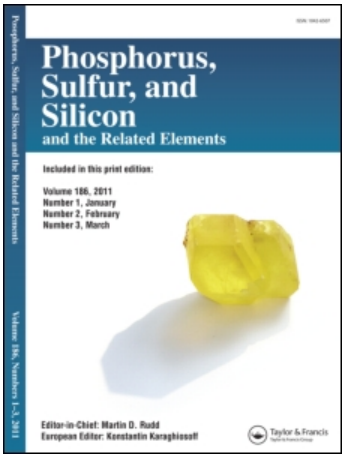

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Rapid Microwave-Assisted Solution Phase Synthesis of 6,8-Disubstituted 2-Phenyl-3-(substituted- benzothiazol-2-yl)-4-[3*H*]-quinazolinones as Novel Anticonvulsants

Sachin S. Laddha[a]; Satyendra P. Bhatnagar[b]
[a] Division of Medicinal Chemistry, R. C. Patel College of Pharmacy, Karvand Naka, Shirpur, Dist., Dhule, India [b] Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, India

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Rapid Microwave-Assisted Solution Phase Synthesis of 6,8-Disubstituted 2-Phenyl-3-(substituted-benzothiazol-2-yl)-4-[3*H*]-quinazolinones as Novel Anticonvulsants

Sachin S. Laddha[1] and Satyendra P. Bhatnagar[2]
[1]Division of Medicinal Chemistry, R. C. Patel College of Pharmacy, Karvand Naka, Shirpur, Dist. Dhule, India
[2]Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, India

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

Keywords 2-Phenyl-3-(benzothiazol-2-yl)-4[3*H*]-quinazolinone; 4-[3*H*]-quinazolinone; anticonvulsant; microwave irradiation; neurotoxicity

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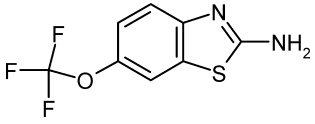
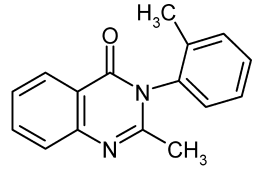
Address correspondence to Sachin S. Laddha, Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, India. E-mail: pinkumanno@rediffmail.com

INTRODUCTION

The development of novel agents, particularly of compounds effective against complex seizures, remains a major focus of antiepileptic drug research.[1] Literature survey reveals that 2-aminobenzothiazole derivatives possess potent anticonvulsant activity.[2,3] In 1985, Riluzole (6-(trifluromethoxy)-2-benzothiazolamine) (Scheme 1) was reported as a potent anticonvulsant agent that functions by action on the voltage-dependent sodium channels.[3–5] Similarly the sedative hypnotic (neurotoxic) properties of another pharmacophore, the 4-[3*H*]-quinazolinones are well documented.[6–18] The prototype in this class of compound is methaqualone (2-methyl-3-ortho-tolyl-4-[3*H*]-quinazolinone) (Scheme 1).[19] In spite of the fact that according to the literature thousands of quinazolinones and 2-aminobenzothiazole related compounds have been synthesized and tested for a possible central nervous system depressant and anticonvulsant activity, no attempt has been made to incorporate the benzothiazole moiety and the quinazoline nucleus in a single molecular framework.



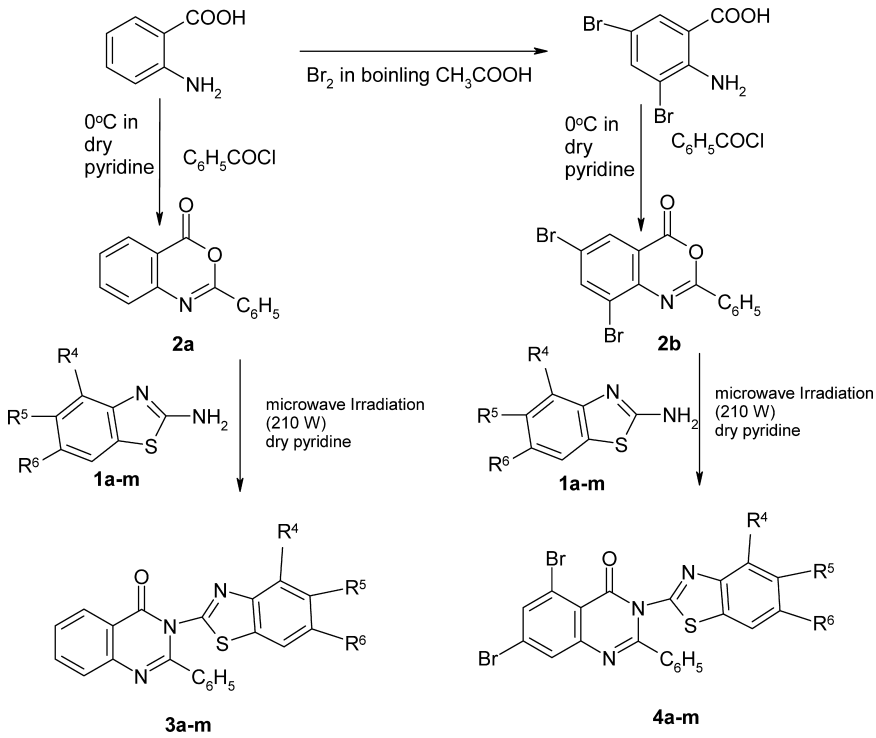
Riluzole



Methaqualone

SCHEME 1

We previously reported[20] a conventional method for the synthesis of 6,8-disubstituted 2-phenyl-3-(benzothiazol-2-yl)-4-[3*H*]-quinazolinones having further substituents in the benzothiazole ring. The synthesis involves the condensation of 2-aminobenzothiazole with 2-phenyl-4*H*-benzo[*d*][1,3] oxazine-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 of reaction times and good yields compared to the purely thermal procedures. In this paper, we report the benefits associated with this new methodology and the established standard experimental conditions. Following the strategy previously reported by us[20] for the synthesis of 6,8-disubstituted 2-phenyl-3-(benzothiazol-2-yl)-4-[3*H*]-quinazolinones further substituented in the benzothiazole ring, it involves long heating (for several hours) of the 2-aminobenzothiazole with 2-phenyl-4*H*- benzo[*d*][1,3]oxazine-4-one in pyridine at reflux temperature. Here we report, the synthesis of 6,8-disubstituted



SCHEME 2

2-phenyl-3-(benzothiazol-2-yl)-4-[3*H*]-quinazolinones **3a-m** and **4a-m**, which was accomplished under microwave irradiation with the aim to develop an original and environmentally friendly procedure. A further scope of our investigations was to evaluate the anticonvulsant activity of the compounds **3a-m** and **4a-m**.

RESULTS AND DISCUSSION

Chemistry

Synthesis of the compounds **3a-m** and **4a-m** was carried out as depicted in Scheme 2. The starting 2-aminobenzothiazoles[21] (**1a-m**), 2-phenyl-4*H*-benzo[*d*][1,3]oxazine-4-one[22] (**2a**) and 6,8-dibromo-2-phenyl-4*H*-benzo[*d*][1,3]oxazine-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 the

2-amino-benzothaizole **1** and 2-phenyl-4*H*-benzo[*d*][1,3]oxazine-4-one **2a** or its dibromo derivative **2b** in dry pyridine were irradiated in a scientific microwave oven at reflux temperature (power input: 210 W). The products were isolated by pouring the reaction solution in a beaker containing crushed ice and 5 mL of conc. HCl. The solid separated (**3** or **4**) was filtered, dried, and recrystallized from an appropriate solvent. The reaction mechanism for the synthesis of compounds **3** and **4** has been reported.[20] The proposed work-up is fast, easy and clean, and presents the advantage of less time and better yields than the conventional method. The transformation proceeded very cleanly and without any traces of side products. The results are summarized in Table I show that in the most cases quantitative conversions were achieved after 10–20 min irradiation.

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

Pharmacology

The anticonvulsant activity of the compounds **3a-m** and **4a-m** was evaluated against Maximum Electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (PTZ) induced seizures in mice.[23] Using the Rotorod procedure the neurotoxicity of all test compounds was assessed in mice. All the tested compounds were administered intraperitoneally at various dose levels ranging from 7–200 mg/kg body weight and the medium effective dose (ED_{50}), the medium toxic dose (TD_{50}) and the protection index (PI) values were determined. Suspensions of the tested compounds in polyethylene glycol were administered to mice 0.5 h or 4 h before evaluation of their activity. The results of anticonvulsant activity and neurotoxicity are presented in Tables II and III.

The Anti MES and Anti sc PTZ (ED_{50} values in Tables II and III) indicated significant anticonvulsant activity for the tested compounds **3a-m** and **4a-m**. However, they were found to be less potent when compared with the reference standard phenytoin (ED_{50}: 6.48 and 7.1 at $t = 0.5$ and 4 h in MES model). The different substituents at 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) at the aromatic ring in general decreases the potency of the tested compounds compared to compounds having electron-donating groups. This is because of the decresed lipophilicity, which in turn inhibits permeability across biological membrane. Further it has been found that

TABLE I Physical and Analytical Data of Compounds 3a-m and 4a-m

	R^4	R^5	R^6	Mol. formula (mol. wt.)	Time (min.)	Yield (%)	M.p. °C observed (reported[20])	Mass (m^+)	Analysis (%) Calculated C	H	N	Found C	H	N
3a	H	H	H	$C_{21}H_{13}N_3OS$ (355.44)	12	90	277–278 (276–278)	355	70.97	3.69	11.82	70.95	3.70	11.81
3b	OCH_3	H	H	$C_{22}H_{15}N_3O_2S$ (385.44)	10	85	(216–218)	385	68.55	3.92	10.90	68.56	3.91	10.88
3c	H	OCH_3	H	$C_{22}H_{15}N_3O_2S$ (385.44)	12	80	189–191 (190–192)	385	68.55	3.92	10.90	68.56	3.95	10.92
3d	H	H	OCH_3	$C_{22}H_{15}N_3O_2S$ (385.44)	14	85	192–194 (192–194)	385	68.55	3.92	10.90	68.56	3.90	10.89
3e	CH_3	H	H	$C_{22}H_{15}N_3OS$ (369.44)	12	80	152–153 (152–154)	369	71.52	4.09	11.37	71.50	4.12	11.36
3f	H	CH_3	H	$C_{22}H_{15}N_3OS$ (369.44)	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	$C_{23}H_{17}N_3O_2S$ (399.47)	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	$C_{23}H_{17}N_3O_2S$ (399.47)	14	80	192–194 (192–194)	399	69.15	4.29	10.52	69.19	4.27	10.53
3j	H	H	Br	$C_{21}H_{12}N_3OSBr$ (434.31)	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	$C_{21}H_{12}N_4O_3S$ (400.41)	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	$C_{23}H_{17}N_3OS$ (383.47)	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	$C_{23}H_{17}N_3O_2S$ (399.47)	14	85	216–218 (216–218)	401	69.15	4.29	10.52	69.16	4.30	10.55

(*Continued on next page*)

TABLE I Physical and Analytical Data of Compounds 3a-m and 4a-m (*Continued*)

									Analysis (%)					
									Calculated			Found		
	R^4	R^5	R^6	Mol. formula (mol. wt.)	Time (min.)	Yield (%)	M.p. °C observed (reported[20])	Mass (m^+)	C	H	N	C	H	N
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	$C_{22}H_{13}N_3O_2SBr_2$ (543.23)	13	85	196–98 (198–200)	545[c]	48.64	2.41	7.74	48.60	2.40	7.78
4c	H	OCH_3	H	$C_{22}H_{13}N_3O_2SBr_2$ (543.23)	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	$C_{22}H_{13}N_3O_2SBr_2$ (543.23)	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	$C_{22}H_{13}N_3OSBr_2$ (527.22)	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	$C_{22}H_{13}N_3OSBr_2$ (527.23)	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	$C_{21}H_{10}N_3OSBr_3$ (592.10)	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	$C_{21}H_{10}N_4O_3SBr_2$ (558.20)	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	$C_{23}H_{15}N_3OSBr_2$ (541.26)	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]Compound **3g** was recrystallized from ethanol and compounds **3a-f** and **3h-m** from glacial acetic acid; [b]CHN analyses were found to be within the limit of ±0.4%; and [c]values represent (M^{++}) due to the appearance of an isotopic peak.

TABLE II Anticonvulsant Activity and Neurotoxicity of Compounds 3a-m in Mice[a]

	MES		scPTZ		Toxicity		
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	PI
3a	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	12.4 (11–20)	18 (16–25)	14 (12–22)	19.5 (15–28)	51.8 (49–60)	55 (50–65)	4.1
3c	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	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	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	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	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	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	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	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	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	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	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. At least 6 animals were used to calculate each ED_{50} and TD_{50} value. In sc PTZ induced seizures test, 200 μL/kg body wt. of 10 μM solution of PTZ was administered by subcutaneous route 15 min after the ip injection of the tested 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 tested compound 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 given as mg kg^{-1}.

TABLE III Anticonvulsant Activity and Neurotoxicity of Compounds 4a-m in Mice[a]

	MES		scPTZ		Toxicity		
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	PI
4a	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	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	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	63 (58–80)	75.2 (70–90)	62 (62–80)	67 (78–102)	94.7 (85–100)	108.3 (85–105)	1.50
4e	40.2 (60–72)	45 (60–75)	42.8 (72–94)	48 (70–90)	68.8 (65–95)	75 (70–85)	1.71
4f	48 (65–72)	38.4 (62–78)	45 (60–78)	47.8 (72–78)	71 (85–90)	75.8 (85–110)	1.47
4g	84.3 (80–100)	100.5 (85–95)	85 (82–108)	101.3 (85–105)	115 (90–100)	142 (92–108)	1.36
4h	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	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	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	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	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	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. At least six animals were used to calculate each ED_{50} and TD_{50} value. In sc PTZ induced seizures test, 200 μL/kg body wt. of 10 μM solution of PTZ was administered by subcutaneous route 15 min after the ip injection of the tested 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 tested compound 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 given as mg kg^{-1}.

the ED_{50} and TD_{50} values of the tested compounds increase significantly at t = 4 h, compared to t = 0.5 h, in contrast to the reference compound, indicating that the tested 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) compared to compounds **3a-f, 3h, 3i, 3l-m** (having electron donating groups). To confirm this phenomenon in vivo, it will be necessary to carry out a kinetic study 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 at the 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. Tables II and III show that PI values >3 were found for more potent compounds in contrast to less lipophilic compounds. Thus, as the lipophilicity increases, so does the toxicity and therefore also the protection index (PI). Among the compounds tested, 2-phenyl-3-(4-methyl-benzothiazol-2-yl)-4(3*H*)-quinazolinone (**3e**) was found to be most potent: ED_{50} = 7.1 and 12.8 in MES model and 10 and 14 in sc PTZ model at t = 0.5 h and 4 h, respectively, and TD_{50} = 37.8 and 43 at t = 0.5 h and 4 h, respectively, with protection index (PI) 5.3.

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

EXPERIMENTAL

General

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

The purity of the compounds was routinely checked by TLC using silica gel-G and the spots were exposed to iodine vapour. IR spectra were recorded using KBr pellets on a Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker WM 400 spectrometer at 360 MHz using TMS as internal standard. Mass spectra (EI-MS) were recorded on a Jeol D-300 spectrometer. Elemental analyses were carried out with Heraeus Carlo Erba 1180 CHN analyzer. All the chemicals were purchased from Aldrich Company Ltd. Dorset (UK).

Synthesis of 2-Aminobenzothiazoles (1a-m)

Compounds **1a-m** were synthesized starting from aniline and substituted anilines using known methods.[21] They were obtained in pure form after recrystallization from ethanol.

Synthesis of 2-Phenyl-4H-benzo[d][1,3]oxazine-4-ones (2a,b)

Compounds **2a,b** were synthesized starting from anthranilic acid and 3,5-dibromoanthranilic acid using known methods.[22] They were recrystallized from ethanol.

Synthesis of 6,8-Disubstituted 2-Phenyl-3-(benzothiazol-2-yl)-quinazolin-4-ones (3a-m and 4a-m)

A solution of the 2-phenyl-4*H*-benzo[*d*][1,3]oxazine-4-one (0.005 mol) in 15 mL of dry pyridine and the corresponding 2-aminobenzothiazole (0.01 mol) was irradiated at reflux temperature (power input: 210 W) until completion of the reaction (TLC, 10 min). After cooling to ambient temperature the reaction mixture was transferred in a beaker containing 100 g of crushed ice and 5 mL of conc. HCl. The solid separated (**3** or **4**) was filtered, dried and recrystallized from glacial acetic acid. The physical data of **3a-m** and **4a-m** prepared by this procedure are listed in Table I. The spectral data of compounds **3a-m** and **4a-m** are all in accordance with the literature.[20]

Pharmacology

Albino mice of either sex weighing between 20-25 g, obtained from National Center for Laboratory Animal Sciences, Hyderabad, India, were used in the 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 the experiment, the general behavior of the animal was normal. All the experimental protocols were approved by the institutional animal ethical committee and the 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 tested compounds (**3a-m** and **4a-m**) and the 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 in the range of 7–200 mg/kg body weight 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 levels 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. Medium effective dose (ED_{50}) was calculated for each compound and is presented in Tables II and III.

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 they were allowed three attempts to remain on the rotating rod for 20 s. Such trained animals were treated with the tested compounds at a various dose levels between 30–200 mg/kg body weight. by intraperitoneal administration. The tested 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 administration, and the neurotoxic effect was recorded in terms of TD_{50}. Based upon these results PI values were calculated as shown in Tables II and III.

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