This is because of decreased lipophilicity, which in turn inhibits permeability across biological membrane. Further it has been found that the ED_{50} and TD_{50} values of test compounds increase significantly at t = 4h, compared to t = 0.5h, in contrast to the reference standard, indicating that the test compounds were metabolized with time in the biological environment. This trend was found to be more pronounced in compounds **3g, 3j, 3k and 4a-m** (having electron withdrawing groups) compare to compounds **3a-f, 3h, 3i, 3l-m** (having electron-donating groups). To confirm this phenomenon in vivo, a kinetic study needed to be carried out in an animal model. Based upon the results it will also be necessary to optimize the lead compound by substituting a series of electron –donating groups on aromatic ring and selectively modifying the quinazoline nucleus. The protection index (PI) values are found to be more significant for determining the relation between lipophilicity and toxicity. Table 2 & 3 shows that PI values >3 were found for more potent compounds in contrast to less lipophilic compounds. Thus, as the lipophilicity an increase so does the toxicity and therefore also the protections index (PI). Among the compounds tested, the 2-phenyl-3- (4-methyl- benzothiazole-2-yl)-4[3H]-quinazolinone (**3e**) was found to be most potent (ED_{50} = 7.1 and 12.8 in MES model and 10 and 14 in scPTZ model at t =0.5h and 4h, respectively, and TD_{50} = 37.8 and 43 at t =0.5h and 4h, respectively, with protection index (PI) 5.3.

Further studies are in progress to optimize this lead compound and fully characterize the mode of action.

Table 1 Microwave assisted synthesis of compound 3a-m

Entry	R_4	R_5	R_6	Mol. formula (Mol. Wt)	Time [Min.]	Yield (%) Observed	m.p. °C Observed (Reported[2])	Mass (m^+)	Analysis %					
									Calculated			Found		
									C	H	N	C	H	N
3a	H	H	H	$C_{21}H_{13}N_3OS$ (355.4)	12	90	277-278 (276-278)	355	70.97	3.69	11.82	70.95	3.70	11.81
3b	OCH_3	H	H	$C_{22}H_{15}N_3O_2S$ (385.4)	10	85	(216-218)	385	68.55	3.92	10.90	68.56	3.91	10.88
3c	H	OCH_3	H	$C_{22}H_{15}N_3O_2S$ (385.4)	12	80	189-191 (190-192)	385	68.55	3.92	10.90	68.56	3.95	10.92
3d	H	H	OCH_3	$C_{22}H_{15}N_3O_2S$ (385.4)	14	85	192-194 (192-194)	385	68.55	3.92	10.90	68.56	3.90	10.89
3e	CH_3	H	H	$C_{22}H_{15}N_3OS$ (369.4)	12	80	152-153 (152-154)	369	71.52	4.09	11.37	71.50	4.12	11.36
3f	H	CH_3	H	$C_{22}H_{15}N_3OS$ (369.4)	13	90	189-180 (180-182)	369	71.52	4.09	11.37	71.54	4.13	11.38
3g	H	Cl	H	$C_{21}H_{12}ClN_3OS$ (389.86)	18	80	198-200 (198-200)	391[c]	64.70	3.10	10.78	64.73	3.11	10.80
3h	H	H	OC_2H_5	$C_{23}H_{17}N_3O_2S$ (399.46)	16	85	141-142 (140-142)	399	69.15	4.29	10.52	69.17	4.26	10.54
3i	H	OC_2H_5	H	$C_{23}H_{17}N_3O_2S$ (399.46)	14	80	192-194 (192-194)	399	69.15	4.29	10.52	69.19	4.27	10.53
3j	H	H	Br	$C_{21}H_{12}N_3OSBr$(434.3)	18	80	209-210 (208-210)	436[c]	58.07	2.78	9.68	58.09	2.75	9.65
3k	H	H	NO_2	$C_{21}H_{12}N_4O_3S$ (400.4)	20	80	262-264 (262-264)	400	62.99	3.02	13.99	62.97	3.05	13.96
3l	CH_3	H	CH_3	$C_{23}H_{17}N_3OS$ (383.4)	14	85	200-201 (200-202)	383	72.04	4.47	10.96	72.05	4.45	10.98
3m	OC_2H_5	H	H	$C_{23}H_{17}N_3O_2S$ (399.46)	14	85	216-218 (216-218)	401	69.15	4.29	10.52	69.16	4.30	10.55
4a	H	H	H	$C_{21}H_{11}N_3OSBr_2$ (513.21)	15	80	248-249 (248-250)	515[c]	49.15	2.16	8.19	49.16	2.17	8.22
4b	OCH_3	H	H	$C_{22}H_{13}N_3O_2SBr_2$ (543.3)	13	85	196-198 (198-200)	545[c]	48.64	2.41	7.74	48.60	2.40	7.78
4c	H	OCH_3	H	$C_{22}H_{13}N_3O_2SBr_2$ (543.3)	15	80	99-101 (98-100)	545[c]	48.64	2.41	7.74	48.62	2.43	7.72
4d	H	H	OCH_3	$C_{22}H_{13}N_3O_2SBr_2$ (543.3)	14	85	206-208 (208-210)	545[c]	48.64	2.41	7.74	48.62	2.40	7.73
4e	CH_3	H	H	$C_{22}H_{13}N_3OSBr_2$ (527.2)	15	80	167-170 (168-170)	529[c]	50.12	2.49	7.97	50.16	2.48	7.96
4f	H	CH_3	H	$C_{22}H_{13}N_3OSBr_2$ (527.2)	14	90	204-206 (204-206)	529[c]	50.12	2.49	7.97	50.15	2.47	7.96
4g	H	Cl	H	$C_{21}H_{10}Br_2ClN_3OS$ (547.65)	20	80	209-210 (208-210)	549[c]	46.06	1.84	7.67	46.05	1.87	7.63
4h	H	H	OC_2H_5	$C_{23}H_{15}N_3O_2SBr_2$ (557.26)	15	80	192-193 (192-194)	559[c]	49.57	2.71	7.54	49.59	2.72	7.52
4i	H	OC_2H_5	H	$C_{23}H_{15}N_3O_2SBr_2$ (557.26)	14	85	202-204 (202-204)	559[c]	49.57	2.71	7.54	49.56	2.70	7.52

4j	H	H	Br	$C_{21}H_{10}N_3OSBr_3$ (592.11)	19	80	165-166 (164-166)	594[c]	42.60	1.70	7.10	42.61	1.69	7.12
4k	H	H	NO_2	$C_{21}H_{10}N_4O_3SBr_2$ (558.2)	20	85	240-241 (240-242)	560[c]	45.19	1.81	10.04	45.18	1.80	10.08
4l	CH_3	H	CH_3	$C_{23}H_{15}N_3OSBr_2$ (541.2)	15	80	170-172 (170-172)	543[c]	51.04	2.79	7.76	51.06	2.76	7.73
4m	OC_2H_5	H	H	$C_{23}H_{15}N_3O_2SBr_2$ (557.26)	15	85	206-207 (206-208)	559[c]	49.57	2.71	7.54	49.53	2.70	7.56

a Compounds **3g** was recrystallised from ethanol, and compounds **3a-f and 3h-m** from glacial acetic acid.

b CHN analysis were found to be within the limit of ±0.4%.

c Values represent (M++2) due to appearance of an isotopic peak.

Table 2. Anticonvulsant and neurotoxicity of compounds 3a-m in mice[a].

Comp	R4	R5	R6	MES		scPTZ		Toxicity		PI
				0.5h	4h	0.5h	4h	0.5h	4h	
3a	H	H	H	20.5 (21-23)	24 (26-28)	21.3 (20-22)	24.2 (24-28)	50.2 (90.102)	60.2 (110-129)	2.45
3b	OCH_3	H	H	12.4 (11-20)	18 (16-25)	14 (12-22)	19.5 (15-28)	51.8 (49-60)	55 (50-65)	4.1
3c	H	OCH_3	H	13.2 (10-17)	19.2 (15-22)	14.3 (10-22)	20 (17-28)	55.3 (50-58)	57.5 (52-65)	4.18
3d	H	H	OCH_3	15.3 (13-24)	22 (17-27)	15.8 (14-28)	24 (20-29)	60.2 (57-68)	64.5 (59-68)	3.93
3e	CH_3	H	H	7.1 (8.2-10.2)	12.8 (14-16)	10 (12.4-13.8)	14 (12.32-16.2)	37.8 (45-70)	43 (68-92)	5.30
3f	H	CH_3	H	8.4 (10-12)	13.3 (18-22)	12.3 (15-17)	15.4 (16-18)	40 (38-60)	44.5 (54-72)	4.77
3g	H	Cl	H	53.5 (46-61)	68.5 (60-82)	55.3 (50-65)	70.3 (80-101)	85.2 (90-110)	110.2 (100-108)	1.59
3h	H	H	OC_2H_5	28.3 (46-50)	32 (60-70)	28.5 (48-60)	32 (60-70)	59.7 (72-90	64.1 (85-110)	2.10
3i	H	OC_2H_5	H	29.2 (50-60)	33.3 (60-72)	29 (40-50)	36 (60-70)	60.6 (87-108)	66.2 (80-100)	2.07
3j	H	H	Br	55.8 (60-80)	72.8 (60-82)	57.00 (60-85)	78.3 (80-95)	85.2 (80-112)	100.1 (80-97)	1.52
3k	H	H	NO_2	60 (80-101)	73.5 (80-107)	62.7 (70-90)	74.4 (80-110)	82.1 (87-102)	103 (80-100)	1.36
3l	CH_3	H	CH_3	12.4 (16-18)	16.2 (23.2-26)	14.3 (16.5-18.1)	18 (22-26)	42.8 (40-62)	46.4 (60-75)	3.44
3m	OC_2H_5	H	H	14.3 (20-22)	18 (28-30)	15.6 (20-30)	20.5 (24-28)	40.3 (45-70)	48 (48-65)	2.82
Std				6.48	7.1	7.5	8.2	42.8	44	6.60
PTN				(6-7)	(6-9)	(6-9)	(7-9)	(36-48)	37-51)	

a-All compounds were administered by ip injection at doses spanning the range 7-200 mg kg^{-1}, 30 min and 4 h before evaluation of activity and at least 6 animals were used to calculate each ED_{50} and TD_{50} values. In scPTZ induced seizures test, 200 mL/kg body wt. of 10 mM solution of PTZ was administered by subcutaneous route 15 min after the ip injection of test compounds; the anticonvulsant activity was recorded at t = 0.5 and 4 h and represented in terms of the ED_{50}, i.e., dose of test compounds required to assure anticonvulsant protection in 50% of animals from hind limb tonic extension (tonic phase); the TD_{50}, dose eliciting minimal neurological toxicity in 50% of animals as assessed by the rotorod test (locomotor deficit); the PI, protection index (PI = TD_{50}/ED_{50}) from MES induced seizures after 0.5 h; ED_{50} and TD_{50} values are expected as mg kg^{-1};

Table 3. Anticonvulsant and neurotoxicity of compounds 4a-m in mice[a].

Comp	R4	R5	R6	MES		scPTZ		Toxicity		PI
				0.5h	4h	0.5h	4h	0.5h	4h	
4a	H	H	H	51.5 (50-60)	54.5 (45-80)	53.5 (55-70)	55.3 (56-70)	80 (80-85)	92 (80-100)	1.55
4b	OCH_3	H	H	63.4 (48-54)	68.3 (50-60)	64.2 (50-62)	72.3 (55-65)	94.3 (80-100)	109 (90-110)	1.48
4c	H	OCH_3	H	62.3 (60-80)	68.2 (75-98)	62 (65-80)	68 (70-100)	94.5 (80-100)	107.5 (90-107)	1.51
4d	H	H	OCH_3	63 (58-80)	75.2 (70-90)	62 (62-80)	67 (78-102)	94.7 (85-100)	108.3 (85-105)	1.50
4e	CH_3	H	H	40.2 (60-72)	45 (60-75)	42.8 (72-94)	48 (70-90)	68.8 (65-95)	75 (70-85)	1.71
4f	H	CH_3	H	48 (65-72)	38.4 (62-78)	45 (60-78)	47.8 (72-78)	71 (85-90)	75.8 (85-110)	1.47
4g	H	Cl	H	84.3 (80-100)	100.5 (85-95)	85 (82-108)	101.3 (85-105)	115 (90-100)	142 (92-108)	1.36
4h	H	H	OC_2H_5	59.8 (78-86)	63 (74-89)	59.5 (80-85)	65 (82-100)	90.5 (80-98)	98.5 (78-110)	1.51
4i	H	OC_2H_5	H	60 (77-87)	64.3 (72-98)	59.3 (64-70)	67 (76-92)	90.5 (80-85)	98.5 (110-120)	1.50
4j	H	H	Br	87.4 (85-105)	102.5 (82-100)	89 (78-100)	110.5 (85-105)	115.7 (87-102)	132.5 (85-105)	1.32
4k	H	H	NO_2	92.9 (78-100)	106.3 (75-89)	94.8 (78-100)	105.4 (88-102)	112.7 (85-105)	135.7 (90-110)	1.21
4l	CH_3		CH_3	43.8 (75-80)	48.5 (85-105)	44 (78-89)	48.5 (95-115)	75.2 (80-110)	78.2 (80-112)	1.71
4m	OC_2H_5	H	H	48.3 (60-72)	49.5 (60-75)	46.5 (73-95)	50 (72-82)	71.5 (65-89)	79.2 (70-85)	1.48
Std				6.48	7.1	7.5	8.2	42.8	44	6.60
PTN				(6-7)	(6-9)	(6-9)	(7-9)	(36-48)	37-51)	

[a]-All compounds were administered by ip injection at doses spanning the range 7-200 mg kg^{-1}, 30 min and 4 h before evaluation of activity and at least 6 animals were used to calculate each ED_{50} and TD_{50} values. In scPTZ induced seizures test, 200 mL/kg body wt. of 10 mM solution of PTZ was administered by subcutaneous route 15 min after the ip injection of test compounds; the anticonvulsant activity was recorded at t = 0.5 and 4 h and represented in terms of the ED_{50}, i.e., dose of test compounds required to assure anticonvulsant protection in 50% of animals from hind limb tonic extension (tonic phase); the TD_{50}, dose eliciting minimal neurological toxicity in 50% of animals as assessed by the rotorod test (locomotor deficit); the PI, protection index (PI = TD_{50}/ED_{50}) from MES induced seizures after 0.5 h; ED_{50} and TD_{50} values are expected as mg kg^{-1}.

Experimental Section

General

The microwave irradiated reactions (MWI) were performed in scientific microwave oven RAGA's microwave oven. Melting points were determined in open capillaries using a Thermonik precision melting point cum boiling point apparatus, Model C-PMB-2 (Mumbai, India) and are uncorrected.

The purity of the compound was routinely checked by TLC using silica gel-G and the spots were exposed in iodine vapour. IR spectra were recorded using KBr pellets on a Perkin-Elmer 337 Spectrophotometer from Perkin Elmer International Incorporation, Rorkreuz, Switzerland (v max cm-1), 1H NMR spectra on Bruker W.M. 400 Spectrometer (Bruker AG, Fallanden, Switzerland) at 360 MHz using TMS as internal standard (chemical shift in δ ppm) and mass spectra (EI-MS) were recorded on a Jeol D-300 spectrometer(Jeol Ltd.,Tokyo,Japan). Elemental analyses were carried out at Heraeus Carlo Erba 1180 CHN analyser (from Heraeus Instrument GmbH, Hanau, Germany). All the chemicals were purchased from Aldrich Company Ltd. Dorset (UK).

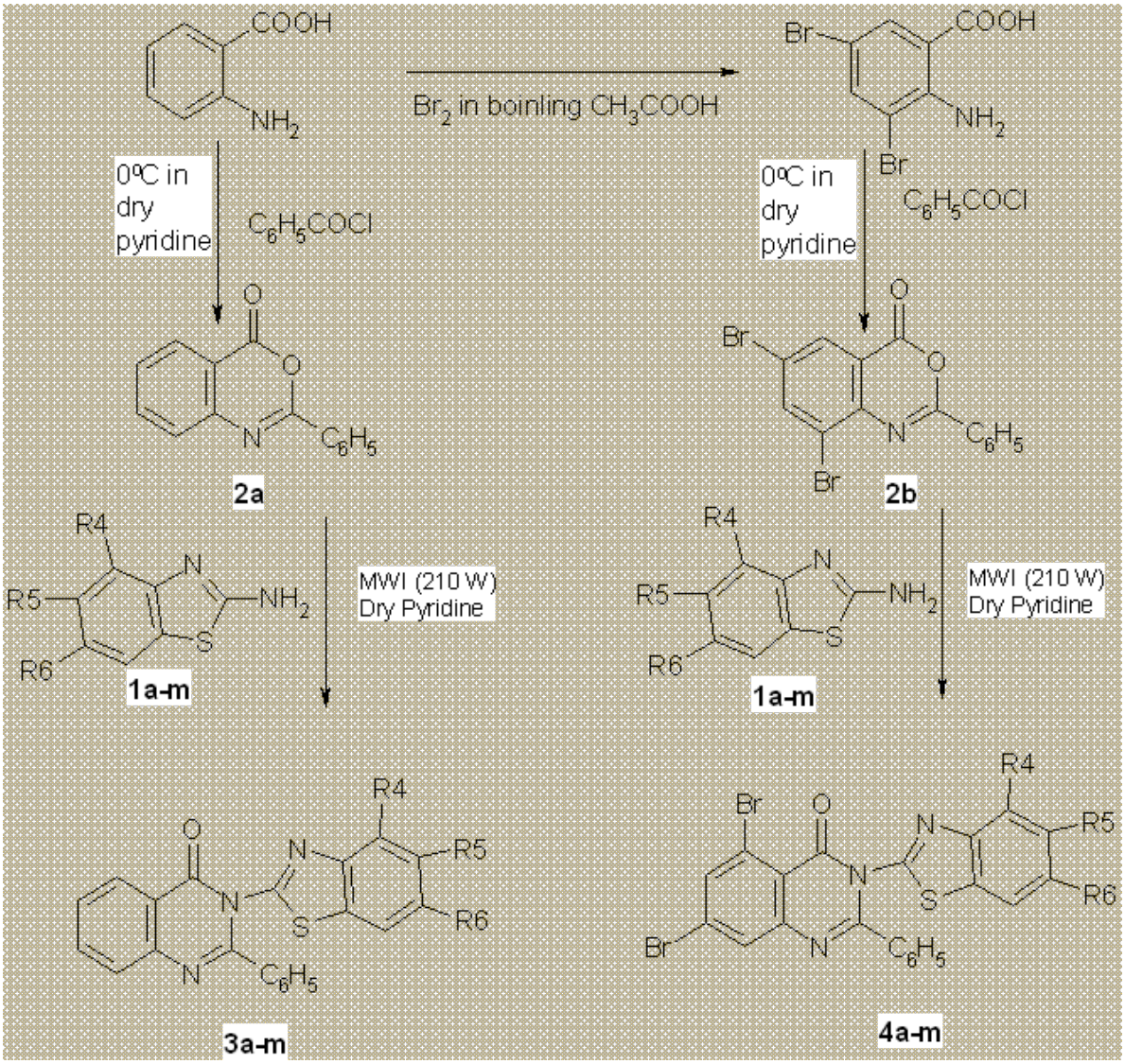


Figure 2 Synthetic scheme

Synthesis of substituted products of 2-aminobenzothiazole (1a-m.)

These compounds were synthesized from aniline and substituted aniline using known methods[21]. The product **1a-m** on recrystallization from ethanol was obtained in pure form.

Synthesis of 6, 8-disubstituted-2-phenyl-3, 1[*H*] - benzoxazine-4-one (2a-b)

These compounds were synthesized from anthranilic acid and 3, 5-dibromoanthranilic acid using known methods [22]. The products **2a-b** were recrystallised from ethanol.

Synthesis of 6, 8-disubstituted 2-phenyl-3-(substituted benzothiazol-2-yl]-quinazolin-4-ones (3a-m & 4a-m.)

A solution of 2-phenyl-3,1(*H*)-benzoxazin-4-one (1.17 g, 0.005 mole) in 15 ml of dry pyridine, 2-aminobenzothiazole (1.5 g, 0.01

mole) was irradiated at reflux temperature (power input: 210 W) until completion (TLC monitoring, 10 min.). After cooling, the reaction mixture was incorporated in a beaker containing 100 gms of crushed ice and 5 ml of conc. HCl. The solid separated (3a) was filtered, dried and recrystallised from glacial acetic acid, yield 1.58 g (90 %), m.p. 277-278 °C. R*f*: 0.60 (rectified spirit). Using the above procedure, twenty six such compounds (3a-m & 4a-m) were synthesized, characterized and their physical data are listed in Table 1.

Compound characterization.

Some representative spectral data for compounds 3a-m & 4a-m:

2-Phenyl-3- (benzothiazol-2-yl)-[3H]-quinazoline-4-one (3a)

IR [KBr; γ] 1620cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$ + DMSO,d in ppm) 7.24-8.04(m, 13H, Ar-H)

2-Phenyl-3-(4-methoxy-benzothiazol-2-yl)-[3H]-quinazoline-4-one (3b)

Yield 1.71 g (85 %), m.p. 216-218 °C, R¦: 0.70(rectified spirit). IR [KBr; γ] 1387 cm^{-1} (C-H stretching), 1618 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 2810 cm^{-1} (O-CH3 stretching), ^{1}H NMR ($CDCl_3$ + DMSO,d in ppm) 6.82-8.14(m, 12H, Ar-H), 3.74 (s, 3H, OCH3)

2-Phenyl-3-(5-methoxy-benzothiazol-2-yl)-[3H]-quinazoline-4-one (3c)

Yield 1.6 g, (80 %), m.p. 189-191 °C, R¦: 0.72 (rectified spirit). IR [KBr; γ] 1377 cm^{-1} (C-H stretching), 1623 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 2812 cm^{-1} (O-CH3 stretching), ^{1}H NMR ($CDCl_3$ + DMSO,d in ppm) 6.80-8.07(m, 12H, Ar-H), 3.74 (s, 3H, OCH3)

2-Phenyl-3-(6-methoxy-benzothiazol-2-yl)-[3H]-quinazolin-4-one (3d)

Yield 1.7 g, [85 %], m.p. 192-194 °C, R¦: 0.83(rectified spirit). IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1624 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 2814 cm^{-1} (O-CH3 stretching), ^{1}H NMR ($CDCl_3$ + DMSO,d in ppm) 6.50-8.08(m, 12H,Ar-H), 3.70 (s, 3H, OCH3)

2-phenyl-3-(4-methyl- benzothiazol-2-yl)-[3H]-quinazoline-4-one (3e)

Yield 1.54 g, (80 %), m.p. 152-153 °C, R¦: 0.83(rectified spirit). IR [KBr; γ] 1374 cm^{-1} (C-H deformation), 1622 cm^{-1} (C=N quinazoline), 1718 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^{1}H NMR ($CDCl_3$ + DMSO,d in ppm) 6.50-7.84 (m, 12H, Ar-H), 2.30 (d, 3H -CH3)

2-phenyl-3- (5-methyl- benzothiazol-2-yl)-[3H]-quinazoline-4-one (3f)

yield 1.73 g, (90%), m.p. 189-180 °C, R¦: 0.76(rectified spirit).IR [KBr; γ] 1370 cm^{-1} (C-H deformation), 1622 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3060 cm^{-1} (Ar-H stretching), ^{1}H NMR ($CDCl_3$ + DMSO,d in ppm) 6.45-7.70 (m, 12H, Ar-H), 2.40 (d, 3H -CH3)

2-phenyl-3- (5-chloro- benzothiazol-2-yl)-[3H]-quinazoline-4-one (3g)

yield 1.63 g, (80 %), m.p. 198-200 °C, R_f: 0.76(rectified spirit). IR [KBr; γ] 712 cm^{-1} (Ar-Cl), 1624 cm^{-1} (C=N quinazoline), 1724 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^1H NMR ($CDCl_3$ + DMSO,d in ppm) 6.50-7.76 (m, 12H, Ar-H)

2-phenyl-3-(6-ethoxy-benzothiazol-2-yl)-[3H]-quinazoline-4-one (3h)

Yield 1.77 g, (85 %), m.p. 141-142 °C, R_f: 0.63(rectified spirit). IR [KBr; γ] 1280 cm^{-1} (Ar-O-C Stretching), 1385 cm^{-1} (C-H in CH3) ,1618 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C = O), 3055 cm-1 (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.50-7.85 (m,12H,Ar-H), 1.1-1.5 (q, 2H , CH2-CH3), 3.5-4.1 (t, 3H, CH2-CH3)

2-phenyl-3- (5-ethoxy -benzothiazol-2-yl)-[3H]-quinazoline-4-one (3i)

Yield 1.67 g, (80 %), m.p. 192-194 °C, R_f: 0.82(rectified spirit). IR [KBr; γ] 1277 cm^{-1} (Ar-O-C Stretching), 1378 cm^{-1} (C-H stretching in CH3), 1628 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C = O), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.10-7.80 (m,12H,Ar-H), 1.1-1.6 (q, 2H, CH2-CH3), 3.5-4.1 (t, 3H, CH2-CH3)

2-phenyl-3- (6-bromo-benzothiazol-2-yl)-[3H]-quinazoline-4-one (3j)

Yield 1.81 g, (80%), m.p. 209-210 °C, R_f: 0.74(rectified spirit). IR [KBr; γ] 612 cm^{-1} (C - Br), 1622 cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 3048 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.44-8.12 (m, 12H, Ar-H).

2-phenyl-3- (6-nitro- benzothiazol-2-yl)-[3H]-quinazoline-4-one (3k)

Yield 1.67 g, (80%), m.p. 262-264 °C, R_f: 0.78(rectified spirit). IR [KBr; γ] 1494 cm^{-1} (- NO2), 1620 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3060 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.77-8.02 (m, 12H, Ar-H).

2-phenyl-3- (4-6-dimethyl- benzothiazol-2-yl)-[3H]-quinazoline-4-one (3l)

Yield 1.7 g,(85 %), m.p. 200-201 °C, R_f: 0.68(Rectified spirit). IR [KBr; γ] 710 cm^{-1} (C-H deformation), 1382 cm^{-1} (C-H stretching in CH3), 1624 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.85-7.65(m,11 H, Ar-H), 1.32 (s, 3H, CH3, in 6th position of benzothiazole), 1.41 (s, 3H, CH3, in 4th position of benzothiazole)

2-phenyl-3- (6-ethoxy- benzothiazol-2-yl)-[3H]-quinazoline-4-one (3m)

Yield 1.64 g, (85%), m.p. 216 – 218 °C, R_f: 0.62(rectified spirit). IR [KBr; γ] 1284 cm^{-1} (Ar-O-C Stretching), 1382 cm^{-1} (C-H in CH3), 1635 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3054 cm^{-1} (Ar-H stretching),^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.81-7.62 (m, 12H, Ar-H), 1.1-1.3 (q, 2H , CH2-CH3), 3.4 - 4.0 (t, 3H, CH2-CH3)

6, 8-Dibromo- 2-phenyl-3- (benzothiazol-2-yl)-[3H]-quinazoline-4-one (4a)

Yield 2.32 g, (80 %), m.p. 248-249 °C, R_f: 0.62(rectified spirit). IR [KBr; γ] 1620 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O], ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.85-7.70 (m, 11H, Ar-H), 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- (4-methoxy -benzothiazol-2-yl)-[3H]-quinazoline-4- one (4b)

Yield 2.6 g, (85 %), m.p. 196-198 °C, R_f: 0.67(rectified spirit). IR [KBr; γ] 1383 cm^{-1} (C-H stretching), 1620cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 2810 cm^{-1} (O-CH3 stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65(m, 10H,Ar-H), 3.80 (s, 3H OCH3) , 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- (5-methoxy -benzothiazol-2-yl)-[3H]- quinazoline-4-one (4c)

Yield 2.45 g, (80%), m.p. 99-101 °C, R_f: 0.78(rectified spirit). IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1620cm^{-1} (C=N quinazoline), 1718 cm^{-1} (C=O), 2810 cm^{-1} (O-CH3 stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65(m, 10H,Ar-H), 3.89 (s, 3H OCH3) , 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo-2-phenyl-3- (6-methoxy- benzothiazol-2-yl)-[3H]-quinazoline-4-one (4d)

Yield 2.6 g, (85%), m.p. 206-208 °C, R_f: 0.74(rectified spirit). IR [KBr; γ] 1380 cm^{-1} (C-H stretching), 1625cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 2810 cm^{-1} (O-CH3 stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65(m, 10H,Ar-H), 3.80 (s, 3H OCH3), 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- (4-methyl- benzothiazol-2-yl)-[3H] -quinazoline-4-one (4e)

Yield 2.38 g, [80 %], m.p. 167-170 °C, R_f: 0.81(rectified spirit). IR [KBr; γ] 1375 cm^{-1} (C-H deformation),1620cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching) , ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.70-7.70 (m, 10H,Ar-H), 2.30 (d, 3H , CH3), 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- (5-methyl- benzothiazol-2-yl)-[3H] -quinazoline-4-one (4f)

yield 2.68 g, (90%), m.p. 204-206°C, R_f=0.64(rectified spirit). IR [KBr; γ] 710 cm^{-1} (Ar-Cl) ,1620cm^{-1} (C=N quinazoline),1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.75 (m,10H,Ar-H) , 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H), 2.35 (d, 3H , CH3)

6, 8-Dibromo- 2-phenyl-3- (5-chloro- benzothiazol-2-yl)-[3H]-quinazoline-4-one (4g)

Yield 2.48 g, [80%], m.p. 209-210 °C, R_f=0.64(rectified spirit). IR [KBr; γ] 1278 cm^{-1} (Ar-O-C Stretching), 1383 cm^{-1} (C-H in CH3), 1620cm^{-1} (C=N quinazoline) ,1722 cm^{-1} (C=O], 3050 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65 (m,10H,Ar-H), 8.3 (d, 1H, J =2.2, H2, HA-Ar-H), 8.1 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- (6-ethoxy- benzothiazol-2-yl)-[3H] -quinazoline-4-one (4h)

Yield 2.52 g, (80%), m.p. 192-193 °C, R_f=0.76(rectified spirit). IR [KBr; γ] 1270 cm^{-1} (Ar-O-C Stretching), 1380 cm^{-1} (C-H stretching in CH3), 1625 cm^{-1} (C=N quinazoline] ,1715 cm^{-1} (C=O), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.60 (m,10H,Ar-H), 1.1-1.6 (q, 2H –CH2-CH3), 3.5-4.1 (t, 3H, CH2-CH3) , 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- [5-ethoxy -benzothiazol-2-yl]-[3H]-quinazoline-4-one (4i)

Yield 2.67 g, (85%), m.p. 202-204 °C, R_f= 0.86(rectified spirit). IR [KBr; γ] 610 cm^{-1} (C-Br), 1620 cm^{-1} (C=N quinazoline), 1720 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-8.25 (m, 10H,Ar-H), 7.9 (d, 1H, J =2.2, H2,

HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H), 1.1-1.6 (q, 2H , CH2-CH3), 3.5-4.1 (t, 3H, CH2-CH3)

6, 8-Dibromo- 2-phenyl-3- (6-bromo-benzothiazol-2-yl)-[3H]-quinazoline-4-one (4j)

Yield 2.68 g, (80%), m.p. 165-166 °C, R_f =0.63 (rectified spirit). IR [KBr; γ] 1490 cm^{-1} (- NO2), 1620 cm^{-1} (C = N quinazoline), 1720 cm^{-1} (C = O), 3050 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.90-8.10(m,10H,Ar-H) , 8.3 (d, 1H, J =2.2, H2, HA-Ar-H), 8.1 (d, 1H, J = 2.2, H2, HB-Ar-H)

6, 8-Dibromo- 2-phenyl-3- (6-nitro- benzothiazol-2-yl]-[3H]-quinazoline-4-one (4k)

Yield 2.68 g, [85 %], m.p. 240-241 °C, R*f* = 0.7 (rectified spirit). IR [KBr; γ] 710 cm^{-1} (C-H deformation) ,1380 cm^{-1} (C-H stretching in CH3), 1620 cm^{-1} (C=N quinazoline) , 1725cm^{-1} (C=O), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65(m,10 H, Ar-H), 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

2-phenyl-3- (4-6-dimethyl- benzothiazol-2-yl)-[3H]-quinazoline-4-one (4l)

Yield 2.44 g,[80 %], m.p. 170-172 °C, R_f: 0.67(rectified spirit). IR [KBr; γ] 710 cm^{-1} (C-H deformation), 1380 cm^{-1} (C-H stretching in CH3), 1620 cm^{-1} (C=N quinazoline) , 1725cm^{-1} (C=O), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65(m,9 H, Ar-H), 1.30 (s, 3H, CH3, in 6th position of benzothiazole), 1.40 (s, 3H, CH3, in 4th position of benzothiazole), 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

2-phenyl-3- (6-ethoxy- benzothiazol-2-yl)-[3H]-quinazoline-4-one (4m)

Yield 2.67 g, [85 %], m.p. 206-208 °C, R_f: 0.63(rectified spirit). IR [KBr; γ] 1280 cm^{-1} (Ar-O-C Stretching), 1385 cm^{-1} (C-H in CH3), 1630cm^{-1} (C=N quinazoline), 1722 cm^{-1} (C=O), 3050 cm^{-1} (Ar-H stretching), ^1H NMR [$CDCl_3$ + DMSO,d in ppm] 6.80-7.65 (m,10H,Ar-H), 1.1-1.4 (q, 2H , CH2-CH3), 3.4 - 4.0 (t, 3H, CH2-CH3), 7.9 (d, 1H, J =2.2, H2, HA-Ar-H), 7.56 (d, 1H, J = 2.2, H2, HB-Ar-H)

Pharmacology

Albino mice of either sex weighing between 20-25 g, obtained from National Center for Laboratory Animal Sciences, Hyderabad, India, were used in present study. Animals were housed in wire-mesh cages under the laboratory conditions (23±2°C), 12-h light. Animals were allowed to acclimatize with free access to food and water for a 24-h period before testing. During the course of experiment, the general behavior of animal was normal. All the experimental protocols were approved by the institutional animal ethical committee and experiments were conducted in accordance with the standard guidelines. The animals were divided into three groups (control, standard and test) and each group consisted of six animals. The homogenous suspension of the test compounds (**3a-m** & **4a-m**) and standard drug (phenytoin) was prepared in polyethylene glycol and distilled water (1:9/ml). All the test compounds were administered intraperitoneally (ip) at a dose of 7-200-mg/kg-body wt., 30 min prior to the start of the experiments. The maximal Electroshock Seizures (MES) were induced by electroconvulsometer (Techno Instruments, Lucknow), using a technique described earlier[23]. The animals were subjected to electroshock (60-mA/0.2 s) via the transauricular electrodes. Further the compounds were evaluated against subcutaneous pentylenetetrazole (PTZ) model in mice. The anticonvulsant effect was assessed by recording the Tonic Hind-limb Extension (THE) at various dose level at t =0.5 and 4 h. Absence of seizure component like hind limb tonic extension with drug treatment was considered to be evidence of protection. Median effective dose (ED50) was calculated for each compound and is presented in Table 2 & 3.

Acute neurotoxicity of all the test compounds was assessed in mice using the method described by Dunham and Miya[24]. Briefly, group of animals (mice) were trained to balance on a rotating rod (3 cm diameter and 6 rpm speed) and was allowed three attempts to remain on the rotating rod for 20 s. Such trained animals were treated with the test compounds at a various dose level 30-200 mg/ kg body wt., by intra peritoneal adminstration. Test compounds were considered to be neurotoxic at a particular dose level if the trained animal showed lack of Rolling Roller Performance. Each of the trained animals was tested in this manner at 30 min and 4 h after the drug adminstration, and the neurotoxic effect was recorded in terms of TD50 and based upon these results PI values were calculated as shown in Table 2 & 3.

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References and Notes

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